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DESIGN AND EVALUATION OF NEBIVOLOL HCl IN THE TREATMENT OF HYPERTENSION

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ABSTRACT
This study focuses on the formulation and evaluation of a fixed-dose combination tablet of Nebivolol HCL for the effective management of hypertension. The tablet contains 2.5 mg of Nebivolol HCL as an immediate-release component. The pre-compression parameters of the powder blends used for the formulation were within pharmacopeial specifications, demonstrating good flow and compressibility. A novel formulation utilizing Croscarmellose sodium for the immediate-release layer was developed using the direct compression technique. Excipients were selected based on favorable drug-excipient compatibility results. The highest in-vitro release of Nebivolol HCL was 85.37% within 30 minutes, and the F1 formulation was selected for tablet preparation. The fixed-dose tablet of Nebivolol HCL aims to improve patient compliance by enhancing dosing frequency and bioavailability. Dissolution and stability studies conducted in accordance with ICH guidelines showed promising results within the initial two months, with further studies ongoing. Upon successful completion of stability studies, bioequivalence testing will be performed. If successful, the developed product could be introduced to the market for improved hypertension management.

KEYWORDS: Nebivolol HCL, Tablet, Hypertension.

1. INTRODUCTION

The best new therapeutic entity in the world is of little value without an appropriate delivery system. Tablet delivery systems can range from simple immediate release formulations to complex extended or modified release dosage forms. The most important role of drug delivery system is to get the drug delivered to the site of action in sufficient amount and at the appropriate rate. However, it must also meet a Number of other essential criteria. These include physical and chemical stability, ability to be economically mass-produced in a manner that assures the proper amount of drug in each and every dosage form and in each batch produced and as far as possible patient acceptability the drug and the delivery systems cannot be separated.

A tablet is defined as a solid pharmaceutical dosage form containing a drug substance with suitable diluents, prepared by either compression or molding methods. In the European Pharmacopoeia, tablets are also defined as "solid preparations, each containing a single dose of one or more active ingredients and obtained by compressing a uniform volume of particles." Tablets remain a popular dosage form due to the advantages they offer both to manufacturers (e.g., simplicity and economy of preparation, stability, and convenience in packing, shipping, and dispensing) and to patients (e.g., accuracy of dosage, compactness, portability, blandness of taste, and ease of administration). Tablet technology has undergone significant improvements, with ongoing efforts to better understand the physical characteristics of powder compaction and the factors that affect the availability of the drug substance from the dosage form after oral administration. Tablet manufacturing equipment continues to improve in both production speed and the uniformity of the compressed tablets.

There are several types of tablets, each designed for specific purposes in drug delivery. The main types include

A. **Immediate-Release tablets:** These are the most common type of tablets and are designed to dissolve quickly once ingested, releasing the drug for immediate absorption. They are typically used for fast therapeutic action.

B. Extended-Release tablets: These tablets are designed to release the drug gradually over an extended period, providing a prolonged therapeutic effect. They are often used for chronic conditions where steady drug levels are needed.

C. Controlled-Release tablets: Similar to extended-release tablets, these are designed to control the release rate of the drug, ensuring that it is released at a consistent rate over a longer period of time. These tablets can be tailored to release the drug in specific amounts at specific intervals.

D. Sustained-Release tablets: These tablets release the drug at a constant rate for a prolonged duration, which helps maintain therapeutic levels over an extended period.

E. Chewable tablets: Designed to be chewed before swallowing, these tablets are often flavored and are useful for children or patients who have difficulty swallowing traditional tablets.

F. Effervescent Tablets: These tablets are formulated to dissolve in water, releasing carbon dioxide, and produce a solution for easier ingestion. They often contain active ingredients that need to be dissolved quickly.

G. Buccal and Sublingual tablets: Buccal tablets are placed between the gum and cheek, while sublingual tablets are placed under the tongue. Both types are designed for absorption through the mucous membranes for faster onset of action.

