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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS ATENOLOL

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ABSTRACT

The aim of the present work is to study the preformulation parameters of fast dissolving tablets. The objective of Preformulation study is to generic information useful to the formulator in developing stable and bioavailable dosage form. The use of Preformulation parameter maximizes the chances in formulation an acceptable, safe, efficacious and stable product and at the same time provides the basis for optimization of the drug product quality. Administration of conventional tablets of Atenolol in has been reported to exhibit fluctuations in plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor sites. The half-life of Atenolol is 6-7 hours hence multiple doses of the drug are needed to maintain a constant plasma concentration for a good therapeutic response, and improve patient compliance, hence the objective of the study was made to develop fast dissolving tablet of Atenolol. 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. In this studies using polymer like AC-DI-SOL, Sodium starch glycolate and which will quickly the release of drug, increasing the bioavailability of the drug and thus decreasing the dosing frequency of the drug. The description and appearance, melting point and solubility were also performed for further characterization & it was found that all results are satisfactory. And B7 is the best formulation among of that and it release 99.5%.

KEY WORDS: Antihypertensive, Preformulation, Ac-di-sol, Sodium starch glycolate

1. INTRODUCTION

Tablets (Leon Lachman, 2001) are solid preparations each containing a single dose of one or more active ingredients and are obtained by compressing uniform volumes of particles. The objective of the design and manufacture of the compressed tablet is to deliver orally the correct amount of drug in the desired location and to have its chemical integrity protected to the point. 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". 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.

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 (Kaushik, 2003). 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. Produce rapid onset of action in such a cases Bioavailability of drug is significantly greater than those observed from conventional tablet dosage form (Wilson, 1987).

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.Atenolol 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 (British Pharmacopoeia, 2001), arrhythmias, and treatment of myocardial infarction after the acute event.

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 disintegrates 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 sublimation technique.

2. MATERIAL AND METHODS

Atenolol is procured from Zydus Cadila,Ahmedabad,Sodium Starch Glycolate,AC-DI-SOL gift sample by Maple Biotech,Pune ,Avicel 102 gift sample by Signet Chemicals,Mumbai. All chemicals used are of analytical grades.

Preformulation studies: Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objective of Preformulation studies are to develop a portfolio of information about the drug substance, so that this information useful to develop formulation. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients. Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product (Cooper, 1986).

Organoleptic Characteristics: The color, odor, and taste of the drug were characterized and recorded using descriptive terminology; the results were shown in the Table No 1.

Table 1. Organoleptic properties of Atenolol

Properties	Results
Description	Crystalline powder
Taste	Taste less
Odour	Odourless
Colour	White

Sieve Analysis: Standard sieves of different meshes were available as per the specifications of USP; sieves were arranged in a nest with courses at the top. A sample of the 40 mesh passed powder is placed on top sieve. This sieve set was fixed to the mechanical shaker apparatus and shaken for a certain period of times. The powder retain on each sieve was weighed and percentage of powder retained on each sieve was calculated using the initial weight taken.

Bulk Density: An accurately weighed quantity of powder, which was previously passed through sieve # 40 [USP] and carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measure was called as the bulk volume and the bulk density is calculated by following formula;

Bulk density = Weight of powder / Bulk volume

Tapped Density: After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Volume was noted as (Va) and again tapped for 750 times and volume was noted as (Vb). If the difference between Va and Vb not greater than 2% then Vb is consider as final tapped volume. The tapped density is calculated by the following formula

Tapped density = Weight of powder / Tapped volume

Carr's Index [Compressibility Index] and Hauser's Ratio: Carr's index and Hausner's ratio measure the propensity of powder to be compressed and the flowability of powder. Carr's index and Hausner's ratio can be calculated from the bulk and tapped density.

Carr's index = Tapped density – Bulk density / Tapped density × 100

Hausner's ratio = Tapped density / Bulk density

Angle of repose: The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\theta = \tan^{-1} h / r$$

Where, h and r are the height and radius of the powder cone, respectively.

Table No 2:- Physical parameters of Atenolol powder (pure)

Parameter	Atenolol
Bulk Density (gm/cm^2)	0.418
Tapped Density (gm/cm^2)	0.633
Compressibility Index	32.43
Hauser's Ratio	1.5
Angle of repose	32.76

Loss on drying: Loss on drying is the loss in weight in % w/w resulting from water and volatile matter of any kind that can be driven off under specific conditions. The rest is carried out on a well-mixed sample of substance. Mix and weigh accurately 1 to 2 gm of the substance. If the substance is the form of large crystals, reduce the particle size to about 2mm by quickly crushing Tare a glass-stoppage shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Put the test specimen in the bottle, replace the cover and accurately weigh the bottle and the contents. Distribute the test specimen as evenly as practicable to a depth of about 5mm generally and not more than 10 mm in the case of bulky materials Place the loaded bottle in the drying chamber (LOD Oven) by removing the stopper and leaving it also in the chamber.

