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Research Article

# FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF ATENOLOL

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**ABSTRACT:**

Atenolol is β1-selective adrenergic blocking agent and widely used in the treatment of hypertension and angina pectoris.Therefor the present investigation was to design a formulation of Mouth dissolving tablet of Atenolol. Mouth dissolving tablets of Atenolol were formulated by Effervescent method, Superdisintegrant addition method, Sublimation method, hot melt method and solid dispersion method by direct compression technique. All the five formulations were evaluated for disintegration time, hardness and friability, among this Superdisintegrant addition method exhibits the lowest disintegration time, hence it is ranked as the best among the five methods. Further nine batches were prepared by using sodium starch glycolate and Ac-di-sol in different concentration. All the formulations were evaluated for weight variation, hardness, friability, drug content, in-vitro disintegration time, wetting time, in-vitro dissolution study. Among all the formulation B7 (containg containing Sodium Starch Glycolate (4%) and Ac-di-sol (3%) was considered to be the best formulation, which release up to 99.90% of the drug in 10 min.

**Keywords:** Atenolol, hypertension, Superdisintegrant addition method, Sodium Starch Glycolate, Ac-di-sol.

## INTRODUCTION:

Recent advances in Novel Drug Delivery System (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is "Mouth Dissolving Tablet"[1-3].The concept of Mouth Dissolving Drug Delivery System emerged from the desire to provide patient with conventional mean of taking their medication. Difficulty in swallowing (Dysphasia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients.[4]

Other categories that experience problems using conventional oral dosage forms includes are the mentally ill, uncooperative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack or coughing. Sometimes it may be difficult to swallow conventional products due to unavailability of water[5]. These problems led to the development of novel type of solid oral dosage form called "Mouth Dissolving Tablets". This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva.[6,] produce rapid onset of action[7] In such a cases Bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.[8] The dispersible tablets allows dissolution or dispersion in water prior to administration but the Mouth Dissolving Tablet instead of dissolving or disintegrating in water is expected to dissolve.

Atenolo is a, β1-selective or cardio selective drugs are the most widely used beta blocker drugs in treatment of cardiovascular diseases such as hypertension, coronary heart disease[11], arrhythmias, and treatment of myocardial infarction after the acute event[9]. Conventional Atenolol tablets available in market are not suitable where quick onset of action is required. Besides, the conventional tablets also show poor patient compliance particularly by the geriatric and pediatric patients who experience difficulty in swallowing, and by those who are bed ridden or who are traveling and do not have an easy access of water. However, oral bioavailability is poor, with about 40% of the drug reaching systemic circulation, which is due to extensive (60%) first pass hepatic metabolism. As the patients with sudden increase blood pressure and acute angina attack, have markedly reduced functional ability and extremely restless, in such cases rapid onset of action is of prime importance. So the patients would be benefited from acute treatment by using proposed drug delivery system. This may help them to return to normal state and resume their functional activities. To provide the patients with the most conventional mode of administration, there was a need to develop rapidly disintegrating dosage form, particularly one that disintegrants and dissolves/disperses in saliva and can be administered without need of water.

In the present study, an attempt has been made to develop mouth dissolving tablets of Atenolol by five different methods governed by direct compression technique. Direct compression[10] represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied for the preparation of oral dispersible tablet because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

## MATERIALS AND METHODS:

### Materials

Atenolol obtaind from Kopran Ltd. (Mumbai, India). Microcrystaline cellulose, Sodium starch glycolate, and Croscarmellose Sodium (Ac-di-sol) were obtained as gift sample from Micro Labs (Banglore, India). Manitol from Loba chemicals (Mumbai, India). Magenisim stearate, talc and Aspartam from S.D. fine chemicals (Mumbai, India). All other materials used were of pharmaceutical grade.

### Selection of tablet methodology

While selecting the tabletting methodology, compressible characteristics of the drug are to be considered. For drugs, which are poorly compressible and have moderate to high dose the most obvious and direct approach would be to follow wet granulation methodology.

For drugs with low to moderate doses, direct compression technique offers various advantages to the pharmaceutical formulator in terms of

In the present study, the direct compression technique was employed to prepare mouth dissolve tablets of Atenolol

## METHODOLOGY

Mouth dissolving tablets of Atenolol were prepared by following five methods using direct compression method.