H. Film-Coated tablets: These tablets are coated with a thin film that helps mask the taste, protect the drug from environmental factors, or control the release of the drug.

I. Enteric-Coated tablets: These tablets are coated with a substance that prevents the tablet from dissolving in the stomach but allows it to dissolve in the more alkaline environment of the intestines. This is typically used to protect the stomach or for drugs that are better absorbed in the intestine.

J. Sugar-Coated tablets: These tablets have a sugar coating that may mask the taste of the drug and improve patient compliance. The coating also provides a protective barrier.

K. Compressed tablets: These are the most common type of tablet, made by compressing powdered drug ingredients and excipients into a solid form. They can be either immediate-release or modified-release tablets.

1) Dispersible tablets: These tablets are designed to be dispersed in water before taking, which makes them easier to swallow and ideal for patients who have difficulty with solid dosage forms.

2. Disease profile

Hypertension, also known as high blood pressure, is a medical condition where the force of the blood against the walls of the arteries is consistently too high. Over time, this increased pressure can lead to serious health problems, such as heart disease, stroke, kidney damage, and eye problems.

2.1 Types of hypertension

Primary (Essential) hypertension: This is the most common type, and the exact cause is unknown. It develops gradually over many years and is influenced by factors such as genetics, poor diet, lack of physical activity, and stress.

Secondary hypertension: This type is caused by an underlying condition, such as kidney disease, hormonal disorders, or the use of certain medications (like birth control pills or pain relievers). Secondary hypertension can appear suddenly and cause higher blood pressure than primary hypertension.

Risk factors for hypertension

- **Age:** Risk increases with age.
- **Family history:** A family history of high blood pressure increases the likelihood.
- **Obesity:** Being overweight puts extra strain on the heart and blood vessels.
- **Physical inactivity:** Lack of exercise can contribute to higher blood pressure.
- **Excessive alcohol or tobacco use:** Both habits can raise blood pressure.
- **High salt (sodium) intake:** Excess salt in the diet can lead to fluid retention, raising blood pressure.
- **Chronic stress**: Long-term stress can contribute to high blood pressure.
- **Other health conditions:** Conditions like diabetes, kidney disease, and sleep apnea can increase the risk of hypertension.

Symptoms

Hypertension is often called a "silent killer" because it usually has no noticeable symptoms. However, in severe cases, it can cause:

- Headaches
- Shortness of breath
- Nosebleeds
- Dizziness or lightheadedness
- Blurred vision

Diagnosis

Hypertension is diagnosed when blood pressure readings consistently exceed 130/80 mmHg. A healthcare provider may take multiple readings over time to confirm the diagnosis.

Treatment

1. **Lifestyle changes**
   - Reducing salt intake, losing weight, engaging in regular physical activity, and reducing alcohol consumption can help control blood pressure.
   - A healthy diet such as the DASH (Dietary Approaches to Stop Hypertension) diet is recommended.

2. **Medications**
   - **Diuretics:** Help the body eliminate excess salt and water, reducing blood pressure.
   - **Beta-blockers:** Reduce the heart rate and the force of the heart's contractions.
   - **ACE inhibitors:** Help relax blood vessels.
   - **Calcium channel blockers:** Help relax blood vessels and reduce the heart's workload.
   - **Angiotensin II receptor blockers (ARBs):** Help relax blood vessels similarly to ACE inhibitors.
   - **Other antihypertensive drugs** may be prescribed based on individual needs.

Complications

If left untreated, hypertension can lead to:

- **Heart disease:** Increased risk of heart attacks, heart failure, and stroke.
- **Kidney damage:** Hypertension can damage the kidneys over time.
- **Vision loss:** Hypertension can damage the blood vessels in the eyes.
- **Cognitive decline:** High blood pressure may contribute to memory loss and dementia.

Prevention

- Maintain a healthy diet, exercise regularly, and monitor blood pressure regularly.
- Avoid smoking, excessive alcohol, and high-sodium foods.
- Manage stress through relaxation techniques such as yoga or meditation.

