A COMPARATIVE QUALITY ANALYSIS OF DIFFERENT MARKETED BRANDS OF NEBIVOLOL TABLET AVAILABLE IN INDIA

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ABSTRACT

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 (A, B, C, and D) of Nebivolol hydrochloride tablets (5 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. The observed result shows that as hardness was increases the percent friability of the tablets was decreased notable in the in all formulations. Hence harder the tablets less will be the percent friability and vice versa. Dissolution study shows that more than 90 of drug releases from the brand A, B & C except brand D (86.5%). Pattern of drug release for the different brand was same. So result conclude that the prescription contain these brand can be interchangeable.

Keyword: Nebivolol Hydrochloride, quality control tests, dissolution profile

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

MATERIALS AND METHODS

Materials and equipment

Nebivolol hydrochloride was a kind gift from Cipla Ltd., bangluru, Potassium dihydrogen phosphate, sodium Acetate, concentrated hydrochloric acid, sodium hydroxide pellets, potassium chloride were purchase from S.D. fine chemicals, Mumbai were used as received. Four brands of Nebivolol hydrochloride tablets (5 mg) were purchased from local market of Mangaluru, India. 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 scanned between the wavelengths of 200-400 nm (UV spectrophotometer, Shimadzu, Kyoto, Japan) to determine the maximum wavelength of absorption [5, 6].

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 was adjusted with buffer solutions of pH 6.8 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 $\lambda_{max.}$ 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 IP

General 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 [7]. 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.

Average wt of tablets (mg)	Max. Permissible limit for deviation (%)
80 or less	±10
More than 80 and less than 250	±7.5
250 or more	±5

Uniformity of content

This test is applicable to tablets that contain less than 10 mg or less than 10% w/w of active ingredient. Uniformity of drug content was performed by determining the content of active ingredient(s) in each of 10 tablets random. Tablet was finely powdered and the powder equivalent to 1 mg of nebivolol was weighed accurately and transferred to a 100 ml volumetric flask. The volume was made up to 100 ml by methanol, kept for stirring under mechanical stirring for 30 min. The solution was filtered and necessary diluted with phosphate buffer pH 6.8 and absorbance was taken at 281 nm using UV spectrometer. The linearity equation obtained from calibration curve was used for the estimation of nebivolol content in the tablets [8].The tablets comply with the test if not

more than one of the individual values thus obtained is outside the limits 85 to 115% of the average value and none is outside the limits 75 to 125% of the average value.

Hardness Test

The crushing strength was determined with Monsanto Hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet, and a zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded and the zero reading is deducted from it. Ten tablets were randomly selected from each brand and the force at which each tablet crushed was recorded [9].

Friability Test

Friability test: twenty tablets from each brand were weighed and subjected to abrasion by employing a Roche friabilator. It consists of a plastic chamber that revolves at 25 rpm. The friabilator is operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets were then dusted and reweighed. The loss in weight should not exceed 1.0% of their original weight as per IP [10].

$$\textbf{\% Friability}=\frac{W_0-W_f}{W_0}\times 100$$

Where, W_0= weight of tablets before test (g), W_f = weight of tablets after test (g),

Disintegration Test

The U.S.P Disintegration test apparatus was used. One tablet was placed in each of the six tubes, followed by the plastic discs. The basket rack assembly was positioned in one liter beaker of water maintained at 37 ± 2^0C. The apparatus was operated such that the tablets remain 2.5cm below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker. The time taken for the tablets to disintegrate and for the particles to completely pass through the screen without any residue remaining was observed. If any residue remains, it should be a soft mass with no palpable firm core. The disintegration time should be within prescribed limit for the tablets (uncoated) to comply with the test.

