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FORMULATION AND EVALUATION OF ORAL DISPERSIBLE TABLETS OF ATENOLOL BY USING SUPER DISINTEGRATES

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ABSTRACT

The aim of this study is to formulate and evaluate an oral dispersible drug delivery system (ODDDS) containing an antihypertensive drug atenolol, by using different super disintegrates. Oral dispersible tablet form is designed to allow administration of an oral solid dosage form in the absence of water or fluid intake. Such tablets readily dissolve or disintegrate in the saliva generally within <60seconds. The main objective of the present study was undertaken for formulation and evaluation of oral dispersible tablets by direct compression technique. In the present project work, an attempt was made to formulate Atenolol as an oral dispersible tablet using different Superdisintegrants (like Crosspovidone, croscarmellose sodium, sodium starch glycolate etc) in different ratios by direct compression method. The formulations were evaluated for hardness, friability, weight variations, thickness, drug content and in vitro dissolution profile.

Keywords:-Atenolol, Super disintegrates, Direct compression method, Crosspovidone, Anti-hypertensive.

INTRODUCTION

Oral drug delivery remains the preferred route for administration of various drugs. Solid dosage forms are popular because of ease of administration accurate dosage, self-medication, pain evasion and most importantly the patient compliance. The faster the drug into solution form, quicker the absorption and onset of clinical effects. Oral dispersible tablets (ODT) are not only indicated for people who have swallowing difficulties, but are also ideal for active people. Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving tablets etc. (Armstrong N *et al.*, 1989) Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which

dissolves or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The advantage of oral dispersible dosage forms are increasingly being recognized in both, industry and academics. The basic approach in development of ODT is the use of Superdisintegrants like cross linked carboxymethy cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrrolidone (polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on tongue, there by release the drug in to the saliva. Swells up to ten fold within 30 seconds when contact water. (Birkedal-hansen H *et al.*, 1993). The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed

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drugs that pass down into the stomach. Atenolol chemically called as (RS)-4-(2-hydroxy-3-isopropylaminopropoxy) phenylacetamide, having Molecular Formula -C₁₄H₂₂N₂O₃, with Molecular Weight 266.3 A white or almost white powder, having Melting Point at 152-155°C. It is β 1receptar Antagonist and freely soluble in methanol, soluble in acetic acid, Propanol, slightly soluble in water, very slightly soluble in acetone, practically insoluble in acetonitrile, ethyl acetate and chloroform. Atenolol used as antihypertensive drug and the Dose is 50 to 100 mg once daily.

MATERIALS AND METHODS

Materials

Atenolol was purchased from A-Z Pharma PVT LTD CHENNAI, India. Crosspovidone was purchased from S.D. Fine Chem. Ltd., Mumbai, India. Mannitol, Magnesium stearate, Talc, Lactose was obtained from Enar Chemicals Pvt Ltd, India. All other the materials used were of analytical grade.

Methodology

Preformulation Studies

Organoleptic Properties

Colour

A small quantity of Atenolol powder was taken in butter paper and viewed in well-illuminated place. (Chandira R *et al.*, 2008; Pankaj shukla *et al.*, 2012)

Taste and odour

Very less quantity Atenolol was used to get taste with the help of tongue as well as smelled to get the odour.

Solubility

The atenolol is freely soluble in methanol, soluble in acetic acid, Propanol, slightly soluble in water, very slightly soluble in acetone, practically insoluble in acetonitrile, ethyl acetate and chloroform.

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 85°C. (Karthikeyan M *et al.*, 2012)

$$W2 - W3 \text{ (or) } n$$

$$\% \text{ Loss on drying} = \frac{W2 - W1}{W2 - W1} \times 100$$

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)

Flow properties

Angle of repose

Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the measure the Flowability of powder /granules. (Chowdary KPR *et al.*, 2011)

Weighed quantities of Atenolol were passed through a funnel kept at a height of 2 cm from the base. The powder is passed till it forms heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated by using the formula.

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

Where, h: Height of the heap of pile r: Radius of base of pile Since particles may be hard and smooth in one and rough and spongy in another, one must express densities with great care. Density is universally defined as weight per unit volume: the difficulty arises when one attempts to determine the volume of particles containing microscopic cracks, internal pores and capillary spaces.