Dry the test specimen at the temperature of 850C.

$$\% \text{ Loss on drying} = \frac{W2 - W3 \text{ (or) } n}{W2 - W1} \times 100$$

Where, W1 = Weight of the empty bottle in grams.
W2 = Weight of the bottle with sample in gram (Before drying)
W3 = Weight of the bottle with sample in grams. (After drying) – As time specified.
Wn = Weight of the bottle with sample after Additional 1 hour drying (constant weight)

Table. 3 Loss on drying

Test	Observation
Loss on drying	0.05% w/w

Analytical method for estimation of the atenolol drug (uv method): In the present investigation, Atenolol was estimated by UV/VIS spectrophotometry in 0.1N HCl. The *in vitro* dissolution study was also carried out in 0.1N HCl (pH 1.2).

Preparation of stock solution: Atenolol (100mg) was accurately weighed and transferred into the 100 ml amber colored volumetric flask. It was dissolved in 0.1N HCl and volume was made up to the mark with 0.1N HCl to get a 1000 µg/ml solution. From this 10 ml was pipette out and then diluted up to 100 ml with 0.1N HCl. From that solution again 10 ml pipetted out and diluted up to 100 ml in amber colored volumetric flask with 0.1N HCl to get a stock solution of 10µg/ml.

UV absorption maxima of atenolol: UV scanning was done for 10µg/ml drug solution from 200-400 nm in 0.1N HCl as a blank using Shimadzu double beam UV/VIS spectrophotometer. The wavelength maximum was found to be at 225 nm.

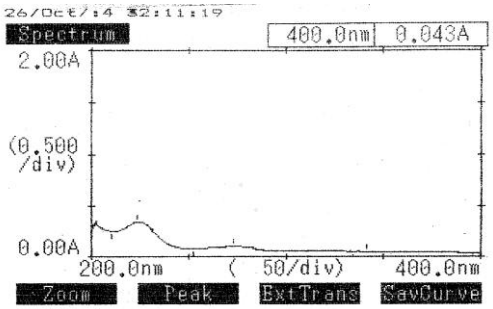


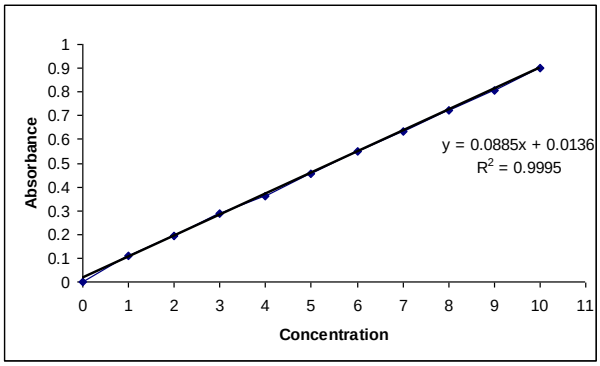
Figure No 1:- UV-Spectrum and Wavelength maxima of Atenolol in 0.1N HCl

Preparation of standard curve: From the stock solution 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 ml were transferred to 10 ml amber colored volumetric flasks and diluted with the 0.1N HCl, up to the mark to obtain Atenolol concentration of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 µg/ml respectively. Absorbance of each solution was measured at 225 nm. The results were a shown in **Table No 4** and **Fig. No. 2**

Table No 4: Standard curve of Atenolol in 0.1N HCl

Concentration (µg/ml)	Absorbance
1	0.132
2	0.161
3	0.243
4	0.322
5	0.393
6	0.485
7	0.567
8	0.632
9	0.720
10	0.808

Fig. No 2: **Standard Calibration Curve of Atenolol**



Compatibility studies: Compatibility with excipients was confirmed by carried out I R studies. The pure drug and its formulations along with excipients were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

Table-4 Formulation of fast dissolving Tablets of Atenolol

Formulation (mg)	B1	B2	B3	B4	B5	B6	B7	B8	B9
Atenolol	25	25	25	25	25	25	25	25	25
Camphor	15	20	30	15	20	30	15	20	30
Manitol	50	50	50	50	50	50	50	50	50
Sodium starch glycolate	8	12	16	8	12	16	8	12	16
Ac-di-sol	2	2	2	4	4	4	6	6	6
Talc	4	4	4	4	4	4	4	4	4
Aerosil	2	2	2	2	2	2	2	2	2
Aspartame	3	3	3	3	3	3	3	3	3
Avicel 102 up to	200	200	200	200	200	200	200	200	200

