



Original Research Article

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DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLETS & COMPARATIVE IN-VITRO DISSOLUTION STUDY OF VARIOUS MARKETED BRANDS OF ATENOLOL TABLETS

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Abstract:

Atenolol is a beta blocker commonly prescribed as a hypertension and for the treatment of angina. The current study was undertaken with the aim of analyzing quality of commercially available brands of atenolol tablets available in market. To assess the quality, locally available 100 mg atenolol tablet of four different manufacturers were selected and certain physico-chemical parameters like weight variation, hardness, friability, disintegration time and dissolution profile etc. were evaluated using in-vitro analytical methods. All the tablet brands met the requirements of IP as they showed acceptable weight variation and friability. Brands were slightly different in hardness, disintegration time and dissolution profile from each other. The hardness of all the brands was found to be in the range of 2.250 ± 1.18 to 4.21 ± 0.11 kg-ft. In water medium the disintegration time of all brands were found to be 0.57 ± 0.45 to 2.22 ± 0.23 min. Five out of seven brands showed better dissolution profile as they released more than 90% drug in 30 min. The study revealed that most of the marketed atenolol tablets met the BP standards for physico-chemical properties which are the indicators of drug quality. It can be concluded that drug products should always comply standard quality parameters that are the prerequisites for getting satisfactory clinical effects.

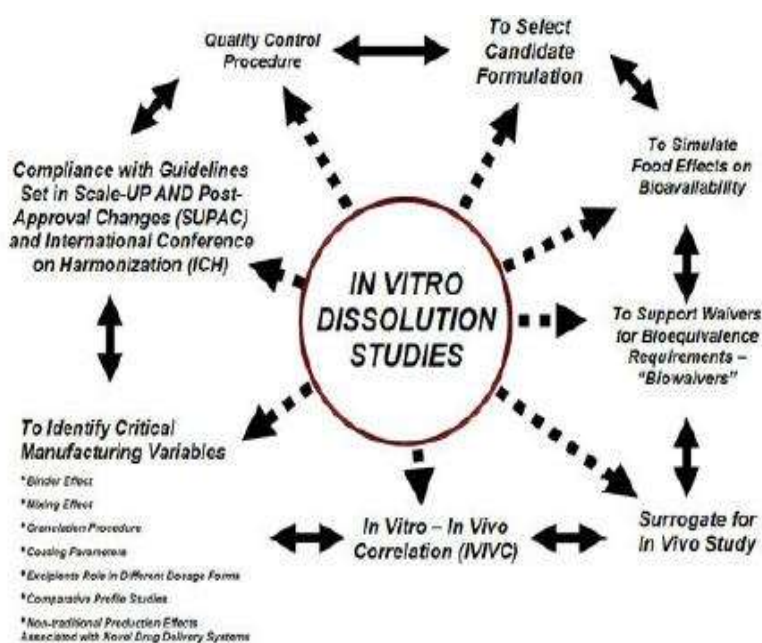
Key words: Atenolol, hypertension, disintegration, dissolution

INTRODUCTION

Dissolution rate may be defined as amount of drug substance that goes in the solution per unit time under standard conditions of liquid/solid interface, temperature and solvent composition. It can be considered as a specific type of certain heterogeneous reaction in which a mass transfer results as a net effect between escape and deposition of solute molecules at a solid surface^[1].

IMPORTANCE

1. Results from in-vitro dissolution rate experiments can be used to explain the observed differences in in-vivo availability.
2. Dissolution testing provides the means to evaluate critical parameters such as adequate bioavailability and provides information necessary to formulator in development of more efficacious and therapeutically optimal dosage forms.
3. Most sensitive and reliable predictors of in-vivo availability.
4. Dissolution analysis of pharmaceutical dosage forms has emerged as single most important test that will ensure quality of product.
5. It can ensure bioavailability of product between batches that meet dissolution criteria.
6. Ensure batch-to-batch quality equivalence both in-vitro and in-vivo, but also to screen formulations during product development to arrive at optimally effective products.
7. Physicochemical properties of model can be understood needed to mimic in-vivo environment. 8. Such models can be used to screen potential drug and their associated formulations for dissolution and absorption characteristics.
8. Serve as quality control procedures, once the form of drug and its formulation have been finalized.



Applications of in vitro dissolution studies.

THEORIES OF DISSOLUTION

1. Diffusion Layer Model (Film Theory)
2. Danckwert's Model (Penetration or Surface Renewal Theory)
3. Interfacial Barrier Model (Double Barrier Mechanism OR Limited Solvation Theory)

DIFFUSION LAYER MODEL (FILM THEORY):

It is a simplest model where dissolution of crystal, immersed in liquid takes place without involving reactive or electrical forces. Consist of two consecutive steps:

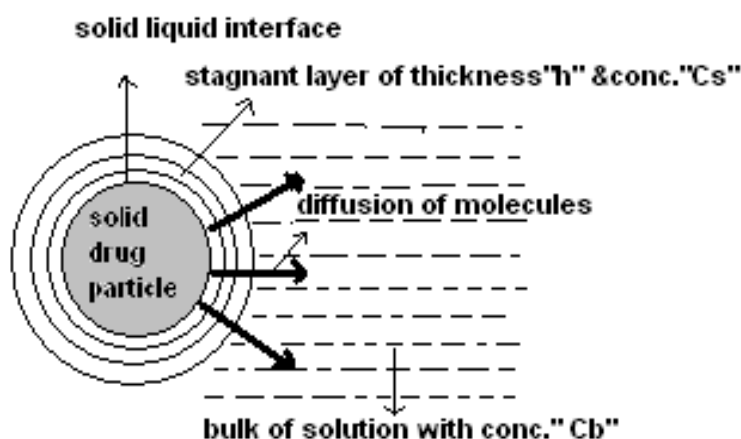


Figure 1.1: Diffusion layer model for drug dissolution

☐ Solution of the solid to form a thin film or layer at the solid/ liquid interface called as stagnant film or diffusion layer which is saturated with the drug this step is usually rapid (instantaneous).

☐ Diffusion of the soluble solute from the stagnant layer to the bulk of the solution this step is slower and is therefore the rate determining step in the drug dissolution. The model is depicted in following fig.