### 1. Super disintegrate addition method[11]

Specified quantity of Atenolol mannitol, Avicel 102, aspartame, Ac-di-sol, aerosol and magnesium stearate were weighed accurately and passed through 60 # screen. All the materials were transferred to mortar and triturated till it mixed uniformly. The resulting powder mixture was compressed into tablets using single punch tablet machine.

### 2. Effervescent method [12]

Specified quantity of Atenolol, mannitol, Avicel 102, aspartame, aerosil and magnesium stearate were weighed accurately and passed through 60 # screen. Sodium bicarbonate and citric acid were accurately weighed and preheated at a temperature of 70$^{o}$C. All the materials were transferred to mortar and triturated till it mixed uniformly. The resulting powder mixture was compressed into tablets using single punch tablet machine

**3. Sublimation method [13]**

Specified quantity of Atenolol, camphor, mannitol, aspartame, aerosil and magnesium stearate were weighed accurately and were passed through 60 # screen prior to mixing. All the materials were transferred to mortar and triturated till it mixed uniformly. The resulting powder mixture was compressed into tablets using single punch tablet machine. The tablets were dried at 60$^{o}$C oven till constant weigh obtained.

**4. Melt technology [14]**

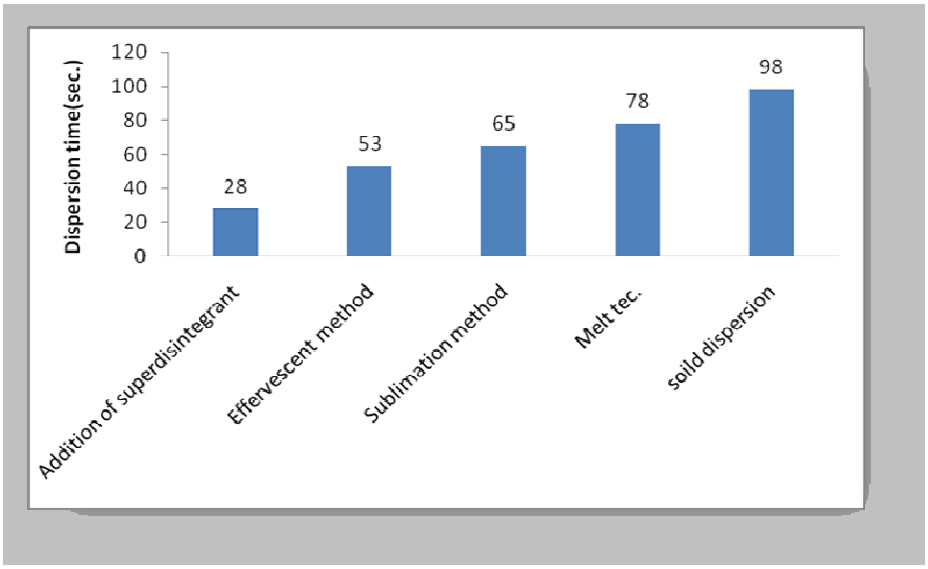
Specified quantities of Atenolol mixed with low mould ability sugars like manitol, sucrose and granulated using high mould ability saccariedes (sorbitol) used as binder .low mould ability sugars used for rapid dissolution and high mould ability saccharide for good binding properties respectively. Granules prepared were lubricated and then compressed into tablets. Final tablets were dried in oven to evaporate the water and to form pores the sugar melt.

**5. Solid dispersion method [15]**

Solid dispersion of Atenolol with PEG-4000 was prepared by solvent evaporation method. In this method accurately weighed quantities of carrier (PEG-4000) in the stated proportions were carefully transferred into the boiling test tube, and dissolved in acetone. To this solution, accurately weighed quanties of Atenolol were added and allowed to dissolve. The solution was transferred to a Petri dish, the solvent was allowed to evaporate at room temperature and dispersion were dried at room temperature 1h, and it dried at $65^{0}$ for 6 hrs.In hot air oven.The mass was crushed, pulverized and shifted through 80 mesh. Granules prepared were lubricated and then compressed into tablets.

Various methods were tried for formulation of mouth dissolving tablets. The disintegration time of tablets prepared by various methods was shown in **Fig. No 1**, it shows that super disintegration addition method exhibits the lowest disintegration time, hence it is the best method as compare to remaining methods. The quicker disintegration time may be attributed to faster water uptake by the tablets.

