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Comparative in Vitro Equivalency Test Assessment of Some Commercially Available Nebivolol Hydrochloride Tablets

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ABSTRACT
Nebivolol hydrochloride is a poorly water soluble drug falls under class II biopharmaceutical classification system, which is β1 receptor antagonist that leads to vasodilatation, decreased peripheral vascular resistance, lowers blood pressure and heart rate. The selection of correct brand of drug by health professionals and patients is difficult day by bay, due to the availability of large number of generic brands in market. The aim of present study was to conduct various quality control tests for different marketed brands of nebivolol tablet available in India as per IP, in order to improve the safety, efficacy and to avoid health risk factors of the people. Four brands of Nebivolol hydrochloride tablets (10 mg) marketed in India, were evaluated for various quality control tests including physical appearance, crown diameter, thickness, uniformity of weight, percentage drug content, hardness, friability, disintegration test, and dissolution test.

KEYWORDS : Nebivolol Hydrochloride, quality control tests, dissolution profile

I. INTRODUCTION

Hypertension is one of the major causes of morbidity, mortality and needs lifelong treatment. It is a major risk factor for cardiovascular disease. “Worldwide nearly 1 billion adults (more than a quarter of world’s population) had hypertension in 2010 and this is predicted to increase 1.56 billion by 2025” . Hypertension is fast gaining the status of a potential epidemic in India. “ Prevalence of hypertension in India is reported to vary from 17 – 21%. The situation is more alarming as hypertension attributes for nearly 10% of all deaths” [1, 2, 3]. “Nebivolol hydrochloride is a highly cardio-selective β1-adrenergic blocking agent which is need for therapeutic management of hypertension and cardiovascular disease.Nebivolol hydrochloride is a drug with low water solubility and high membrane permeability included in class 2 of the Biopharmaceutical Drug Classification System. The drawbacks associated with this drug are poor solubility which leads to low bioavailability of drug [4, 5]. Nebivolol tablets of different brands may have different types and/or amount of diluents, disintegrants, lubricants, or other excipients. They may be also subjected to different compression forces which affect the hardness, friability, disintegration and dissolution rate of a formulation. The variation in results of these tests may also affect the bioavailability of formulation. Also a common truth is, not “all the manufacturers are equally accepted to the consumers. In a general sense most of the consumers choose the popular brands of medicines though they are not really concerned about the potency and overall quality of the drugs. Hence in the present study various quality control tests were performed for different marketed brands of nebivolol tablet accessible in India as per Indian Pharmacopoeia 2018, in order to improve the safety, efficacy and to avoid health risk factors of the people[6].

II. MATERIALS AND METHODS

Material

- Four brands of Nebivolol hydrochloride tablets (10 mg) were purchased from local market . Following instruments and equipment’s were used.
- Dissolution Test Apparatus: USP type II apparatus (Paddle), Electrolab Tablet Dissolution Tester USP TDT-06
- UV Visible Spectrophotometer:Shimadzu UV-1560
- Monsanto Hardness Tester
- Disintegration Test Apparatus: Electrolab tablet disintegration tester USP

Method

Analytical method development by UV spectroscopy

UV spectroscopy Primary stock solution of 1.0 mg/ml Nebivolol Hydrochloride was prepared by dissolving 10.0 mg of drug in 10.0 ml of methanol. From this, a solution of strength 10.0 µg/ml was prepared by serial dilutions. This solution was

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scanned between the wavelengths of 200-400 nm (UV spectrophotometer, Shimadzu) to determine the maximum wavelength of absorption [7].Calibration curve of Nebivolol Hydrochloride Primary stock solution of Nebivolol Hydrochloride of strength 1.0mg/ml was prepared in methanol. From this 1ml of solution was diluted with 10ml methanol to get a secondary stock solution i.e.100 µg/ml. Appropriate aliquots were taken into different 10ml volumetric flasks and the volume to get a drug concentration of 5, 10, 15, 20, 25 and 30µg/ml. This solution was scanned in the UV range of 281 nm in opposition to a solvent blank to determine the λmax. Calibration curves. Concentration vs. absorbance was plotted to study the Beer-Lambert's Law and regression equations for Nebivolol Hydrochloride. Quality control test for tablets as per IPGeneral Appearance Test Observe the tablets and note the shape, color, odour, and taste if any. Crown diameter and thickness of the tablets was measured with a Verniercalipers. For that 20 tablets from 4 brands were taken and measure the diameter and thickness in order to determine the average diameter and thickness of the tablets. Uniformity of weight 20 tablets from each of the 4 brands were weighed individually with an analytical weighing balance. The average weight for each brand was determined as well as the percentage deviation from the mean value were calculated using the formula given by Banker and Anderson [8]. The tablets comply with the test if not more than two tablets have a percentage deviation outside the permissible limit and if no tablet differs by more than twice this limit.