Tapped density

Weighed quantity of Atenolol was taken into a graduated cylinder, volume occupied by granules was noted down. Then cylinder was subjected to 500/ 750 and 1250 taps in tapped density tester (Electro Lab USPII) According to USP, the blend was subjected for 500 taps the % Volume variation was calculated by following formula. (Feldman M, *et al.*, 1997)

$$Pt = m/Vi$$

Where, M: Mass of the blend Vi: Tapped Volume

Compressibility index

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that obtained from density determination. Weighed quantities of Atenolol were transferred to 50 ml graduated cylinder, volume occupied by granules was noted down. Then cylinder was subjected to 500/750 and 1250 taps in tapped density tester (Electro Lab USPII) the difference between two tabs should be less than 2%. The percentage of compressibility Index is calculated by using formula.

$$CI = \frac{V_o - V_i}{V_o} \times 100$$

Where, V_o : Untapped density V_i : Tapped density

Hausner's ratio

It is measurement of frictional resistance of the drug. The Ideal range should be 1.2 -1.5, it was determined by the ratio of tapped density and bulk density.

$$\text{Hausner's Ratio} = \frac{V_o}{V_i}$$

Where, V_o : Untapped density V_i : Tapped density

Drug-excipients compatibility studies

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with Excipients. It is the first step in the rational development of dosage form. The active ingredient (Atenolol) with various excipients in 1:1 and 1:10 ratio were taken in glass vial and kept at various conditions (40°C/75%RH and 60°C/80%RH) in stability chamber. (Hubsher JA, *et al.*, 1979)

The study is carried out in open and closed glass vials for a period of 1 Month. The samples were withdrawn at intervals of 7, 15 and 30 days and characteristic like colour change, water content and Related substances was recorded. Finally the compatible mixtures were selected for formulation.

Evaluation of Atenolol Tablets

Hardness Test

Tablet requires a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. 16, 17, 18. Tablet hardness has been defined, as the force required breaking a tablet a diametric compression test. The hardness of the tablet was found using Monsanto hardness and Pfizer tester. (Jivraj M, *et al.*, 2000)

Friability

Friability is the loss in weight of tablet in the container due to removal of fine particle from their surface.

The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%). 10 tablets were initially weighed (initial weight) and transferred into the friabilator. The Friabilator was operated at 25 rpm for 4 mins. The tablets were weighed again (final weight).

The % friability was then calculated by the following formula

$$F = \frac{\text{Initial wt} - \text{Final wt}}{\text{Initial wt}} \times 100$$

Thickness

The thickness of the tablets was measured using Digital Vernier Caliper. It is expressed in mm.

Weight Variation Test

With a tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of the tablet being made is routinely measured to help ensure that a tablet contain proper amount of drug. Twenty tablets were selected at random and the average weight was determined.

Not more than two of the individual weights deviated from the average weight by more than limit. The percentage deviation shown in table and none deviated by more than twice the percentage In house specification limit of Percentage deviation of fabricated tablets The results are tabulated in the following table

Disintegration test

The U.S.P. device to test disintegration uses 6 glass tubes that are 3" long; open at the top and 10 mesh screens at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at $37 \pm 2^\circ\text{C}$ such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. (Lachman L *et al.*, 2009)

Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. (Raymond C *et al.*, 2006)

According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass.

Disintegration time: Uncoated tablet: 5-30 minutes

Assay

Procedure of Standard Curve

50mg drug dissolve it in 50ml methanol and from that 10ml was taken in a 100ml volumetric flask and make up the volume up to 100ml with phosphate buffer ph 6.8. This is stock solution of concentration 100µg/ml.

From this stock solution 1ml was taken in 10ml volumetric flask and makes up the volume up to 10ml with phosphate buffer ph 6.8. (10µg/ml). Respectively solutions of concentrations 10, 20, 30, 40, 50µg/ml was prepared.

Their absorbance was measured in UV visible spectrophotometer and a calibration curve was plotted for time versus absorbance and from that graph standard concentration was determined.

Preparation of Ph6.8 Phosphate Buffer

27.4 gm potassium di hydrogen phosphate was weighed and make up to the volume with 100 ml distilled water 8.5 gm of NAOH was taken and make up the volume with 100 ml of distilled water. From the above solution 50 ml of potassium di hydrogen phosphate solution was taken and 39.7 ml NAOH is solution was taken and kept in 1000 ml volumetric flask and make up the volume up to 1000 ml with distilled water.

Preparation of Sample Solution

Set the dissolution test apparatus as per the above conditions. Place one tablet to each in 6 dissolution bowl. Run the apparatus for one hour. Withdraw 10 ml of the sample in the above time intervals from each bowl, replacing the same amount every time with fresh dissolution medium. Collect the sample and filter the solution through filter paper. Collect the filtrate. Pipette 5ml of this solution into 25ml volumetric flask, and make up the volume with dissolution medium.