**Fig-1: Column graph of dispersion time of mouth dissolving tablets Prepared by different methods**




Comprative evaluation of five methods showed Super disintegrate addition method is a better alternative to other methods as its formulation rapidly disintegrate in oral cavity.Hence, further procedures were carried out using superdisintegrant addition method

**Methods**

**Formulation of Mouth dissolving tablet of Atenolol by addition of superdisintegrants method**

Atenolol tablet each containg 25mg of drug was prepared as per the formule given in (table 1).The formulations F1to F9 were prepared,using superdisintegrant addition method by the direct compression technique[16].Various superdisintegrants were used for formulation of mouth dissolving tablets. In this formulation Ac-di-sol and Sodium starch glycolate were used as a superdisintegrant. Avicel 102 used as diluent cum disintegrant[17]. The mechanism of Avicel 102 is interlocking .The particle size of Avicel 102 is small. The decrease in particle size increases binding strength and decreases disintegration time so here we used Avicel 102.Manitol used as a Sweetening agent, tablet and capsule diluents, tonicity agent. Aspartame It enhances flavor systems and can be used to mask some unpleasant taste characteristics; Magnesium Stearate with Aerosil as a flow promoter.The composition of each batch is shown in table( 01).Weighed the Atenolol, mannitol, Avicel 102, super disintegrants, aspartame, aerosol and magnesium stearate accurately and passed through 60 # screen. All the materials were transferred to mortar and triturated till it mixed uniformly. The resulting powder mixture was compressed into tablets using single punch tablet machine.

**Table-1: Composition of Orodispersible Tablet of Atenolol.**

| Formulation | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Atenolol (mg) | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Manitol | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Sodium starch glycolate | 8 | 12 | 16 | 8 | 12 | 16 | 8 | 12 | 16 |
| Croscarmello-se sodium | 2 | 2 | 2 | 4 | 4 | 4 | 6 | 6 | 6 |
| Aerosil | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Aspartame | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Magnesium Stearate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Avicel 102 Up to | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

**Evaluation of mouth dissolving tablets**

**Hardness**

Hardness or tablet crushing strength ($f_c$) (the force required to break a tablet in a diametric compression) was measured using Monsanto tablet hardness tester. It is expressed in $kg/cm^2$

**Friability:** Friability of the tablet determined using Roche friabiltor. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25rpm and dropping a tablet at l height

of 6 inches in each revolution. Preweighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de-dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

**Weight variation:** Rendomly 20 tablets were selected after compression and the mean weight by determined.None of the tablet deviated from the average weight by more than ±7.5(USPXX).

**In-vitro Disintegration time:**

The in-vitro disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

**Wetting time:**

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. According to the following equation proposed by Washburn E.W (1921), the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

$$dl/dt = r\gamma\cos\theta/(4\eta l)$$

Where l is the length of penetration, r is the capillary radius, $\gamma$ is the surface tension, $\eta$ is the liquid viscosity, t is the time, and $\theta$ is the contact angle. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place.

A piece of tissue paper folded double was placed in a Petri dish (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37 $^{o}$C.

Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.

**Assay:**

Twenty tablets from each batch were weighed accurately and powdered powder equivalent to 100 mg Atenolol was shaken with 100ml of 0.1N Hydrochloric acid in 100 ml amber colored volumetric flask and from this 10 ml was pipette out and then dilute up to 100 ml. From standard solution again 10 ml pipette out and diluted up to 100 ml in 100 ml amber colored volumetric flask. Resulting solution was filtered and assayed at 225 nm and content of Atenolol was calculated.

**In-Vitro Dissolution study [18, 19]**

**Dissolution test: -** All the nine formulation of prepared Mouth Dissolving Tablets of Atenolol were subjected to in-vitro release studies were carried out using dissolution apparatus. Standard USP or IP dissolution apparatus have been used to study in vitro release profile using rotating paddle.*In vitro* release rate study of mouth dissolving tablet of Atenolol was carried out using the Apparatus 2 (Paddle apparatus) method. The dissolution apparatus was covered with the black color polythine to protect the solution from light. The dissolution test was carried out using 900 ml of 0.1 N HCl, at 37 $\pm$ $0.5^0$C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 2, 4, 6, 8 and 10 min and withdrawn volume was replaced with fresh dissolution media.Absorption of filtered solution was checked by UV spectroscopy (Shimadzu,Japan) and assayed at 225 nm.Dissolution rate of studied for all designed formulation and conventional tablet.