☐ Fick's law covers only diffusions under steady state conditions. Modifying it Noyes & Whitney established another equation

$$\frac{dC}{dt} = k (C_s - C_b) \quad \text{————— (A)}$$

$\frac{dC}{dt}$ = dissolution rate of the drug

k = dissolution rate constant (first order)

C_s = conc. of drug in stagnant layer (saturation or max. drug solubility)

C_b = conc. of the drug in bulk of the solution at time t

Brunner & Tolloczko incorporated surface area 'A' in Noyes & Whitney Equation.

$$dc/dt = k_1 A (C_s - C_b)$$

Afterwards Brunner, incorporated Fick's law of diffusion & expanded his given eq to include diffusion coefficient 'D', thickness of stagnant diffusion layer 'h' & volume of dissolution medium 'v'.

$$\frac{dC}{dt} = \frac{D A k_{w/o} (C_s - C_b)}{V h} \quad \text{--- (B)}$$

D = diffusion coefficient of the drug

A = surface area of dissolving solid

$k_{w/o}$ = water / oil partition coefficient of the drug considering the fact that dissolution body fluid are aqueous since the rapidity with which a drug dissolved depends on the $k_{w/o}$, it is also called as the intrinsic dissolution rate constant

V = volume of dissolution medium

h = thickness of stagnant layer

($C_s - C_b$) = conc. gradient for diffusion

This equation describes a first-order dissolution kinetics. It represents dissolution under non-sink conditions.

$C_s \gg C_b$ so,

$$\frac{dC}{dt} = \frac{A k_{w/o}}{V h} C_s$$

C_s & D are constant for each specific chemical substance

$$\frac{dC}{dt} = k_1 \frac{A}{V h} \quad \text{--- (} \because k_1 = k_{w/o} D C_s \text{)}$$

V & A kept constant during dissolution test

$$\frac{dC}{dt} = k \quad \text{--- (C)}$$

Dissolution rate under sink condition follows zero order dissolution rate.

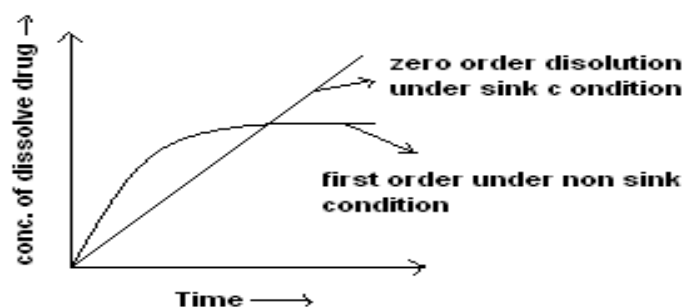


Figure 1.2: Dissolution rate curve

For obtaining IVIVC sink condition can be achieved by:

1. Bathing the dissolving solid in fresh solvent from time to time. Increasing the volume of dissolution fluid.
2. Removing the dissolved drug by partitioning it from the aqueous phase of dissolution fluid into the organic phase placed either above or below the dissolution fluid for e.g. hexane or chloroform.
3. Adding a water miscible solvent such as alcohol to the dissolution fluid.
4. By adding selected adsorbents to remove the dissolution drug.

In vitro sink condition is so maintained that C_b always less than 10% of C_s .

HIXON-CROWELL CUBE ROOT RELATIONSHIP

Major assumptions in Noyes-Whitney relationship is that the S.A.(A) term remains constant throughout dissoln process. This is true for some formulations, such as transversal patches.

However, size of drug particles from tablets, capsules and suspensions will decrease as drug dissolves^[3,4].

This decrease in size of particles changes the effective S.A.

- Thus, Hixon & Crowell modified the eq to represent rate of appearance of solute by weight in solution by multiplying both sides of volume term.

$$W_0^{1/3} - W^{1/3} = kt$$

W_0 = original mass of drug

W = mass of drug remaining to dissolve at time t

K = dissolution rate constant

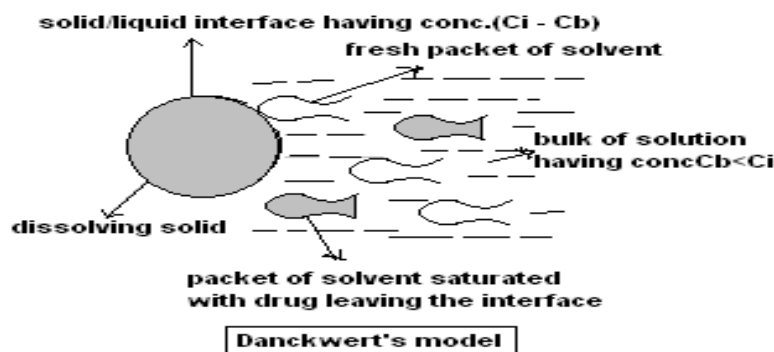
DANCKWERT'S MODEL (PENETRATION OR SURFACE RENEWAL THEORY)

- This theory assumes that solid-soln equilibrium is achieved at interface and mass transport is slow step in dissoln process.
- The model could be visualized as a very thin film having a conc. C_i which is less than saturation, as it is constantly being exposed to fresh surfaces of liquid having a conc. much less than C_i . Acc. to model, the agitated fluid consist of mass of eddies or packets that are continuously being exposed to new surfaces of solid and then carried back to bulk of liquid.
- Diffusion occurs into each of these packets during short time in which the packet is in contact with surface of solid.
- Since turbulence actually extends to surface, there is no laminar boundary layer and so no stagnant film exists. Instead, surface continually being replaced with fresh liquid

$$V \frac{dC}{dt} = \frac{dm}{dt} = A(C_s - C_b) \sqrt{rD}$$

where m = mass of solid dissolution

r = rate of surface renewal (or the interfacial tension)

**INTERFACIAL BARRIER MODEL (DOUBLE BARRIER OR LIMITED SOLVATION THEORY)**

The Diffusion layer model and the Dankwert's model were based on two assumptions:

1. The rate determining step that controls dissolution is the mass transport.
2. Solid solution equilibrium is achieved at the solid/liquid interface.

According to interfacial barrier model, an intermediate conc. can exist at the interface as a result of salvation mechanism and is a function of solubility rather than diffusion^[4].

☐ When considering the dissolution of the crystal will have a different interfacial barrier given by following equation,

$$G = k_i (C_s - C_b)$$

Where G = dissolution per unit area

k_i = effective interfacial transport constant

- ☐ In this theory, the diffusivity D may not be independent of saturation conc. C_s .
- ☐ The interfacial barrier model can be extended to both Diffusion layer model and the Dankwert's model.

1.3 OFFICIAL DOSSOLUTION MONOGRAPHS

- According to I.P. & E.P. for solid dosage forms (tablets and capsules) dissolution apparatus used are:
 1. Apparatus I – PADDLE APPARATUS
 2. Apparatus II – BASKET APPARATUS
- According to B.P. apparatus used are:
 1. Apparatus I – BASKET APPARATUS
 2. Apparatus II – PADDLE APPARATUS
 3. Apparatus III – FLOW THROUGH CELL APPARATUS

Table No. 1.1: According to USP 30 dissolution apparatus used are

USP App	DESCRIPTION	ROT. SPEED	DOSAGE FORM
I	BASKET	50-120 rpm	IR, DR, ER
II	PADDLE	25-50 rpm	IR, DR, ER
III	RECIPROCATING CYLINDER	6-35 dpm	IR, ER
IV	FLOW-THRU CELL	N/A	ER, POORLY SOLUBLE API
V	PADDLE OVER DISK	25-50 rpm	TRANSDERMAL
VI	CYLINDER	N/A	TRANSDERMAL
VII	RECIPROCATING HOLDER	30 rpm	ER

CONDITIONS (for all in general)

1. Temp. - $37 \pm 0.5^\circ\text{C}$
2. H - ± 0.05 unit in specified monograph
3. Capacity – 1000 ml
4. Distance between inside bottom of vessel and paddle/basket is maintained at 25 ± 2 mm.