RESULTS AND DISCUSSION

Organoleptic Properties

These tests were performed as per procedure. The results

are illustrated in following table.

Physical Characteristics

Solubility

Atenolol found to be slightly soluble in water, sparingly soluble in methanol and practically insoluble in methylene chloride. (Srivastava KC *et al.*, 1989)

Loss on Drying

This test was performed as per the procedure in Preformulation studies and the results were as follows:-

Physical Parameters of Atenolol

After the wet granulation process physical parameters of the Atenolol were performed as per the procedure in materials and methodology and results found as follows,

Tablet Formulations

Different tablet formulations were prepared using direct compression method. Formulations were taken based on the following procedure with different Directly Compressible Vehicle of Excipients for following three formulations,

Table 1. Standard limit of tablet

S.No.	Average weight of tablet	Percentage
1.	80 mg or less	+ 10 %
2.	More than 80 mg and less than 250 mg	+ 7.5%
3.	250 mg or more	+ 5 %

Table 2. Organoleptic Properties

S.No	Tests	Observation
1	Colour	White or almost white powder
2	Taste	Bitter
3	Odour	Odourless

Table 3. Loss on Drying

Test	Observation
Loss on drying	0.05% w/w

Table 4. Physical Parameters of Atenolol

Physical Parameter	Formulation 1	Formulation 2	Formulation 3
Angle of Repose	27.50	27.42	27 ⁰ .54'
Bulk density In g/ml	0.391	0.381	0.418
Tapped density in g/ml	0.4615	0.4315	0.4866
Compressibility Index	15.20%	14.85%	12.43%
Hausner's ratio	1.172	1.164	1.152
Flow	Good	Good	Excellent

Table 5. Formulation of Atenolol

Ingredients Used	F -1	Ingredients Used	F-2	Ingredients Used	F-3
Atenolol	50	Atenolol	50	Atenolol	50
Crossprovidone	10	Cross Carmilose Sodium	10	Sodium Starch Glycolate	10
Lactose	112	Lactose	112	Lactose	112
Starch	38	Starch	38	Starch	38
Talc	4.5	Talc	4.5	Talc	4.5
Magnesium Stearate	4.5	Magnesium Stearate	4.5	Magnesium Stearate	4.5

Average Weight of the tablet = 220 mg

Table 6. Category of Drug and Excipients

S.NO	Ingredients	Category
1	Atenolol	Active Ingredient
2	Lactose	Diluents
3	Starch	Directly Compressible Vehicle
4	Cross Carmilose Sodium	Super Disintegrant
5	Cross Providone	Super Disintegrant
6	Sodium Starch Glycolate	Super Disintegrant
6	Talc	Glident
7	Magnesium Stearate	Lubricant

Evaluation test for Atenolol tablets**Table 7. Hardness of the Tablets**

S.NO	Formulation	Hardness (Kg/cm ²)
1	Formulation-1	3.83
2	Formulation-2	3.16
3	Formulation-3	3.66

Table 8. Friability Test

S.NO	Formulation	Weight of 10 Tablets		% Friability
		Before	After	
1	Formulation-1	2.320	2.298	0.94
2	Formulation-2	2.314	2.300	0.60
3	Formulation-3	2.298	2.287	0.47

Table 9 .Weight Variation Test

S.NO	Formulation	Formulation 1	Formulation 2	Formulation 3
1	Tablet 1	220	224	220
2	Tablet 2	224	223	222
3	Tablet 3	225	223	220

Invitro Dissolution Profile**Table 10. Percentage of Drug Release**

Time	Formulation -1	Formulation -2	Formulation-3
5 Min	46.46	55.60	62.46
10 Min	52.55	67.79	74.65
20 Min	59.41	77.69	86.83
30 Min	66.27	85.31	92.93
40 Min	72.36	92.17	99.03

Table 11. Standard Calibration Curve for Atenolol in pH 6.8 Buffer

S.No	Concentration	Absorbance (λ_{max} 224) in pH 6.8 Buffer
1.	2	0.090
2.	4	0.157
3.	6	0.229
4.	8	0.309
5.	10	0.371

Table 12. Formulation-1

S.No	Test Required	Observation/Results
1	Description	White, circular, Biconvex tablets
2	Average Weight	223 mg
3	Hardness	4 kg/cm ²
4	Dissolution 5 min 10min 20 min 30 min 40 min	46.46 52.55 59.41 66.27 72.36
5	Assay Each tablet contain Atenolol	44.5 mg

Table 13. Percentage of Drug Release

S. No	Time	Percentage of Drug Release
1	5 Min	46.46
2	10 Min	52.55
3	20 Min	59.41
4	30 Min	66.27
5	40 Min	72.36

In This experiment we have got the % of drug release only 72.36%.