Dissolution Test

Dissolution test was performed using USP type II apparatus (paddle type) at 50 rpm in 3 replicates for each brand. The dissolution medium was 900 ml of phosphate buffer of pH 6.8, which was maintained at 37 ± 0.5 °C. The paddle was introduced into the medium and fixed so that it's the lower surface was at a height of 2.5cm from the bottom of the vessel. At predetermined intervals (0.5, 10,15,30,60 & 90 min), 5 ml of aliquots was withdrawn and replaced with equal volume of fresh pre-warmed dissolution medium to maintain an ideal sink condition. The samples were filtered through whatman filter paper and diluted to suitable concentration using phosphate buffer of pH 6.8 and absorbance was taken at 281 nm using UV spectrometer. The concentration of this solution was calculated from the standard plot for Nebivolol. The percentage of Nebivolol that has dissolved in the medium in 90 min was calculated and compared with the limit prescribed in the monograph [11, 12].

RESULTS & DISCUSSION

Analytical Method development by UV spectrophotometer

Sample solution containing 10 µg/ml of Nebivolol hydrochloride was measured against phosphate buffer of pH 6.8 and showed a peak at 281nm as shown in fig 1. So this was selected as a λ_{max} for the current study and the same adopted for further investigations.

Calibration curve was plotted by measuring absorbance of drug solution at 281nm. The standard calibration plot of the drug was prepared in phosphate buffer pH 6.8. The UV absorption data of nebivolol at 281 nm showed good linearity with the regression coefficient (R^2) of 0.993 over the concentration range 5 -25 µg/ ml passing through the origin as shown in table 1 and fig 2. Hence it follows the Beer - Lamberts law.

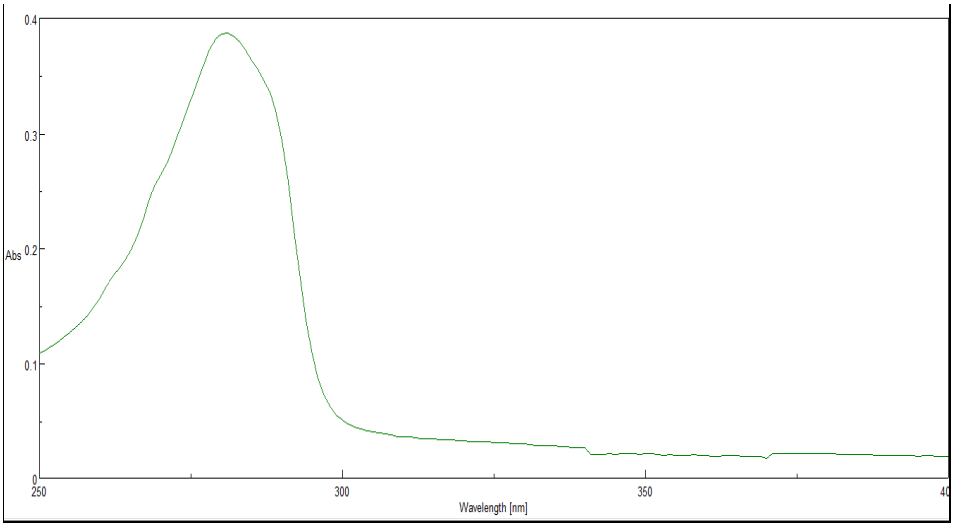

Figure 1: U.V. Spectrum of Nebivolol Hydrochloride in phosphate buffer of pH 6.8

Table 1 Standard plot of Nebivolol Hydrochloride in the phosphate buffer pH 6.8 at 281 nm

Sl.no	Concentration (µg/ml)	Absorbance at 280nm
1	0	0
2	5	0.102
3	10	0.173
4	15	0.258
5	20	0.323
6	25	0.401