1. PRELIMINARY CHARACTERIZATION OF DRUG

1 Color, odour and appearance of API

Nebivolol HCl API was evaluated for parameters like color, odour & appearance are shown in result**.**

2. Melting point for Nebivolol hydrochloride was determined by open capillary method and compared with literature values given in results.

3. Nebivolol hydrochloride factor calculations

Moleculaer weight of Nebivolol hydrochloride: 441.9

Moleculaer weight of Nebivolol: 405.44

Factor = molecular weight of nebivolol / molecular weight of nebivolol Hydrochloride

Factor = 405.44/441.9

Factor = 0.917

Solubility: The solubility was determined in methanol at a concentration of 3mg/mL as follows and are given in results**.**

Methanol: Weighed approx 32.72 mg of Nebivolol HCl (Equivalent to 30 mg of Nebivolol) and sonicated for 5-10 minutes to dissolve in 10 ml of Methanol.

2 Selection of analytical wavelength

1. Selection of solvent

Methanol was selected as the solvent for dissolving Nebivolol hydrochloride.

2. Preparation of standard stock solutions

In order to prepare stock solution, weighed accurately 10.91 mg Nebivolol hydrochloride (Equivalent to 10 mg of Nebivolol) and transferred into 50 ml volumetric flask, added 35 ml of methanol and sonicated to dissolve the standard completely and diluted up to the mark with methanol (200 PPM). Further diluted 1 mL to 20 mL with methanol. (10 PPM)

3. Selection of analytical wavelength

Methanol as a blank and Nebivolol standard solution (10 PPM) was scanned from 400 nm to 200 nm. Absorption maxima was determined for drug. Nebivolol showed maximum absorbance at 282 nm shown in results.

4. Evaluation of Marketed test samples:

Selected test samples are evaluated for following tests:

1)Appearance, Description and Dimensions
2)Average weight calculation
3)Friability
4)Hardness
5)Disintegration test
6)Content uniformity
7)Dissolution

1) Appearance, description and Dimensions:

The appearance of the tablet such as colour, shape, size, surface texture and dimensions observed, measured and recorded.

2) Average weight calculation: Placed 20 tablets on weighing balance and weight recorded and calculated average weight as follows:

Average weight (mg) = Weight of 20 tablets (mg) / 20

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3) Friability:

The factors that cause tablets to chip, cap or shatter are friction and shock. The friability test is linked to tablet hardness is used to asses a tablets ability to tolerate abrasion during packing, handling and shipping. The Roche Friabilator was used to measure it.

Number of tablets selected in such a way that its total weight will approximately 6.5 gms were put in the device and subjected for tumbling at 25 RPM for 4 minutes, during tumbling they fall 6 inches in each rotation. After four minutes of this treatment or 100 revolutions, the tablets were weighed and the weight was compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test was considered generally acceptable and any broken or smashed tablets were not picked. The percentage friability was determined by the formula:

%Friability = (W_1-W_2) / W_1 X 100

W1 = Weight of tablets before tumbling

W2 = Weight of tablets after tumbling

4) Hardness:

Hardness crushing strength is used to assess whether or not a tablet machine require a pressure modification. If the tablet is too hard, it may not dissolve in time necessary to fulfil the dissolving criteria, if it is too soft it may not be able to resist further processing such as coating packing and shipping procedures.

Procedure:

Tested the hardness of tablet by placing the tablet between two jaws by using Monsanto type hardness tester. One of the jaws then moves towards the tablet pushing it against the fixed jaw until the tablet breaks. The load at which the tablet fails across the diameter is then recorded.