**Result and disuccion**

The present investigation was undertaken to febricate and evaluate fast dissolving tablet of atenolol by direct compression method**.** Atenolol has a low solubility characteristics, dissolution is the rate limiting step in the drug absorption present work involves atteempt to improve dissolution trate through formulation of fast dissolving tabet of atenolol. Various methods (five different methods) were tried for formulation of mouth dissolving tablets. The disintegration time of tablets prepared by various methods shows that super disintegration addition method exhibits the lowest disintegration time, hence it is the best method as compare to remaining methods.

In the formulation method of super disintegration addition method, the use of superdisintegrants for fast dissolving tablet is highly effective and economical. These superdisintegrants accelerate disintegration of tablets by their ability of absorb a large ammount of water[20] when exposed to an aquous envionrment. However, the rate

of drug dissolution is greatly influenced by disintegration of the tablet.Prepare fast dissolving tablet by gets dispersed in the mouth quickly and releases the drug early as compared to its conventional tablet.

A total number of nine formulation were prepared by direct comression.Two different superdisintegrant Sodium starch glycolate and Croscarmellose sodium-were tried to achieve fast dispersion of tablet. Blends evaluated **(table2**) were found to have excellent flowability**.** In the preformulation study of Atenolol was characterized for bulk, tapped density and angle of repose. Results of the compressibility index, Hauser's ratio and angle of repose show that the all material has sufficient compressibility and flow properties. Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and superdisintegrant were studied. The peaks obtained in the spectrum of each formulation correlates with the peaks of pure drug of Atenolol. This indicates that the drug was compatible with the formulation components (**figar. 2) and (figar. 3)**

However In vitro Disintegration time was found to be in the range 25.3 to 59.4 sec. From all formulations, B7 (4% SSG & 3%Ac-di-sol) has minimum disintegration time. Formulations containing Ac-di-sol has taken more time for disintegration because of its gelling properties (**figar.4).** Wetting Time was found to be in the range 29.1 to 89 sec. (figar.5) from all formulations, B7 (10% L-HPC) has minimum wetting time.

All the 9 formulations were subjected to in vitro dissolution studies by using 0.1N HCl. Dissolution data shows that formulation B7 shows improved dissolution as compared to other formulations. B7 shows near about 99.90% drug release in 10 min. In vitro dissolution study was carried out for conventional marketed Atenolol tablet and compared with best formulation B7 (4% SSG & 3%Ac-di-sol). B7 had taken 10 minutes for complete drug release while conventional tablet taken 45 minutes for completes drug release. (**Table. 3)**

Stability study was carried out for the optimized formulation according to ICH guide lines at 2–8° C (controlled sample), Room temperature and 40° C for 1 month**.(Table 4)**The results showed that there was no significant change in physical and chemical parameter of the tablet, hence the formulation was found to be stable.

From the above result and discussion it is concluded that formulation of Mouth dissolving tablet of Atenolol containing Sodium Starch Glycolate (4 %) and Ac- di- sol (3%) i.e. B7 can be taken as an ideal or optimized formulation of Mouth dissolving tablets for 99.90% release within 10 min. The study shows that the dissolution rate of atenolol can be enhanced through the grat extent by addition of superdisintegrant methods.The rapid drug

dissolution might be due to easy breakdown of the particles due to porous structur formation after super disintegration addition method,and rapid absorption of drugs into the dissolution medium.

**Conclusion**: - The line of investigation can be conclude that fast dissolving tablet of atenolol with Sodium Starch Glycolate (4 %) and Ac- di- sol (3%) as the superdisintegrant is an alternative to and better than the conventional tablet dosage form used in management of hypertension.The prepare tablet disintegrate within in few seconds without need of water. The major advantage of MDT will surely enhance the increased bioavailability, rapid onset of action, low side effects, good stability and most important patient compliance.

**Table-2**: **Evaluation of the Powder Blend.**

| BATCH CODE | BULK DENSITY | TAPPED DENSITY | ANGLE OF REPOSE | % COMPRESSIBILITY | HAUSNER RATIO |
|---|---|---|---|---|---|
| B1 | 0.50 | 0.58 | 25.32 | 16.25 | 1.163 |
| B2 | 0.53 | 0.62 | 26.23 | 18.23 | 1.200 |
| B3 | 0.58 | 0.56 | 28.23 | 14.06 | 1.164 |
| B4 | 0.54 | 0.78 | 23.56 | 14.52 | 1.170 |
| B5 | 0.56 | 0.54 | 24.33 | 13.25 | 1.135 |
| B6 | 0.59 | 0.77 | 29.36 | 17.23 | 1.152 |
| B7 | 0.51 | 0.71 | 24.56 | 12.56 | 1.207 |
| B8 | 0.53 | 0.69 | 31.21 | 18.31 | 1.212 |
| B9 | 0.54 | 0.72 | 30.12 | 19.18 | 1.237 |