Table-5 Physical parameters of mouth dissolving Tablet

Batch code	Weight variation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (sec)	wetting time (sec)	Assay (%)
B1	pass	2.56	3.4	0.73	31.6 ±1.25	66.0 ±1.35	98.14
B2	pass	2.57	2.5	0.76	43.7 ±2.46	67.8 ±0.35	99.02
B3	pass	2.60	2.5	0.79	56.4 ±2.42	89.0 ±0.85	100.51
B4	pass	2.63	3.2	0.74	27.6 ±1.22	32.4 ±1.15	98.91
B5	pass	2.65	3.0	0.78	30.6 ±1.25	66.0 ±1.35	100.04
B6	pass	2.66	2.5	0.80	34.0 ±1.00	35.0 ±0.95	99.86
B7	pass	2.51	3.0	0.69	22.3 ±0.58	29.1 ±1.05	98.92
B8	pass	2.52	2.5	0.65	32.5 ±0.50	41.7 ±1.45	101.05
B9	pass	2.54	2.5	0.66	33.5 ±0.50	34.12±1.45	100.3

Table-6.Cumulative percent drug released vs. time (zero order kinetics)

Time (min)	Cumulative percentage Drug Release								
	B1	B2	B3	B4	B5	B6	B7	B8	B9
0	0	0	0	0	0	0	0	0	0
2	64.7	60.8	57.0	74.9	71.4	69.0	73.4	73.6	72.6
4	76.0	65.7	60.9	83.3	81.9	79.9	85.0	84.3	80.8
6	83.7	79.0	72.6	91.6	89.7	88.8	94.5	90.8	89.5
8	90.1	86.3	84.7	96.5	95.3	94.9	97.7	97.7	94.4
10	94.4	96.2	95.3	99.6	98.0	97.6	99.5	98.7	97.9