5. For enteric coated dosage form it is first dissolved in 0.1 N HCl & then in buffer of pH 6.8 to measure drug release. (Limit – NMT 10% of drug should dissolve in the acid after 2 hr. and about 75% of it should dissolve in the buffer after 45 min.)

1) Apparatus I- Basket Apparatus

suppository basket

Unless otherwise specified in the individual monograph, use 40-mesh cloth.

- Useful for: Capsules, Beads, Delayed release / Enteric Coated dosage forms, Floating dosage forms
- Standard volume: 900/1000 ml, 1, 2, 4 liter vessels

- **Advantages:**

- 1) More than 200 monographs.
- 2) Full pH change during the test
- 3) Can be easily automated which is important for routine investigation.

- **Disadvantages:**

- 1) Disintegration-dissolution interaction
- 2) Hydrodynamic Dead zone under the basket.
- 3) Degassing is particularly important
- 4) Limited volume-----sink condition for poorly soluble drugs...

2) Apparatus-II - Paddle Apparatus.

METHOD OF FIRST CHOICE

- The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started.
- A small, loose piece of non-reactive material such as not more than a few turns of wire helix may be attached to dosage units that would otherwise float.
- Other validated sinker devices may be used.

Standard volume: 900/1000 ml **Advantages:**

1. Easy to use
2. Robust
3. Can be easily adapted to apparatus
4. Long experience
5. pH change possible
6. Can be easily automated which is important for routine investigations

Disadvantages:

1. pH/media change is often difficult
2. Hydrodynamics are complex, they vary with site of the dosage form in the vessel (sticking, floating) and therefore may significantly affect drug dissolution
3. Coning.

Limitations of USP Apparatus 1 and 2:

1. USP2 (and USP1) Apparatus has plenty of HYDRODYNAMICS. Complicated 3-dimensional flow generated by the paddle.
2. Significant impact of convective transport –Conditions used (50 – 100 rpm) highly exaggerates flow in the GI.
3. If Static-tank model used – sink conditions artificially generated to simulate sink in GI.
4. Use of solvents and surfactants non-native to GI.

3) Apparatus III – Reciprocating cylinder

- The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; stainless steel fittings (type 316 or equivalent) and screens that are made of suitable nonsorbing and nonreactive material (polypropylene) and that are designed to fit the tops and bottoms of the reciprocating cylinders; and a motor and drive assembly to reciprocate the cylinders vertically inside the vessels.
- The vessels are partially immersed in a suitable water bath of any convenient size that permits holding the temperature at $37^{\circ} \pm 0.5$ during the test.
- The dosage unit is placed in reciprocating cylinder & the cylinder is allowed to move in upward and downward direction constantly. Release of drug into solvent within the cylinder measured.

Useful for: Tablets, Beads, controlled release formulations Standard volume: 200-250 ml/station

Advantages:

- 1) Easy to change the pH-profiles
- 2) Hydrodynamics can be directly influenced by varying the dip rate.

Disadvantages:

- 1) small volume (max. 250 ml)
- 2) Little experience
- 3) Limited data

4) Apparatus V – Paddle over disk

- Use the paddle and vessel assembly from Apparatus 2 with the addition of a

stainless steel disk assembly designed for holding the transdermal system at the bottom of the vessel.

- Other appropriate devices may be used, provided they do not sorb, react with, or interfere with the specimen being tested
- The disk assembly for holding the transdermal system is designed to minimize any “dead” volume between the disk assembly and the bottom of the vessel.
- The disk assembly holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade
- The vessel may be covered during the test to minimize evaporation.

Useful for: Transdermal patches Standard volume: 900 ml

Disadvantages: Disk assembly restricts the patch size.

US 724 APPARATUS

Transdermal Patch Retainer (Hanson Style)

- Borosilicate Glass
- 17 mesh is standard (others available)
- Accommodates patches of up to 90mm

5) Apparatus V – cylinder

- Use the vessel assembly from Apparatus 1 except to replace the basket and shaft with a stainless steel cylinder stirring element and to maintain the temperature at 32 ± 0.5 during the test.
- The dosage unit is placed on the cylinder at the beginning of each test, to the exterior of the cylinder such that the long axis of the system fits around the circumference of the cylinder & removes trapped air bubbles.
- Place the cylinder in the apparatus, and immediately rotate at the rate specified in the individual monograph.

6) Apparatus VI – reciprocating holder

- The assembly consists of a set of volumetrically calibrated solution containers made of glass or other suitable inert material, a motor and drive assembly to reciprocate the system vertically and a set of suitable sample holders.
- The solution containers are partially immersed in a suitable water bath of any convenient size that permits maintaining the temperature, inside the containers at 32 ± 0.5
- For Coated tablet drug delivery system attach each system to be tested to a suitable sample holder (e.g., by gluing system edge with 2-cyano acrylate glue onto the end

of a plastic rod or by placing the system into a small nylon net bag at the end of a plastic rod or within a metal coil attached to a metal rod).

- For Transdermal drug delivery system attach the system to a suitable sized sample holder with a suitable O-ring such that the back of the system is adjacent to and centered on the bottom of the disk-shaped sample holder or centered around the circumference of the cylindrical-shaped sample holder. Trim the excess substrate with a sharp blade
- For Other drug delivery systems attach each system to be tested to a suitable holder as described in the individual monograph.
- Suspend each sample holder from a vertically reciprocating shaker such that each system is continuously immersed in an accurately measured volume of Dissolution Medium within a calibrated container.
- Reciprocate at a frequency of about 30 cycles per minute with amplitude of about 2 cm, or as specified in the individual monograph, for the specified time in the medium specified for each time point.
- Perform the analysis as directed in the individual monograph.