**Figar-4: Column graph of the Disintegration time (Sec) of various batches**.

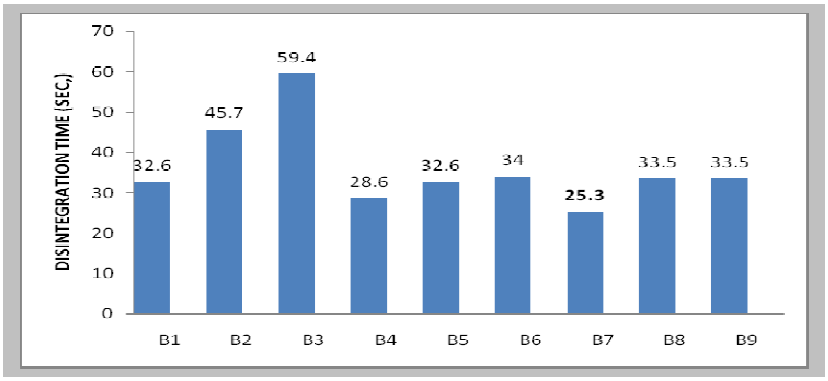


**Fig-5: Column graph of the Wetting time (Sec) of various batches.**

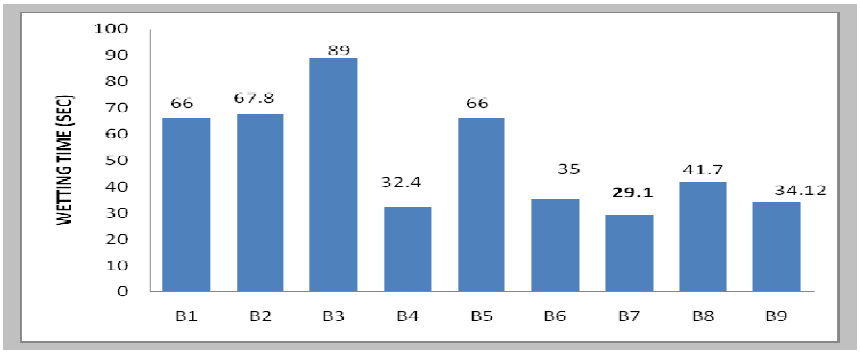



**Table-3: The following are the results of the dissolution studies of the formulated tablet and marketed tablet.**

| Sr.No | Time (Min) | Cumulative percentage Drug Release | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | MT |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 2 | 64.75 | 60.82 | 57.00 | 74.97 | 71.47 | 69.06 | **75.77** | 73.64 | 72.65 | 21.24 |
| 3 | 4 | 76.09 | 65.75 | 60.97 | 83.39 | 81.97 | 79.91 | **88.09** | 84.34 | 80.88 | 23.04 |
| 4 | 6 | 83.79 | 79.04 | 72.65 | 91.68 | 89.75 | 88.85 | **93.08** | 90.85 | 89.58 | 26.64 |
| 5 | 8 | 90.19 | 86.34 | 84.78 | 96.65 | 95.32 | 94.90 | **98.08** | 97.79 | 94.46 | 32.61 |
| 6 | 10 | 99.4 | 96.22 | 95.32 | 99.6 | 98.08 | 97.61 | **99.89** | 98.75 | 97.90 | 54.71 |

**Table-4: Stability study of in-vitro dissolution for formulation B9 stored at temperature 40°C/75 % RH 40°C.**

| TIME (MIN) | CUMULATIVE % DRUG RELEASE | | | |
|---|---|---|---|---|
| | Controlled | After 15 days | After 30 days | After 60 days |
| 0 | 0 | 0 | 0 | 0 |
| 2 | 75.77 | 73.25 | 73.00 | 72.89 |
| 4 | 88.09 | 87.80 | 87.25 | 86.90 |
| 6 | 93.08 | 92.77 | 92.25 | 92.05 |
| 8 | 98.08 | 97.94 | 97.50 | 97.25 |
| 10 | 99.89 | 98.88 | 98.79 | 98.10 |

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