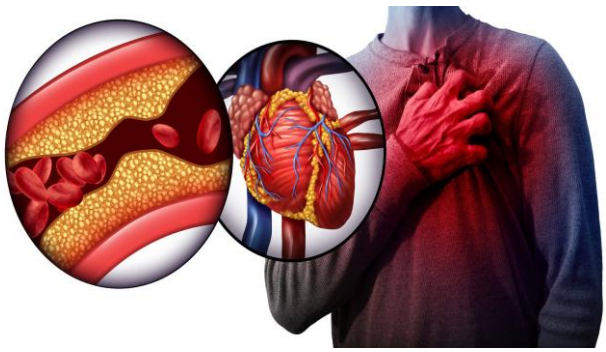

Fig. 1: Hypertension.

3. **Drug profile**

A. **Molecular formula:** $C_{22}H_{25}F_2NO_4$,HCL

B. **Molecular weight:** 441.9 g/mol

C. **Chemical name:** (1RS,1'RS)-1,1'-[(2RS,2'SR)bis(6-fluoro-3,4-dihydro-2H-1-benzopyran-2-yl)]- 2,2'-iminodiethanol hydrochloride

D. **Description:** A white to off – white powder

E. **Solubility:** Nebivolol Hydrochloride issoluble in methanol, dimethylsulfoxide, N,N- Dimethyl formamide, sparingly soluble in ethanol, propylene glycol, polyethylene glycol and very slightly soluble in dichloromethane, hexane, and toluene.

F. **Melting point:** 223.0 to 228.0°C

G. **Therapeutic category:** Anti-hypertensive

H. **Coating agent:** Titanium dioxide

I. **Bioavailability:** 12-96 %

J. **Route of administration:** By mouth

K. **Metabolism:** Liver

L. **Elimination Half - Life:**10 hours

M. **Excretion:** kidney and fecal

N. **Protein binding:** Nebivolol is 98% bound to plasma proteins, mostly to serum albumin.

O. **Mode of action:** This medication belongs to a class of drugs known as beta blockers. It works by blocking the action of certain natural substances in your body, such as epinephrine, on the heart and blood vessels. This effect lowers heart rate, blood pressure, and strain on the heart.

P. **Uses:** It is used to treat high blood pressure and heart failure. Nebivolol is used in the treatment of angina to decrease the heart rate and contractile force. This is relevant in patients who need to decrease the oxygen demand of the heart so that the blood supplied from constricted arteries be adequate. ACE inhibitors, angiotensin II receptor antagonists, calcium-channel blockers, and thiazide diuretics are generally preferred over beta blockers for the treatment of primary hypertension in the absence of co-morbidities.

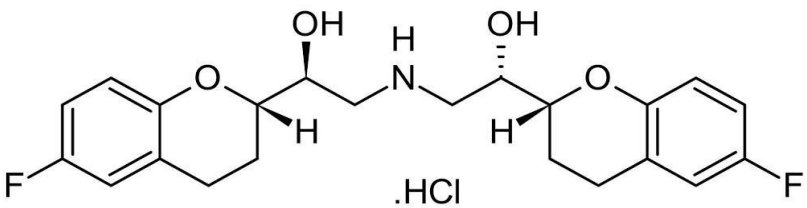

Fig. 2: Structure of nebivolol hydrochloride.

4. MATERIALS AND METHODS

4.1. Methods

4.1.1 Pre-formulation study

- Physical observation of Nebivolol HCL
- Drug–Excipient compatibility studies.

4.1.2 Formulation and Evaluation of Tablets

- Formulation of Immediate-release of Nebivolol HCL.
- Evaluation of Immediate-release of Nebivolol HCL.
- Invitro dissolution study for different formulations.
- Stability study for selected formulation.

4.2 Pre-Formulations tudies

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

4.2.1 Determination of bulk Density and Tapped density

An accurately weighed quantity of the blend (W), was carefully poured into the graduated cylinder and the volume (V0) was measured. Then the graduated cylinder with lid, set into the density determination apparatus. The density apparatus was set for 250 taps/min. and after that the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density and tapped density were calculated by using the following formulas.