• **DISSOLUTION TESTING**

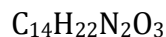
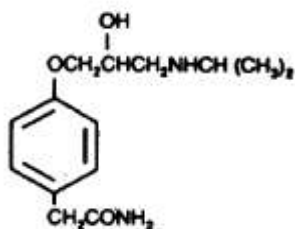
The definition of dissolution is deceptively simple. It is the process in which a solid substance goes into solution. For dosage forms containing an active solid ingredient, the rate of dissolution may be critical to absorption. Obviously, in most instances, dissolution of the active solid material is affected by a variety of factors such as the media in which the drug is dissolving, the temperature of the media, and the affinity for the solid particles to dissolve in the media. There are numerous other factors, such as excipients, coatings, and pH, which have an effect on the rate of dissolution. While the most rapid absorption is from a solution, most dosage forms are solids, either tablets or capsules. One must also consider dissolution from suspensions and suppositories. Several chapters in this text cover various dosage forms as the theme for the discussion on dissolution. The theory is the same regardless of the dosage form design, but obviously, the rate of dissolution and the limitations are different for each individual dosage form. Any process of drug release and subsequent absorption into the blood stream must consider dissolution of the solid. Wetting of the material, be it hydrophilic or *hydrophobic*, is the first critical step and precedes deaggregation. This process may also be considered disintegration. The drug then dissolves into the dissolution media, be it *in vitro* or *in vivo*. As a rule, suspensions dissolve faster than capsules since some deaggregation has already occurred. Tablets usually have the slowest dissolution rate, either by design to allow a sustained, controlled release or by the nature of the wetting process. The earliest obvious reference to dissolution (1897) was

by Noyes and Whitney, where they stated that the dissolution rate is governed by the rate of diffusion of a saturated thin layer forming instantly around the dissolving material.

The work of Noyes and Whitney concentrated on physico-chemical aspects and not bioavailability. In 1951, Edwards showed that aspirin tablets would have poor analgesic activity due to poor dissolution. Theoretical models of dissolution continued to be developed in the early 1900s by Brunner, when he adapted Fick's Law of diffusion. In the 1930s the cube root law, which describes a linear relationship between dissolution rate and cube root of time, came into favor. By the 1950s, dissolution was further studied and began to be recognized as a factor in bioequivalence, although it was not until the 1960s

TENORMIN®

Atenolol a synthetic, beta1-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4 -[2'-hydroxy-3'-[(1- methylethyl) amino] propoxy]-. The molecular and structural formulas are:



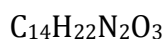
Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ mL at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/mL at 25°C) and less soluble in chloroform (3 mg/mL at 25°C).

TENORMIN (atenolol tablets) is available as 25, 50 and 100 mg tablets for oral administration.

MATERIALS AND METHODOLOGY

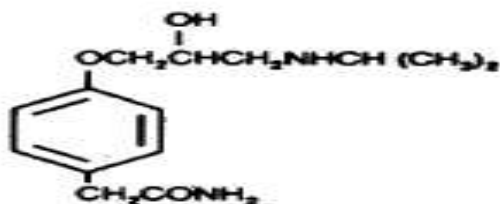
Drug Profile: Atenolol

Chemical formula:-



IUPAC name :-

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



Structure

Protein binding :-	Plasma protein binding is 6-16%
Metabolism :-	Hepatic (minimal)
Half life :-	6-7 hours

Medicine use

Atenolol belongs to a class of drugs known as beta blocker. It works by blocking the action of certain natural chemicals in your body, such, epinephrine on the heart rate, blood pressure, and strain on the heart.

Atenolol is used with or without other medications to treat high blood pressure. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. This medication is also used to treat chest pain (angina) and to improve survival after a heart attack.

Indication

- **Hypertension**
- TENORMIN (atenolol tablets) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.
- **Angina Pectoris Due to Coronary Atherosclerosis**
- TENORMIN (atenolol tablets) is indicated for the long-term management of patients with angina pectoris.
- **Acute Myocardial Infarction**

TENORMIN (atenolol tablets) is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows

Potential Adverse Effects

In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol tablets).

Hematologic: Agranulocytosis.

Allergic:Fever , combined with aching and sore throat , laryngospasm, and respiratory distress.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash.

Overdosage

Overdosage with TENORMIN (atenolol tablets) has been reported with patients surviving acute doses as high as 5 g. One death was reported in a man who may have taken as much as 10 g acutely.

The predominant symptoms reported following TENORMIN (atenolol tablets) overdose are lethargy , disorder of respiratory drive, wheezing, sinus pause and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic blocking agent and which might also be expected in TENORMIN (atenolol tablets) overdose are congestive heart failure, hypotension, bronchospasm and/or hypoglycemia.

Treatment of overdose should be directed to the removal of any unabsorbed drug by induced emesis , gastric lavage, or administration of activated charcoal. TENORMIN (atenolol tablets) can be removed from the general circulation by hemodialysis.. Other treatment modalities should be employed at the physician's discretion and may include:

Bradycardia: Atropine intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CARDIAC FAILURE: Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

HYPOTENSION: Vasopressors such as dopamine or norepinephrine (levarterenol). Monitor blood pressure continuously.

BRONCHOSPASM: A beta2 stimulant such as isoproterenol or terbutaline and/or aminophylline.

HYPOGLYCEMIA: Intravenous glucose.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support.

MANUFACTURES

- Able laboratories inc
- Apothecon sub bristol myers squibb co
- Aurobindo pharma ltd

- Caraco pharmaceutical laboratories ltd
- Dava pharmaceuticals inc
- Genpharm pharmaceuticals inc
- Ipca laboratories ltd
- Ipr pharmaceuticals inc
- Mutual pharmaceutical co inc
- Mylan pharmaceuticals inc
- Northstar healthcare holdings ltd
- Nostrum laboratories inc
- Pliva inc
- Sandoz inc
- Scs pharmaceuticals
- Teva pharmaceuticals usa inc
- Teva pharmaceuticals usa
- Unique pharmaceutical laboratories
- Watson laboratories inc
- Zydus pharmaceuticals usa incAstrazeneca lp

PHARMACOKINETICS

Absorption: About 50% to 60% of an atenolol dose is absorbed.

Distribution: Distributed into most tissues and fluids except the brain and CSF; about 5% to 15% is protein-bound.

Metabolism: Metabolized minimally.

Excretion: About 40% to 50% of a given dose is excreted unchanged in urine; remainder is excreted as unchanged drug and metabolites in feces. In patients with normal renal function, plasma half-life is 6 to 7 hours; half-life increases as renal function decreases

Table no. Various famous manufacturer of Atenolo

s.no	Brand name	Manufactures	Dose	Mfg. date	Epiry date
1	Aloten	Core healthcareLtd	100mg	5-03-14	8-7-16
2	Anol	Psycoremedks	100mg	6-9-14	6-9-18
3	Allnor	VHPsciencesLimited	100mg	9-2-13	9-2-16

5.2METHOD USE

(a) Identification by IR

- ❖ In this the drug has been identified through FT-IR spectra of the pure drug was recorded using **Perkin-Elmer Model 883 FTIR-spectrophotometer** between the ranges of 400 to 4000 cm^{-1} by KBr press pellet technique.