Table 14. Formulation -2

S. NO	Test Required	Observation/Results
1	Description	White, circular, Biconvex tablets
2	Average Weight	224 mg
3	Hardness	4.5 kg/cm ²
4	Dissolution 5 min 10min 20 min 30 min 40 min	55.60 67.79 77.69 85.31 92.17
5	ASSAY Each tablet contain ATENOLOL	46.4mg

Table 15. Percentage of Drug Release

S. NO	TIME	Percentage of Drug Release
1	5 Min	55.60
2	10 Min	67.79
3	20 Min	77.69
4	30 Min	85.31
5	40 Min	92.17

Table 16. Formulation -3

S.NO	Test Required	Observation/Results
1	Description	White, circular, Biconvex tablets
2	Average Weight	221 mg
3	Hardness	5 kg/cm ²
4	Dissolution	
	5 min	62.46
	10min	74.65
	20 min	86.83
	30 min	92.93
	40 min	99.03
5	ASSAY Each tablet contain atenolol	49.2mg

Table- 17. Percentage of Drug Release

S. NO	Time	Percentage of Drug Release
1	5 Min	62.46
2	10 Min	74.65
3	20 Min	86.83
4	30 Min	92.93
5	40 Min	99.03

Table 18. Percentage of Drug Release

Time	Formulation -1	Formulation -2	Formulation-3
5 Min	46.46	55.60	62.46
10 Min	52.55	67.79	74.65
20 Min	59.41	77.69	86.83
30 Min	66.27	85.31	92.93
40 Min	72.26	92.17	99.03