5) Disintegration test:

In order for a medication to be absorbed from solid dosage form after oral administration, it must first be in solution and the first critical step towards this step is generally tablet disintegration. 6 tablets were introduced in each tube and immersed in water at 37ºC±2ºC and disintegration time was noted.

6) Content uniformity

To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units.

The uniformity of dosage units can be demonstrated by either of two methods, Content Uniformity or Weight Variation. The test for Content Uniformity of preparations presented in dosage units is based on the assay of the individual content of drug substance(s) in a number of dosage units to determine whether the individual content is within the limits set.

Procedure for Content uniformity of dosage form:

Preparation of Standard solution:

Weighed about 10.91 mg Of Nebivolol HCl standard (Equivalent to 10 mg of Nebivolol) and transferred in 20 mL volumetric flask, added 15 mL of methanol, sonicate to dissolve it, made volume up to the mark with methanol. (500 PPM of Nebivolol)

Pipette out 1.0 ml from standard stock solution and transferred into 20 ml volumetric flask and made volume up to the mark with Methanol (25 PPM of Nebivolol). Measured the absorbance of standard solution at 282 nm on UV-spectrophotometer.

Sample test procedure for content uniformity:

Taken clean and dried 10 volumetric flask of 50 mL. Place one tablet in each flask, added 30-35 mL of methanol. Sonicated the samples for 15 minutes with intermittent shaking. Allowed the solutions to cool at R.T. Made the volume up to the mark with methanol (200 PPM of Nebivolol). Filtered the solution through 0.45 µ Nylon syringe filter. Further diluted 2.5 mL of filtrate to 20 mL with methanol (25 PPM of Nebivolol). Measured the absorbance of test solutions at 282 nm on UV-spectrophotometer [9].

Calculate the % content of Nebivolol in each tablet as follows:

$$\% \text{ content of nebivolol in tablet} = \frac{\text{test sample absorbance}}{\text{Std absorbance}} \times \frac{\text{nebivolol HCL std wt}}{20} \times \frac{1}{20} \times \text{Factor} \times \frac{50}{\text{Label claim of nebivolol}} \times 100$$

2.5

Determine % Content of Nebivolol in each tablet, Mean content of 10 tablet, Standard deviation, % RSD for % Content of Nebivolol and acceptance value (AV)

Acceptance value = | M-X | + ks

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Where,
M= Reference value
X= Average of content uniformity value
K= Acceptability constant (2.4 for 10 tables)
S= Standard deviation for content uniformity value of 10 tablets

7) Dissolution:

The process of solid solute entering a solution is known as dissolution. It is defined as the quantity of drug material that enters solution per unit time under standardized circumstances of liquid/solid interface, temperature and solvent composition in the pharmaceutical business. Similar dissolution pattern in official media as that of innovator was considered which is in accordance with the USFDA rules and regulations for the approval of ANDA.[10]

Selection of analytical wavelength for Nebivolol in Dissolution media (0.01 N HCl)

Preparation 0.01 N HCl:

Pipette out 0.85 mL of hydrochloric acid and diluted up to 1000 mL with water.

Selection of Concentration of Nebivolol Standard solution of UV scan:

Dissolution study conducted on a tablet containing 10 mg of Nebivolol in 900 mL of dissolution media, when 100% drug gets dissolved (10 mg of Nebivolol in 900 mL of dissolution media), concentration will be 11.11 PPM (Aprox 11 PPM) of Nebivolol. Hence we will prepare 11 PPM of Nebivolol in 0.01 N HCl to find abosrrption maxima in dissolution media.

Preparation of Nebivolol Standard solution in 0.01 N HCl (11 PPM) for system suitability: weighed accurately 12.0 mg Nebivolol HCl (Equivalent to 11 mg of Nebivolol) and transferred into 50 ml volumetric flask, added 2.5 ml of methanol and sonicated to dissolve the standard completely and diluted up to the mark with 0.01 N HCl. (220 PPM).

Further diluted 1 mL to 20 mL with dissolution media. (11 PPM)

Note: This solution is also used for system suitability

Solutions for UV scan:

Blank (0.01 N HCl) solution and Nebivolol standard solution (11 PPM) was scanned from 400 nm to 200 nm. Absorption maxima was determined for drug. 280 nm selected for Nebivolol analysis for Dissolution testing.