(b) Hardness testing

Hardness testing was conducted for all the formulations using instrument – Monssnto Tester

2.25kg/cm

(c) Friability test

The friability test of the all formulations was carried out by appropriate procedure using Friability apparatus.

0.666%

(d) Uniformlity in weight

The weight variation was determined by random selection of 20 tablets from each batch. According to USP the variation should be not more than 7.5% for tablets weighing less than 250 mg. Weight variation observed was because of the variation in flow property of different blends. But the results found to pass the limits.

100mg

(e) Determination of drug content

Percent drug content uniformity was determined by appropriate procedure Using Elico UV Spectrophotometer.

99.7

(f) Disintegration time of Atenolol tablet

Instrument- Disintegration apparatus
24sec.

(g) Dissolution of atenolol tablet by IP

Drug dissolution study was performed using USP apparatus I containing suitable media for dissolution. The dissolution was conducted for 8 hour and in the experiment. The basic data of *in vitro* release of Atenolol for all the batches was analyzed statically.

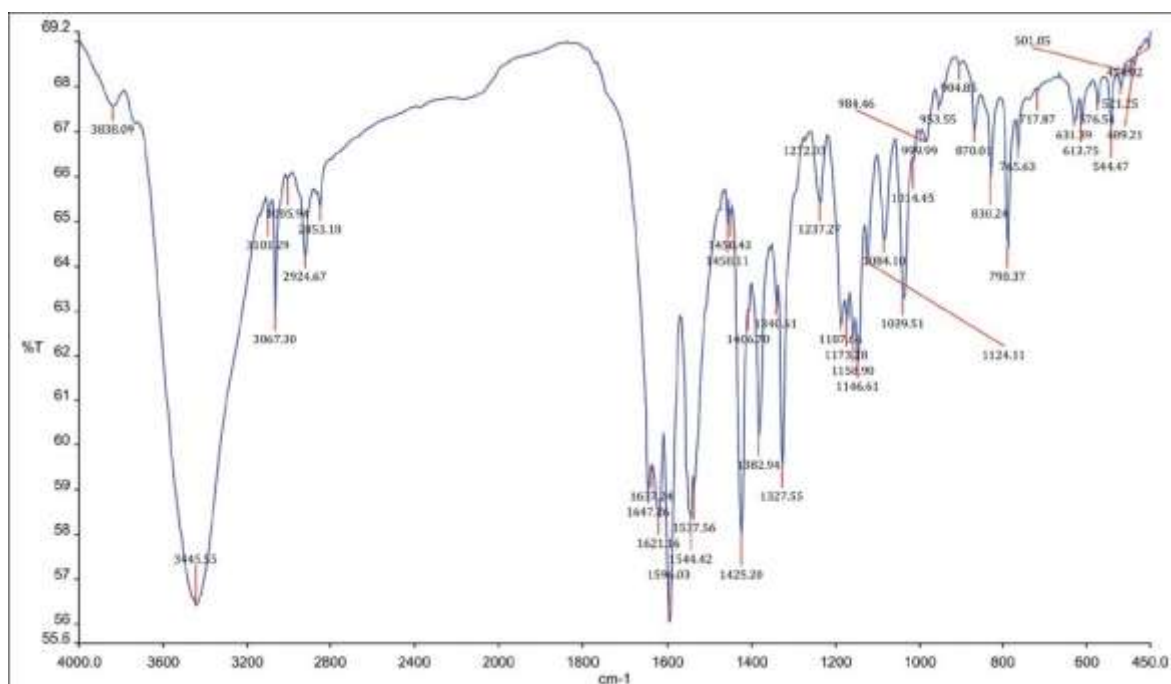


Figure 5.1: FT-IR Spectra of Atenolol

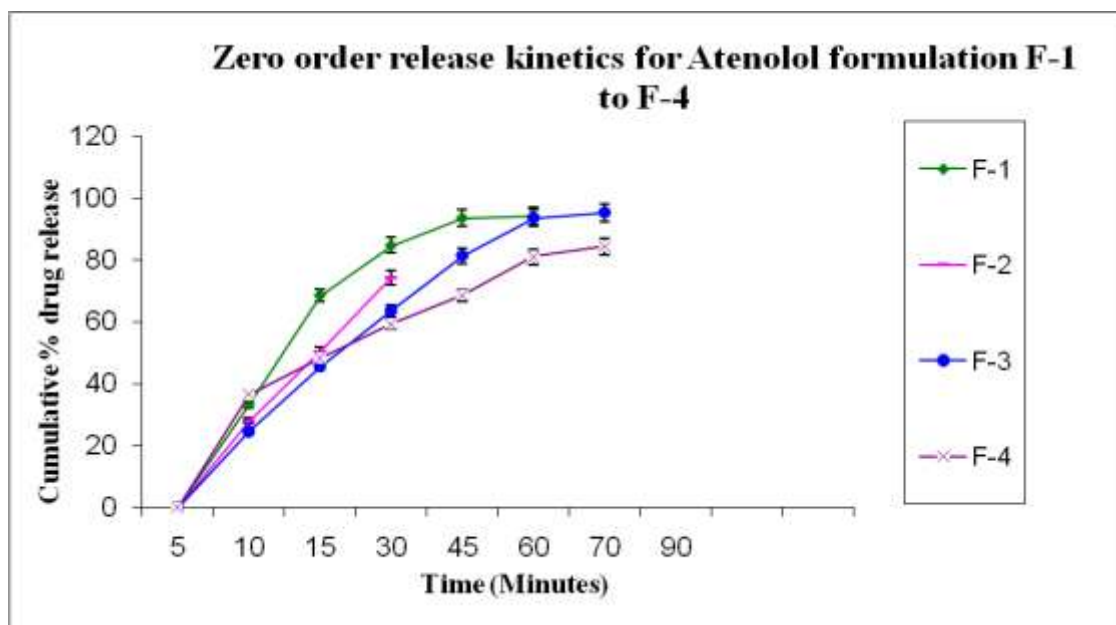


Figure 5.2: Dissolution Profile at pH 6.8 Buffer solution

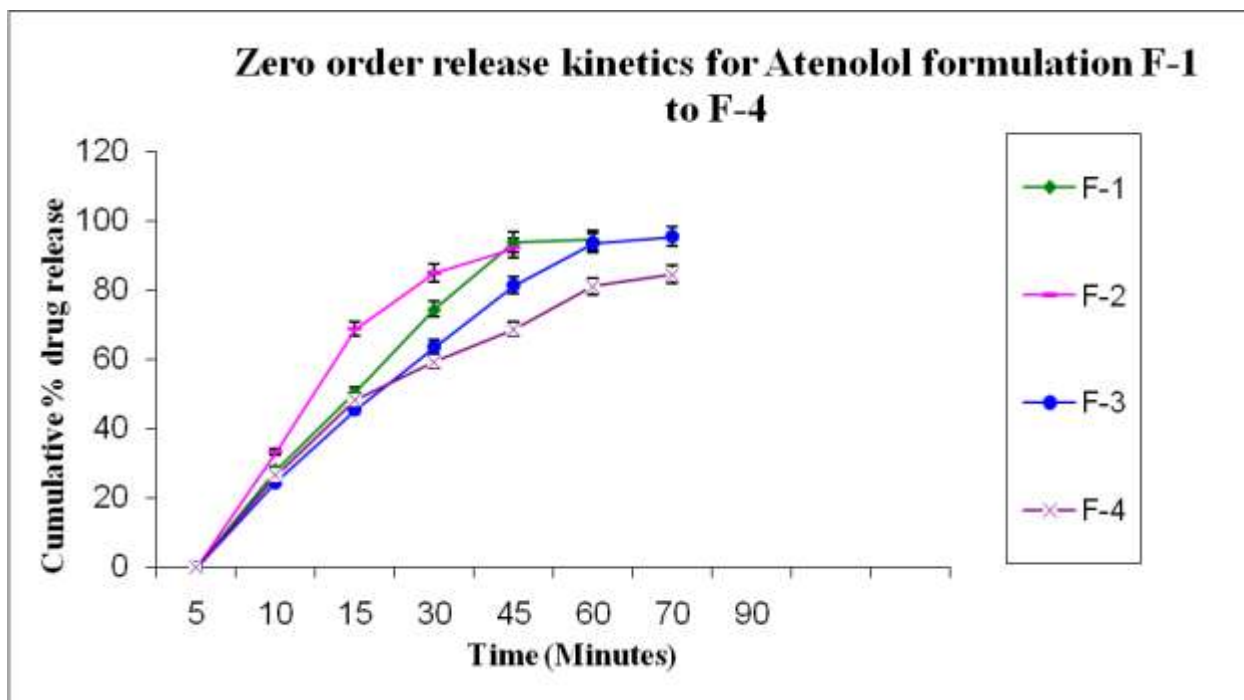


Figure 5.3: Dissolution Profile at pH 4.5 Buffer solution

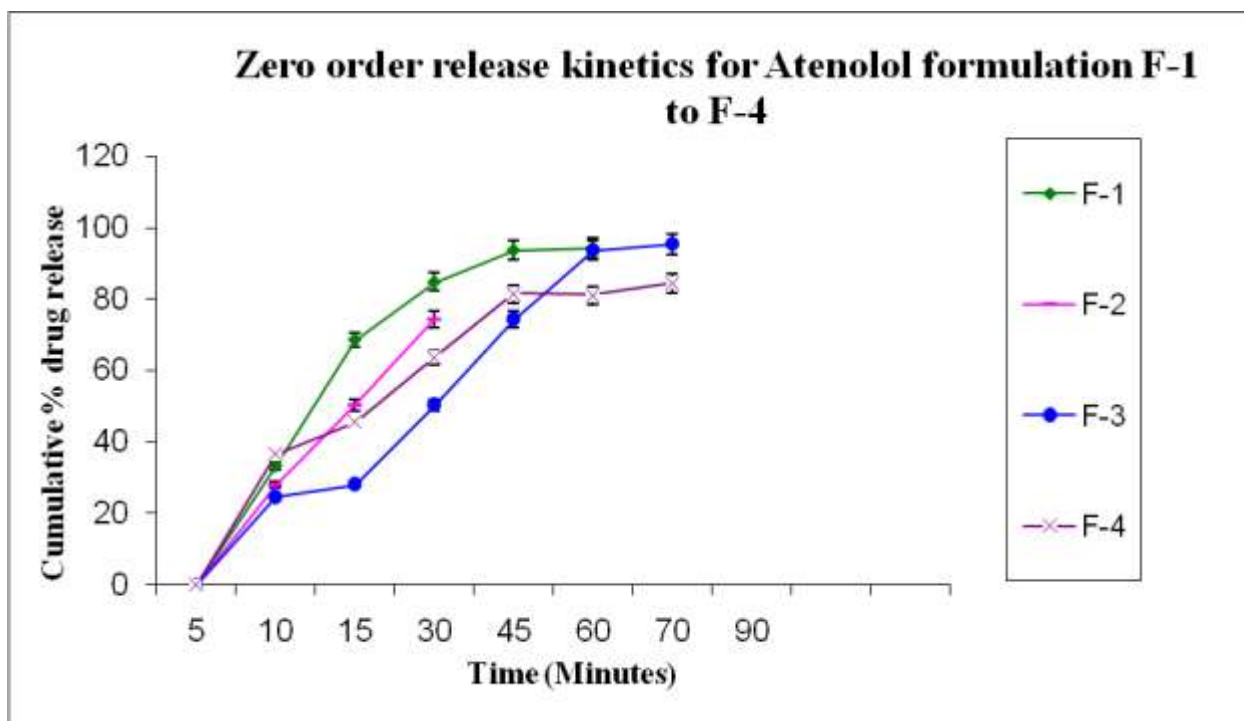


Figure 5.Dissolution Profile in Distill water