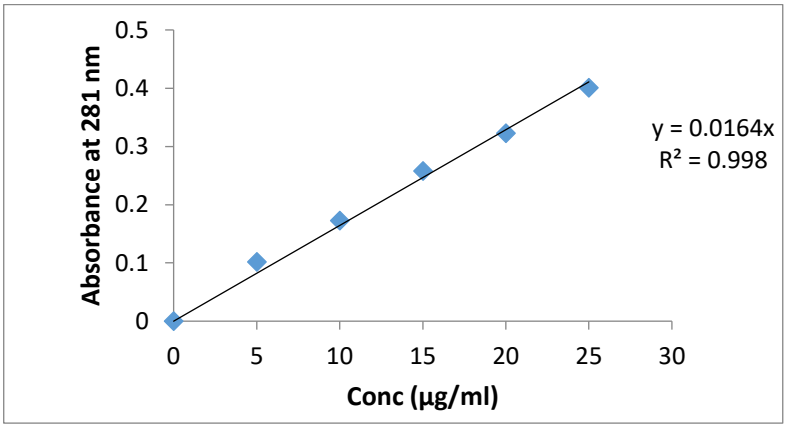

Figure 2: Standard plot of Nebivolol Hydrochloride in the phosphate buffer pH 6.8 at 281 nm

Quality control test for tablets as per IP

General Appearance Test

The general appearance for all the brands of Nebivolol HCl tablets is shown Table 2, the shape of these brands were identified as round, color as white, all the tested brands were tasteless and odourless. The crown diameter of all brands A, B, C and D in the range of 7.4 to 8.1mm and the thicknesses is all most same i.e., 3.1 mm with less standard deviation. The problem related to weight and content uniformity of table can be detected early by monitoring the diameter and thickness of the tablets at regular intervals.

Table 2. Summary of physical parameters of the different brand

Sl. No	General appearance	Brand			
		Brand A	Brand B	Brand C	Brand D
1	Shape	Round	Round	Round	Round
2	Color	White	White	White	White
3	Taste	No Taste	No taste	No taste	No taste
4	Odour	odourless	odourless	odourless	odourless
5	Crown diameter (mm)	8.1± 0.03	7.4± 0.06	8.1± 0.04	7.9 ± 0.03
6	Thickness (mm)	3.1± 0.06	3.1± 0.04	3.1± 0.03	3.0± 0.05

Uniformity of weight

The weight of all four brands of nebivolol tablets was determined with the help of an electronic balance and the observed results have been included in the table 3. (Mean values ± SD, n=20). As per IP, for the average weight of tablets (mg) are 80 or less the maximum percentage differences allowed ±10 and for the limit 80-250 mg, the percentage difference should be ±7.5 and more than 250mg this should be ±5. From the results, it was obvious that weight variation limit values of all branded tablets were less than 7.5 which are within limit.

Hardness and friability of tablets

Hardness is one of the most important physical features for evaluating tablet. It may affect tablet friability, disintegration time, and dissolution rate, and alter result will affect the bioavailability of drug. If the tablet is hard then it cannot disintegrate within the specified time and if the tablet is soft then it becomes challenge to withstand the handling during coating or packaging. Therefore, adequate tablet hardness and resistance to powdering are necessary for acceptance of table batch. Oral tablets normally have a hardness of 4 to 8 or 10 kg. Here, only one brand was within the range.

As the hardness of the tablets was increased gradually there was a notable decrease in the percent friability in all formulations. So harder the tablets less will be the percent friability and vice versa. Here, brands A, B and D have percent friability below 1%, and

brands C percent friability above 1%, which indicates tablets from brand C may face difficulty during storage or transportation.

Uniformity of content

Drug content was determined according to method given in IP. The % drug content was found to be between 97 to 99%. Result shows that the nebivolol present in all four brands are within specific limit.

Disintegration Test

The rate of drug absorption and therapeutic efficacy of the drug is dependent upon the disintegration time. IP specifies that uncoated tablets should disintegrate within 15 minute. As results shown in table 4 all the brands met the official criteria and disintegrated within 2 mints only.