Fig 1. Standard Curve for Atenolol

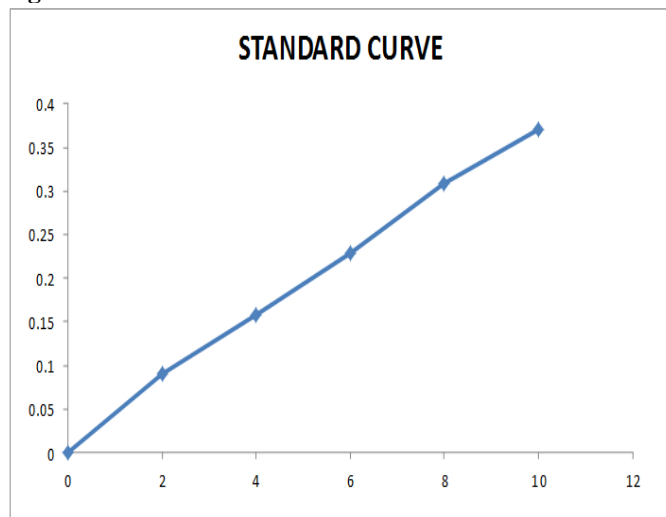


Fig 2. Invitro release of Formulation-1

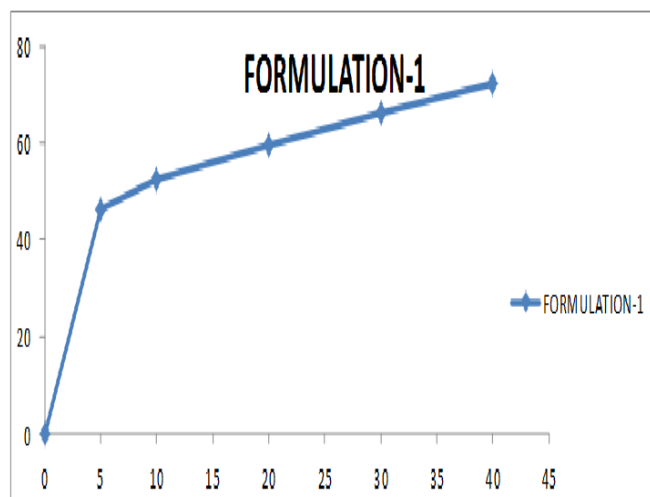
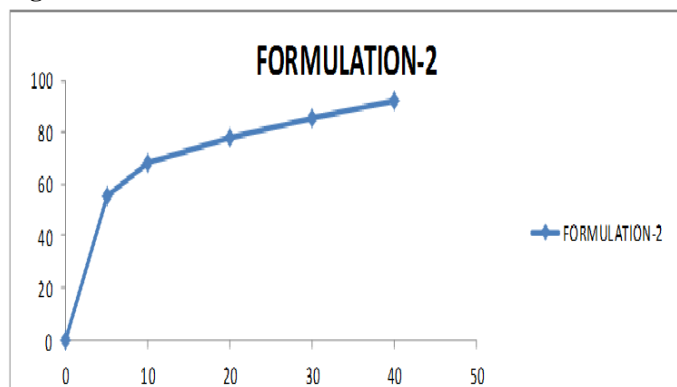
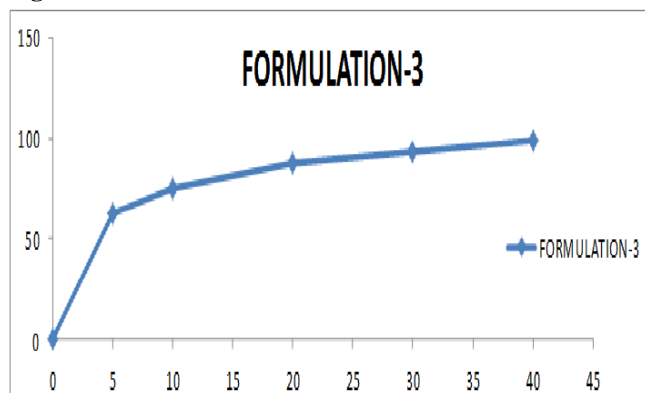
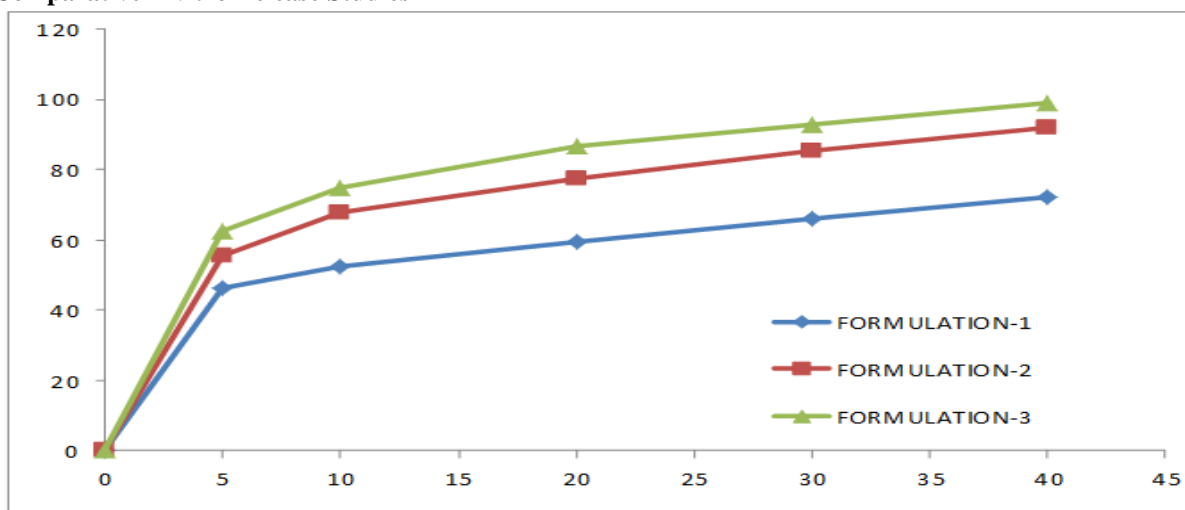


Fig 3. In Vitro Release of Formulation-2**Fig 4. In Vitro Release of Formulation-3****Fig 5. Comparative In Vitro Release Studies**

CONCLUSION

From the present study, the following conclusions are the Oral dispersible tablets of atenolol using super disintegrating agents were found to be good without chipping, capping and sticking. The drug content was uniform in all the formulations of tablets prepared. The drug-subliming and superdisintegrating agent ratio was found to influence the release of drug from the formulations. As the level of superdisintegrating agent changed, the drug release rates were found to be increased in the Formulation -III. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the absorption leading to its increased bioavailability.

Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in the plasma drug levels resulting in either manifestation of side effects or reduction in drug concentration at the receptor site. Advantages of oral dispersible tablet will surely enhance the patient compliance, low dosing, rapid onset of action and fewer side effects. From the study, it can be concluded

that using super disintegrates in tablets showed better disintegration and drug release as compared to normal tablets.

Prepared formulations were stable during 45 days storage period at controlled 40°C and 75% RH. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the absorption leading to its increased bioavailability. It was concluded that oral dispersible tablets of atenolol can be prepared successfully as it satisfies all the criteria as an oral dispersible tablet and would be alternative to the currently available conventional tablets.

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