Table No. 5.1: Percentage release profile of various formulations

Mediu	Time	Aten-1 %	Aten-2 %	Aten-3 %	Aten-4 %
pH 1.2	5	85.939 ± 1.06	79.59	67.09 ± 8.00	84.202 ± 1.09
	10	90.895 ± 2.32	81.00	75.04 ± 5.22	85.597 ± 1.74
	15	90.8354 ± 2.31	82.89	77.202 ± 4.26	86.0286 ± 1.17
	30	91.0808 ± 2.25	84.12	80.166 ± 3.27	85.9878 ± 1.54
	45	91.2436 ± 2.05	85.06	83.68 ± 2.36	87.0905 ± 1.21
	60	91.65 ± 1.88	86.20	85.418 ± 2.05	87.7684 ± 1.06
	70	91.8982 ± 1.68	88.44	88.752 ± 1.86	88.1112 ± 1.13
	90	92.108 ± 1.58	90.86	89.76 ± 1.45	88.2776 ± 1.25
F2		Innovator	5	47.27	
F1		Innovator	7	11	4
pH 4.5	5	61.99 ± 12.55	84.21	79.272 ± 2.79	72.796 ± 1.01
	10	79.696 ± 2.66	87.52	84.078 ± 2.80	73.55 ± 1.26
	15	82.382 ± 1.49	87.96	86.288 ± 1.62	75.422 ± 1.29
	30	85.582 ± 2.30	88.38	88.62 ± 1.37	77.752 ± 1.90
	45	87.01 ± 2.12	89.47	89.862 ± 1.02	79.002 ± 1.85
	60	88.502 ± 0.92	90.47	91.788 ± 1.38	81.304 ± 1.86
	70	91.436 ± 2.26	91.22	92.646 ± 1.46	81.662 ± 2.11
	90	92.34 ± 1.45	92.46	93.154 ± 1.73	82.28 ± 2.42
F2		Innovator			53.4
F1		Innovator	6	5	10
pH 6.8	5	58.054 ± 3.80	63.55	48.744 ± 7.39	73.482 ± 3.66
	10	62.5092 ± 2.08	65.87	81.144 ± 9.12	86.89 ± 4.00
	15	64.6526 ± 2.36	67.02	87.102 ± 5.33	90 ± 3.58
	30	68.0234 ± 4.06	70.46	91.234 ± 1.41	91.682 ± 2.94
	45	100.22 ± 5.75	79.91	92.236 ± 1.39	96.35 ± 2.13
	60	103.92 ± 0.82	84.50	92.754 ± 1.25	97.25 ± 1.72
	70	104.15 ± 0.89	89.42	93.286 ± 1.39	99.32 ± 1.50
	90	104.34 ± 0.87	90.29	93.65 ± 1.67	99.45 ± 1.45
F2		Innovator	4		
F1		innovator	1	17	16