Dissolution parameters:

Dissolution Media: 0.01 N HCl
Media Volume: 900 mL
Bowl temperature: 37 ± 0.5ºC
Apparatus: USP type II (Paddle)
RPM: 50
Time points: 10, 20, 30 and 45 Minutes.
Aliquot volume: 10 mL

Analysis Method:

Method: UV-spectroscopy
Wavelength: 280 nm
Pathlength: 1 CM
Diluent: 0.01 N HCl

Preparation of test samples for Dissolution:

Transfer 900 mL of Dissolution media in dissolution bowl previously maintained at 37°C. Attached USP appratus II (Paddle) and set at 50 RPM. Transfer one tablet in each bowl previously maintained at 37°C and subject for dissolution. Run the Dissolution program for 45 minutes. Withdraw the 10 mL of aliquot at the time point of 10, 20, 30 and 45 minutes and replace with 10 mL of dissolution media. Filter the solution through suitable 0.45 µ PVDF syringe filter discarding 3 mL of filtrate. Performed on 6 tablets for each product. (Concentration of Nebivolol is 11.11 PPM of after 100% dissolution)

% Dissolution formula:

$$\% \text{ Dissolution} = \frac{\text{test sample absorbance}}{\text{Std absorbance}} \times \frac{\text{Nebivolol STD wt (mg)}}{50} \times \frac{1}{20} \times \frac{900}{10} \times \text{Factor} \times 100$$

% Dissolution determined at each time point for each product.

F2 value calculated for Nebicard 10, Nodon 10 and Nebistol 10 products, w.r.t. Nebistar 10 tablet as Innovator (RLD) product.

III. RESULT AND DISCUSSION

PRELIMINARY CHARACTERIZATION AND IDENTIFICATION OF DRUG

1. Color, odour and appearance

Color, odour and appearance of Drug

Sr No	Name	Colour, odor and appearance of drug
1	Nebivolol HCL	White , odourless and slightly amorphous powder

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2. Melting point determination

Melting point of Drug

Sr No	Name	Std melting point	Obs melting point
1	Nebivolol HCL	223-228 °C	226°C

3. Solubility study

Solubility study of Nebivolol HCl

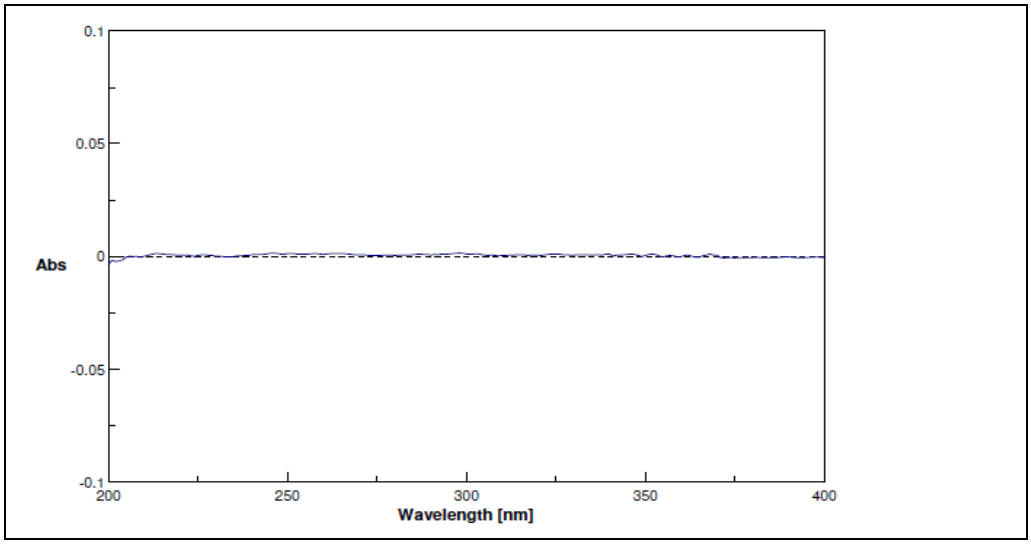
Sr No	Name of solvent	Observation
1	Methanol	Soluble