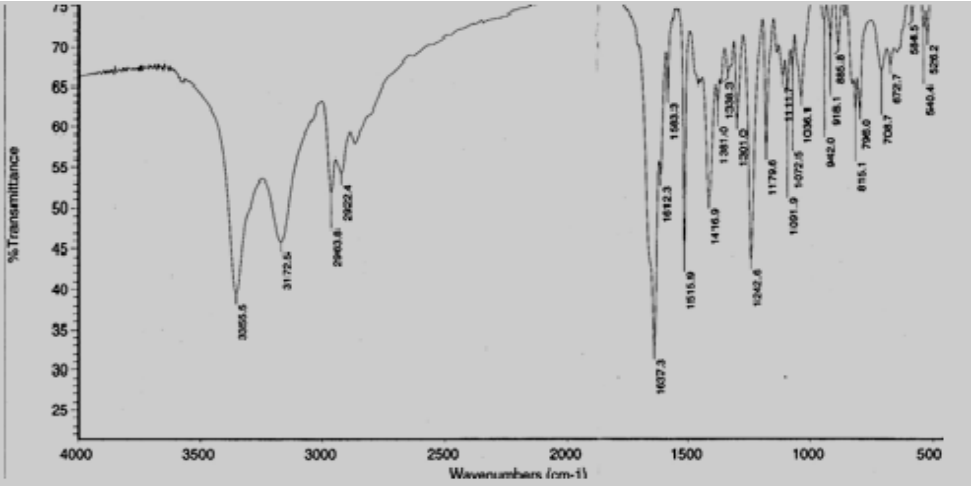


Fig No. 3 IR Spectra of Atenolol

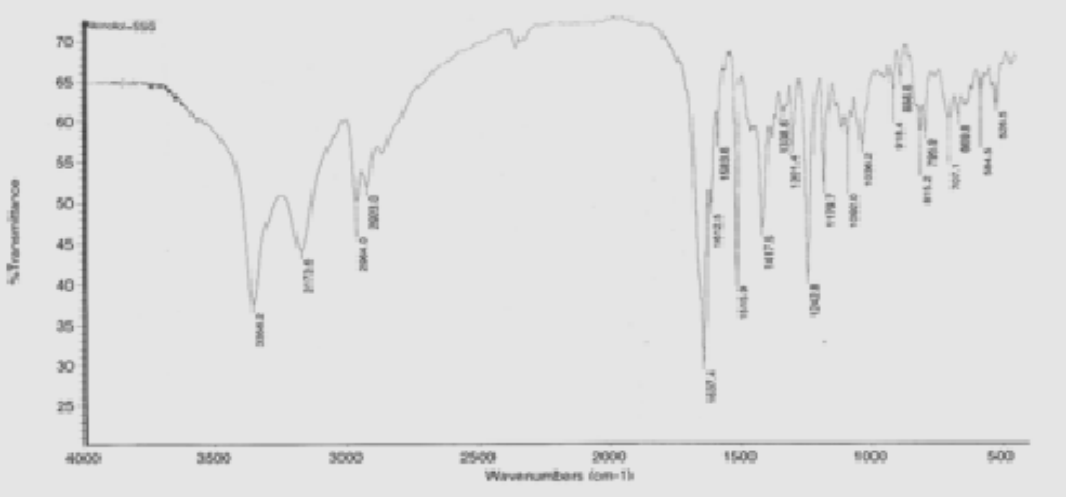


Fig No. 4 IR Spectra of Atenolol + SSG

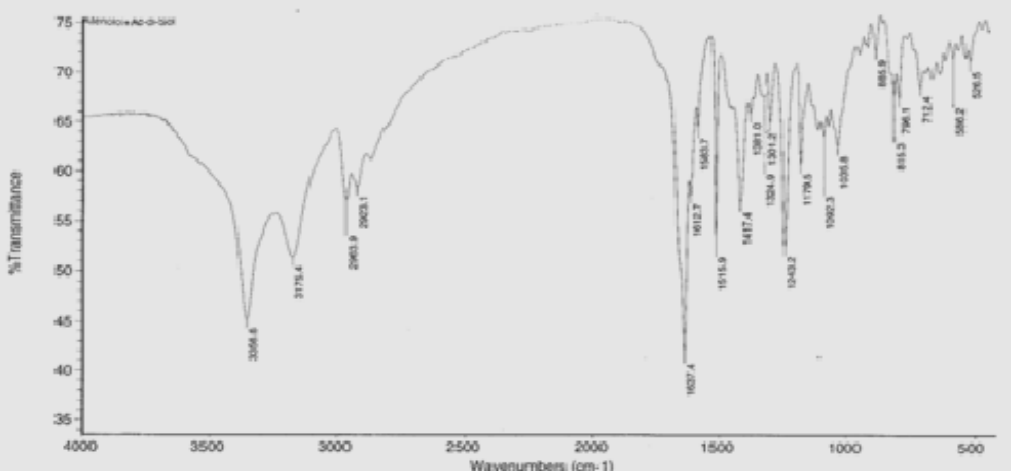


Fig No. 5 IR Spectra of Atenolol + Ac-di-sol

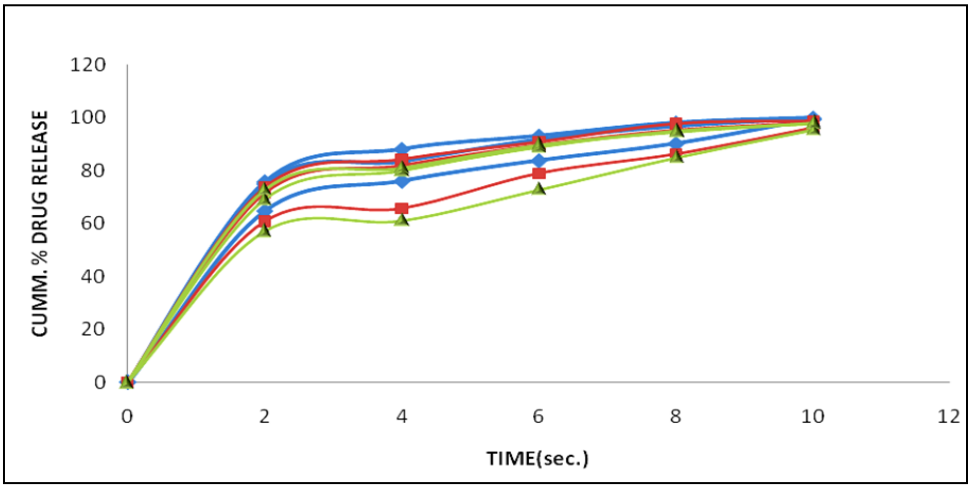


Figure-6 Invitro Cumulative % Drug Releasd V/S Time For Formulation (B1 To B9) Of Atenolol

3. CONCLUSION

Atenolol is an anti-hypertensive and anti-anginal drug. This is the most frequently prescribed drug in treatment of various heart related problems. Conventional Atenolol tablets available in market are not suitable where quick onset of action is required. To overcome these problems, there is a need to develop a rapidly disintegrating dosage form, particularly one that would rapidly disintegrate in saliva and could be administered without water anywhere anytime. No such mouth dissolving tablet of Atenolol is available in the market. The present investigation was aimed to evaluate the possibility of using different parameters for the development of fast dissolving of Atenolol. Preformulation studies were done using various parameters such as identification test of Atenolol. The description and appearance, melting point and solubility were also performed for further characterization & it was found that all results are satisfactory. And B7 is the best formulation among of that.

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