Table no. 5.2: Various parameters of different tablet formulation of Atenolol

Brands	Uniformity of M	Thickness M	Diameter m	Hardness kg/cm	Disintegration min	Content Assay %
Aten-	434.3 ± 1.02	5.8 ± 0.03	10.8 ± 0.03	7.5 ± 1.0	4.59 ± 0.56	99.65 ± 2.1
Aten-	339 ± 1.23	5.3 ± 0.011	10 ± 0.01	3.1 ± 1.03	2.5 ± 1.01	103.1 ± 0.99
Aten-	415 ± 1.48	4.6 ± 0.05	10.6 ± 0.04	6.5 ± 0.65	5.53 ± 1.24	101.31 ± 1.75
Aten-	394.5 ± 0.89	5.5 ± 0.02	9.8 ± 0.03	7.5 ± 0.87	6.0 ± 0.98	100.56 ± 1.32

Physicochemical properties of 4 different brands of Atenolol 100 mg tablets.

The primary goal of dissolution testing is to use as a qualitative tool to provide measurement of the bioavailability of a drug. Generic drugs are copies of innovator drug products. So they are promoted for use in practice because they are usually less expensive than the innovator products, thereby improving access to life-saving drugs, especially in developing countries.

In case of present study four different brands of Atenolol tablets immediate release has been studied for their bioequivalence studies. First the dissolution was run in distilled water because under the normal circumstances, the dissolution testing should be conducted at 37 C in distilled water then noted into different dissolution mediums (pH 1.2, 4.5, 6.8) to cover the whole GIT environment of different pH. The FDA recommended dissolution medium for atenolol is 0.1N HCl, Because it is not freely soluble in water but a good releasing pattern of atenolol in water also.

Preparation of fast dissolving tablets

Fast dissolving tablets of atenolol were prepared by direct compression method. All the ingredients (except granular directly compressible excipients) were passed through # 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 150mg using 8.5mm concave flat punches on 12-station Karnavati Mini press-II tablet machine.

Analysis of atenolol was carried out UV –Vis Spectrophotometer, Electronic balance, 10 ml of fresh medium already equilibrated to 37 C was replaced into dissolution medium after each sampling in order to maintain sink condition.

Six tablets per brand were used for the study.

The filtered samples were analyzed by the Ultra –violet spectrophotometric method (UV) at 254 nm wavelength.

The concentration and the percentage release in each time interval was determination.

Standard preparation

Weigh accurately and dissolve 50 mg atenolol in 100 ml of medium (pH=1.2,4.5 and 6.8 separately).Pipette out 2 ml from stock solution and dilute up to 100 ml with respective medium to obtain final concentration of 10 µg/ml.

EXPERIMENTATION

1. **Study design:** The study of in-vitro quality analysis of available atenolol tablet brands in Bangladesh was studied by the evaluation of weight variation, hardness, friability, and disintegration time and dissolution profile. The study was conducted using various standard test methods related to estimate the quality of tablets.
2. **Sample collection and identification:** four brands of atenolol tablets were purchased from various medicine shops. They were randomly marked from Aten1

to Aten2. The samples were properly checked for their manufacturing license numbers, batch numbers and date of manufacture and expiry dates. The entire tablet brands were containing labeled shelf life of three years from the date of manufacture and before two years of labeled expiry date it was taken for the evaluation. The labeled active ingredient was 0100mg of atenolol and all were packaged in strip or in blister. Reference standard of atenolol (99.87%) was collected from Incepta Pharmaceuticals Limited.

3. **Analytical methods:** In this study, following quality control tests were performed for the evaluation of all the atenolol tablet brands.
4. **Weight variation test:** The acceptable range of weight variation for tablets should not exceed 10% or more having average weight of 80 mg or less (British Pharmacopoeia, 2005). For each brand, ten tablets were randomly selected and weighed individually using an analytical balance. The average weights were determined using the following formula.

$$\text{Weight variation (\%)} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

1. **Hardness test:** Hardness of randomly selected ten tablets was determined for all the brands using 'Monsanto' type hardness tester. Finally the mean crushing strengths were determined.
2. **Friability test:** In the study, it was determined by using Electrolab EF-2 Friabilator (USP) and the values of friability were expressed in percentage (%). From each selected brands ten tablets were individually weighed and transferred into friabilator which was operated at 25 rpm and continued up to 4 minutes (100 revolutions). Then the tablets weights were measured again and the percent (%) of friability was calculated using following formula.

$$\% \text{ of Friability} = \frac{\text{Weight before test} - \text{Weight after test}}{\text{Weight before test}} \times 100$$

1. **Disintegration time test:** The instrument used for this test was Disintegration tester -USP; (Electro lab EF 2L; with disc in distilled water medium. To test for disintegration time three tablets of each brand were placed in each tube and the basket rack is positioned in a 1 liter beaker of water at $37 \pm 0.50^\circ\text{C}$. The time required to break of each tablet into minute particles and pass out through the mesh was recorded. Then the mean disintegration time was calculated for every brands.
2. **Dissolution test:** For all brands of studied tablets, dissolution test was carried out

using Dissolution Tester – USP Apparatus-1 (Basket type). Individually 3 tablets of each brand were placed in 3 different beakers in dissolution medium containing 900 ml of 0.1NHCl buffer (pH 7.4). The process was done at a speed of 100 rpm by maintaining temperature at $37 \pm 1^\circ\text{C}$ in each test. At regular time intervals of 10 minutes samples were withdrawn as 5 ml which was predetermined and same method was continued up to 30 minutes by replacing equal quantity of fresh dissolution medium. The filtered samples were diluted suitably and analyzed by using UV Spectrophotometer (UV Spectrophotometer: UV-1800-240V) at 260 nm for atenolol and percentage (%) of drug release was calculated by measuring the absorbance.