4. Selection of solvent

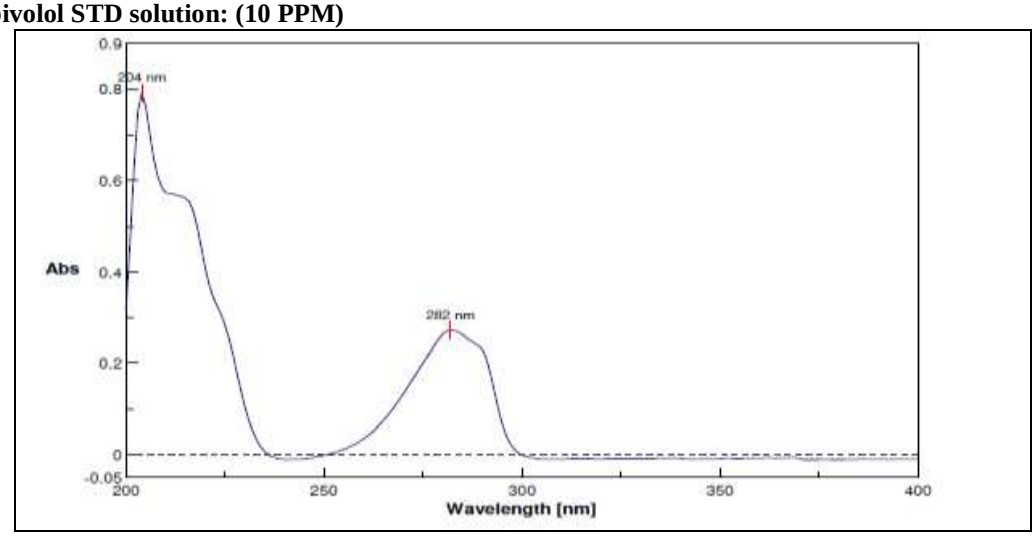
Methanol was selected as the solvent for dissolving Nebivolol HCl.

2. Selection of analytical wavelength

1) Blank Methanol:



2) Nebivolol STD solution: (10 PPM)



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Observation: The standard solution was scanned from 400 nm to 200 nm. Wavelength of maximum absorption was determined for drug. Nebivolol HCl showed maximum absorbance at 282 nm. It is shown in **Figure No.2**. Therefore 282 nm considered as an analytical wavelength for further determination.

3. Selection of Marketed Test samples:

1) Appearance, Description and Dimensions:

Sr No	Product Name	Appearance	Dimensions
1	Nebistar 10	White color, round shape, flat surface on both sides	Diameter : 9.1 mm Thickness : 3.6 mm
2	Nebicard 10	Light orange color, round shape, flat surface	Diameter : 8.1 mm Thickness : 3.2 mm
3	Nodon 10	White color , round shape , flat surface on both sides	Diameter : 8.2 mm Thickness : 3.2 mm
4	Nebistol 10	White color, round shape, flat surface on both sides	Diameter : 8.1 mm Thickness : 3.2 mm

2) Average weight calculation

Sr No	Product Name	Weight of 20 tablets	Average weight
1	Nebistar 10	5902.4	295.1
2	Nebicard 10	4012.4	200.6
3	Nodon 10	4086.4	204.3
4	Nebistol 10	4032.8	201.6

3) Friability

Sr No.	Product Name	W1	W2	% Friability
1	Nebistar 10	6494.6	6481.2	0.21
2	Nebicard 10	6422.4	6412.4	0.16
3	Nodon 10	6538.1	6519.7	0.28
4	Nebistol 10	6444.7	6430.4	0.21

4) Hardness

Sr No.	Product Name	Hardness (kg/cm^2)
1	Nebistar 10	5.0
2	Nebicard 10	4.0
3	Nodon 10	3.5
4	Nebistol 10	3.0

5) Disintegration Time

Sr No.	Product Name	Disintegration Time (mm:ss)
1	Nebistar 10	04:47
2	Nebicard 10	05:20
3	Nodon 10	03:37
4	Nebistol 10	04:11

6) content uniformity

a) system suitability for content uniformity

Sr No	Standard solution	Absorbance
1	Standard 1	0.6841
2	Standard 2	0.6829
3	Standard 3	0.6851