Table 3. Weight variation, hardness and friability of different brands of Nebivolol hydrochloride tablets

Brand code	Weight variation (mg)	Hardness (kg/cm2)	Friability (%)
Brand A	198 ±4.0	4.15± 0.36	0.505
Brand B	126.5±6.5	3.15± 0.35	0.775
Brand C	135.5±6.7	2.20 ± 0.21	1.119
Brand D	156.5±5.7	3.05± 0.25	0.649

Table 4. Percentage drug content, Disintegration time, and % drug release at 90 mins of different brands of Nebivolol hydrochloride tablets

Brand code	% Drug content	Disintegration time (min)	(%) Drug release at 90 min
Brand A	97.6±1.4	3.16± 0.40	97.2 ± 3.5

Brand B	97.9±2.2	1.58± 0.20	93.2 ± 2.4
Brand C	98.2±2.1	3.91± 0.49	91.0 ± 2.8
Brand D	99.2±1.1	1.08± 0.21	86.5 ± 3.1

Dissolution profile

The dissolution profile of four brands was shown in table 5. Results shows that, the percentage drug release for most of the brands was more than 90% except brands D was found to 86.5% at the end of 90 mins. The results obtained from the study revealed that most of the brands passed the IP general specifications. The release pattern of drugs from all brand were same although they were manufactured by different companies using different excipients in different ratio. On the basis of releasing factor these brand can be used interchangeably in prescription.

Table 5: *In vitro* dissolution Profile of different brands of Nebivolol tablets

Time (min)	**% cummulative drug release**			
	A	**B**	**C**	**D**
0	0.0 ± 0	0.0 ± 0.0	0.0± 0.0	0.0 ± 0.0
05	18.0 ± 0.8	45.6 ± 2.8	24.8 ± 1.6	26.1 ± 2.9
10	21.5 ± 2.8	52.6 ± 4.1	41.8 ± 3.9	33.9 ± 3.2
15	36.1 ± 2.3	59.9 ± 1.6	51.4 ± 3.4	45.2 ± 4.2
30	58.7 ± 3.3	65.6 ± 2.8	67.2 ± 4.1	66.6 ± 1.7
45	73.5 ± 1.6	72.9 ± 0.8	77.4 ± 2.4	79.1 ± 3.2
60	97.2 ± 3.5	93.2 ± 2.4	91.0 ± 2.8	86.5 ± 3.1

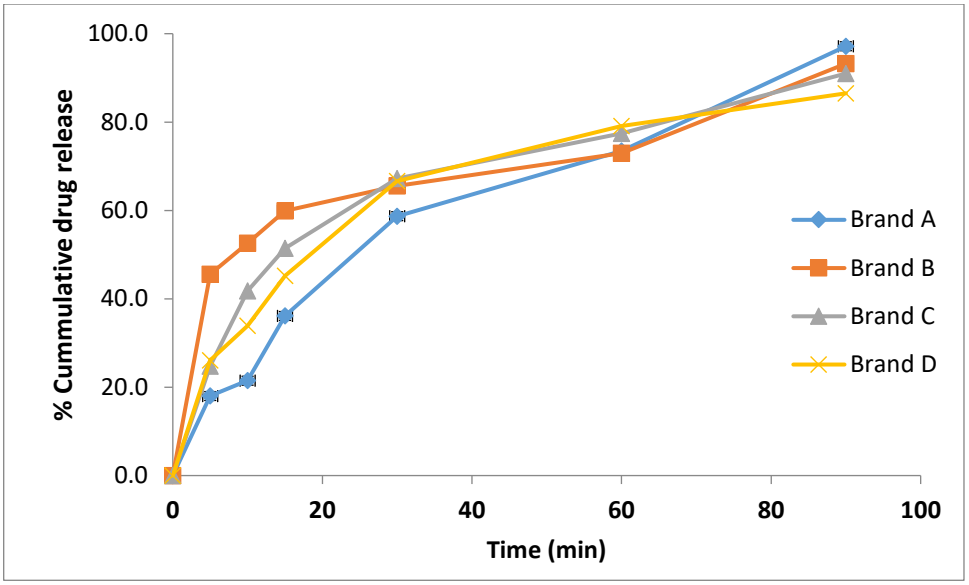

Figure 3: Comparative *in vitro* dissolution profile of different brands of Nebivolol tablets

CONCLUSIONS

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. This study illustrates the current scenario of different quality parameters of drug products manufactured by local companies. It is a general psychology that the drug products manufactured by small level companies may be poor as compared to leading companies available in the market or vice versa. But this investigation will help to change the view of the people.

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