1. Preparation of the stock solution

10 mg of the atenolol standard powder was weighted precisely and transferred to a 100 mL volumetric flask. A solvent mixture of methanol : water (9:1 V/V) was added to the flask and made the volume exactly to 100 mL. Therefore, a 0.1mg/mL or 100 $\mu\text{g/mL}$ of the active ingredient was made. 1 mL of this solution was taken with microsyringe and transferred into a 100 mL volumetric flask and made the volume exactly to 100 mL with the above mentioned solvent mixture. Therefore, the final concentration of 1 $\mu\text{g/mL}$ was obtained and used for the preparation of various concentration solutions necessary for plotting the calibration curve.

2. Preparation of the standard solutions

For plotting the calibration curve, concentrations of 0.2, 0.4, 0.6, 0.8 and 1 $\mu\text{g/mL}$ were needed. From the above mentioned stock solution, 2, 4, 6, 8 and 10 mL were taken and each one was placed in an individual 10 mL volumetric flask, then made the volumes exactly to 10 mL by adding the solvent mixture of methanol:water (9:1 V/V) to each of the flasks. Therefore, solutions with concentrations of 0.2, 0.4, 0.6, 0.8 and 1 $\mu\text{g/mL}$ were obtained which would be used for plotting the calibration curve and injection into the HPLC instrument.

3. Determination of λ_{max} of atenolol standard powder

The UV spectrum of atenolol standard powder in methanol:water (9:1 V/V) was taken. The λ_{max} was determined as 254 nm.

4. Plotting the standard calibration curve

For plotting the standard curve, five times and each time 20 μL from each of the standard solutions prepared in (6) was injected into the HPLC instrument from the lowest to the

highest concentrations. The chromatograms and the relevant data such as peak area, peak height, retention time, etc. were recorded and saved as Peak – Report tables in the software program (Table 5). For the assurance of the accuracy and precision of the measurement method, the whole procedures for plotting the calibration curve were repeated three times within a day and twice between two consecutive days. Then, the calibration curve was plotted (Figure 2). On the basis of the calibration curve (Figure 2), the unknown samples were injected into the HPLC instrument and the chromatograms were recorded, then the amounts of the unknown samples were determined.

Table no. 5.4 HPLC data obtained from the injection of samples prepared from atenolol standard powder with given concentrations

Concentration µg/mL	Retention time (t_R) min.	Height, mv	Area, mv*min
0.2	1.633	11.77± 0.18	0.98±0.050
0.4	1.633	23.57± 0.19	1.97±0.032
0.6	1.633	34 ± 0.45	2.85±0.030
0.8	1.633	46.01± 0.16	3.72±0.045
1.0	1.633	56.7 ± 0.29	4.67±0.030

SOLUBILITY STUDY

Soluble in ethanol, sparingly soluble in water, slightly soluble in dichloro methane, practically in soluble in ether.

Test of physic-chemical parameter of atenolol of different market brands

- Physical appearance :- White powder
- Identification by IR:- 300nm
- Hardness testing:- 2.25kg/cm
- Friability test:- 0.666%
- Uniformity in weight:- 100mg

6. RESULT AND DISCUSSION

Three atenolol brands having label strength of 100mg were purchased from a local market of India. All tests were performed within product expiry dates during study period. The compendia standards are weight variation of tablet, drug content, disintegration time, and

dissolution, whereas hardness and friability are non compendia standards. The friability test is now included in the United State Pharmacopeia (USP, 1995). The uniformity of weight determination for three brands of atenolol tablets gave values that are within limits. There was different mean weight of all brands because of different excipient used in the different brands. For consumer requirement and also for packaging of tablets thickness and diameter parameters are also necessary for uniformity of tablets.

For assurance of uniform potency of tablet, weight variation is not sufficient. The potency of tablets is expressed in terms of grams, milligrams, or micrograms of drug per tablet and is given as the label strength of the product.

The formulated fast dissolving tablets of atenolol may be useful for anti-hypertensive, which can improve the patient compliance and hence can minimize the pre-mature therapeutic droplates Leading to better therapeutic efficiency.

Friability percentages of the tablets were calculated using the following formula:
 $\% \text{Friability} = [(W_1 - W_2) / W_1] \times 100$

Where W_1 is the initial weight of the 20 tablets and W_2 is the final weight of the 20 tablets. The maximum acceptable friability range should be within 0.5-1%, on condition that it does not affect the apparent shape of the tablet.⁶

For the determination of % release of the tablets, the following calculations were done:

- $$\begin{aligned} & \text{Active ingredient of the tablet used (mg)} \\ 5. \quad \text{Concentration } (\mu\text{g/mL}) &= \frac{\text{Active ingredient of the tablet used (mg)}}{\text{Total volume of the dissolution medium (mL)}} \\ 6. \quad \text{This concentration was considered as 100\% drug release.} \\ & \text{The Amount (from the HPLC Peak Report data)} \\ 7. \quad \% \text{ Release} &= \frac{\text{The Amount (from the HPLC Peak Report data)}}{\text{Concentration } (\mu\text{g/mL})} \times 100 \end{aligned}$$

Determination of the degree of hardness, friability percentage and disintegration time of the tablets were made by using the corresponding instruments. Weight variations were measured by analytical balance. The various results obtained in this research have shown that:

- i) Atenolol tablets manufactured by core health limited had the highest whereas those manufactured by Unichem laboratory had the lowest degree of hardness,
- ii) Friability percentages of all four types of the tablets were within the internationally well-known pharmacopoeia acceptable range.
- iii) Disintegration times of all four types of the tablets were within the expected range.

CONCLUSION

The post-market monitoring is very crucial for effective clinical outcome. The dissolution study has emphasized that pharmaceutical equivalence indicated that the products have same drug molecules with approximately same pattern of dissolution release profile. On the basis of this in-vitro profile we can evaluate the therapeutic level of the drug in vivo. By making fine tuning in the bioequivalence study we can reduce the time, cost and unnecessary exposure of healthy subjects to medicines and finally to market the quality generic drug products.

From the study it was identified that weight variation and friability test of atenolol tablet brands met the specification of B.P. Variations were obtained in hardness, disintegration time and dissolution profile. On the other hand almost all atenolol tablet brands showed better disintegration time but some were slightly different in their dissolution profile which is related to its absorption property. Manufacturers should always maintain highest standard for all quality parameters of any medicine because better quality ensures better medicine to get desired therapeutic effect.

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