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4	Standard 4	0.6837
5	Standard 5	0.6841
	Mean	0.6840
	Std dev	0.0008
	% RSD	0.116

b) content uniformity of Nebistar, Nebicard, Nodon, Nebistol 10 mg

Tablet	% content of Nebistar 10	% content of Nebicard 10	% content of Nodon 10	% content of Nebistol 10
1	96.7	96.2	98.1	95.1
2	98.7	92.7	96.9	99.3
3	94.8	98.7	99.1	98.7
4	94.8	99.8	95.6	98.3
5	99.3	96.5	98.6	100.3
6	98.4	92	97.1	98.2
7	95.8	94.3	99.1	95.7
8	95.6	97.8	98.7	97
9	96.8	95.6	96.9	99.2
10	98.4	97.2	96.3	97.1
	Mean = 96.9 Std Dev = 1.6753 % RSD = 1.729	Mean = 96.1 Std Dev = 2.5072 %RSD = 2.609	Mean = 97.6 Std Dev = 1.2411 %RSD = 1.272	Mean = 97.9 Std Dev = 1.6475 % RSD = 1.683

7) Dissolution study results

a) selection of wavelength

Uv scan of nebivolol in Dissolution media

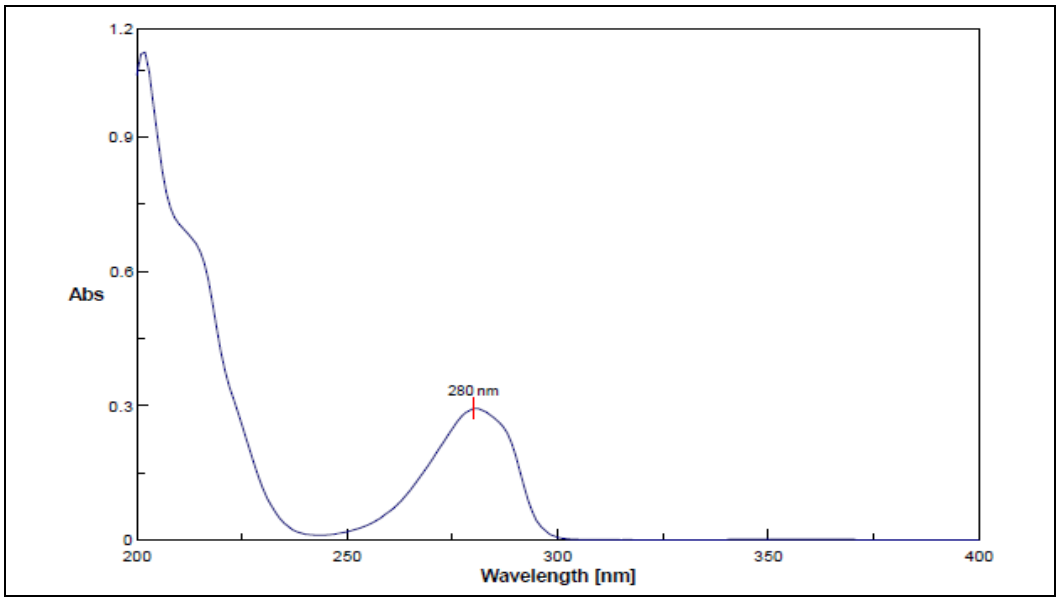

Fig: UV scan of Nebivolol Standard solution in dissolution media.

Observation: The standard solution was scanned from 400 nm to 200 nm. Wavelength of maximum absorption was determined for drug. Nebivolol shows maximum absorption at 280 nm.

Conclusion: 280 nm selected as a absorption maxima.

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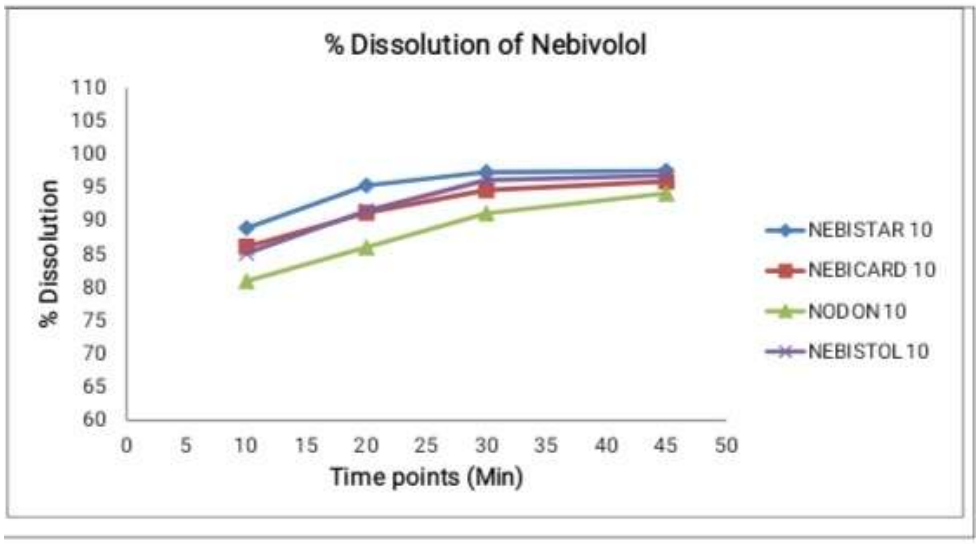
Dissolution results of all products

Time point (Min)	% Dissolution of Nebistar 10	% Dissolution of Nebicard 10	% Dissolution of Nodon 10	% Dissolution of Nebistol 10
10	88.9	86.1	80.9	85.1
20	95.3	91.2	86	91.5
30	97.3	94.6	91.1	96.1
45	97.5	95.9	94.1	96.8



Observation summary for absolute difference for % dissolution value w.r.t. Nebistar 10 tablet results:

Time point (min)	Nebistar 10	Nebicard 10	Nodon 10	Nebistol 10
10	NA	2.80	8	3.80
20	NA	4.10	9.3	3.80
30	NA	2.70	6.2	1.20
45	NA	1.60	3.4	0.70

Acceptance criteria: Absolute difference at each time point: NMT 5.0

Observation summary for f1 and f2 value w.r.t. Nebistar 10 tablet results

Product Name	F1 value (similarity factor)	F2 value (dissimilarity factor)
Nebicard 10	**3**	**75**
Nodon 10	**7**	**57**
Nebistol 10	**3**	**77**

Acceptance criteria: F2 value: 50-100
F1 Value: NMT 15.0

Data interpretation:

Absolute difference for Mean dissolution value for each time point as well as F2 values for Nebicard 10 and Nebistol 10 product found well within acceptance limit w.r.t. RLD product. Hence it can be conclude that selected generic Nebivolol products i.e. Nebicard 10 and Nebistol **10 found In-vitro bioequivalent to that of RLD product. (Nebistar tablet)**

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F2 value for Nodon 10 tablet passes the criteria but absolute difference value between Mean dissolution value not passes the criteria. Hence it can be conclude that Nodon 10 tablet was **not** found In-vitro bioequivalent to that of RLD product. (Nebistar tablet)

Interpretation of Dissolution study:

Bioequivalence studies are special type of studies where two drugs or two sets of formulation of the same drug are compared to show that they have nearly equal bioavailability and PK/PD parameters. These studies are often done for generic drugs or when a formulation of a drug is changed during development.

After the expiration of a patent, pharmaceutical companies can manufacture and market the generic version of the innovator's drug provided their abbreviated new drug application (ANDA) is approved. To be approved, generic companies must prove that their product is bioequivalent to that of the innovator.

Before going to start In-vivo study, Generic product must show same dissolution release profile because under IVIVC (in-vitro in-vivo correlation), In-vitro release profile of generic product is compared with release profile of Innovator product. During in-vitro correlation study, Dissolution study conducted on both products and similarity factor (F2) determined for Generic product. IN-vivo study is not performed until F2 value for generic product pass the criteria.

Out of Selected 3 generic products, 2 products i.e. Nebicard 10 and Nebistol 10 have the same drug release profile to that of innovator Product.

Nodon 10 tablet not have same drug release profile to that of innovator.

Among these 3 products, **Nebistol 10** have highest similarity value (77).

IV. CONCLUSION :

In the present scenario large number of multi generic brand of drug are available in market so to compare there sufficient therapeutic activity of the dosage form in-vitro tests play a significant role. The presented results show that all four brands of nebivolol tablets seem to have good overall quality and adequate potency. The dissolution profile of all tables shows similar pattern on drug release. So this investigation will change the views of people that standard and generic medicines have same effect and they can shift from standard to generic.

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