Bulk Density = W/ V0
Tapped Density = W/Vf

4.2.2 Compressibility Index (CI)

It was obtained from bulk and tapped densities. It was calculated by using the following formula

CI=100 x(Vo-Vf)/ Vo

4.2.3 Hausner ratio

It indicates the flow properties of a powder. It is measured by ratio of tapped density to bulk density.

Hausner Ratio = Tapped density / Bulk density

4.2.4 Sieve analysis

The A series of sieves were arranged in order of decreasing of pore diameter (Increasing in Sieve no.) i.e. sieve numbers #20,#40, #60, #80, #100. 100 grams of blend were weight accurately and transferred to sieve #20, which was kept on the top. The sieves were shaken in an electro magnetic sieve shaker for 10 minutes at power 16. Then the drug retain on each sieve were taken, weighed separately and expressed in terms of percentage (%).

4.2.4 Loss on Drying (LOD)

It was measured by Electronic LOD measurement apparatus. Above 500 mg of blend was taken on aluminum plate of the apparatus. The blend was kept at 105℃ for 5 minutes. After that the displayed result was noted in terms of % w/w.

4.3 Formulation of Immediate Release Nebivolol HCL Tablet

Table 1: Immediate release formulation of Nebivolol HCL.

S. No	Ingredients	F1	F2	F3	F4	F5
1.	Nebivolol HCL	0.01365kg	0.01365kg	0.01365kg	0.01365kg	0.01365kg
2.	Isopropyl alcohol	0.300L	0.300L	0.300L	0.300L	0.300L
3.	Methylene dichloride	0.150L	0.150L	0.150L	0.150L	0.150L
4.	Beta cyclodextrin	0.595kg	0.595kg	0.595kg	0.595kg	0.595kg
5.	Croscarmellose Sodium	0.100kg	0.100kg	0.100kg	0.100kg	0.095kg
6.	Crospovidone	0.0625kg	0.0625kg	0.0645kg	0.0625kg	0.0625kg
7.	Povidone (k30)	0.025kg	0.027kg	0.023kg	0.023kg	0.030kg
8.	Magnesium stearate	0.012kg	0.012kg	0.012kg	0.012kg	0.012kg
9.	Sodium starch glycolate	0.037kg	0.037kg	0.037kg	0.037kg	0.037kg
10.	Colloidal silicon dioxide (Aerosil)	0.0075kg	0.0075kg	0.0075kg	0.0075kg	0.0075kg
11.	Talcum	0.012kg	0.012kg	0.012kg	0.012kg	0.012kg

Procedure: The method used to formulate the Nebivolol HCL is wet granulation method. Dispense all the ingredients as per the batch size for formulation F1. Shift Nebivolol HCL, betacyclodextrin, croscarmellose sodium, crospovidone, povidone (k30) through mesh size (#) 30 separately. Mix above ingredients geometrically ratio and blend for 15mins in a Ribbon mixer add solvents are Isopropyl alcohol, methylene dichloride on above mixer. The above mixer load on tray dryer for drying1hr. After add lubricants are magnesium stearate, talcum and disintegrant agent is colloidal silicon dioxide. Shift the above granules sieve on 20# mesh size. Finally sieve lubrications materials 30# mesh size and add above granule thoroughly mix in the cone blender. The ingredient ratios of excipients Immediate release formulation of Nebivolol HCL in table 1.

4.4 Evaluation of Nebivolol HCL

4.4.1 Description

For checking appearance of tabletstakeabout60tablets from are presentative sample.

4.4.2 Dimensions

Check the dimensions of tablets using a venire caliper. Take randomly 10 tablets from the representative sample and check individual tablet dimensions.

4.4.3 Hardness
Clean the hardness tester and put the tablet between the sliding plates of the Hardness Tester.

4.4.4 Friability
Weight accurately 20 tablets; put the tablets in the friability test apparatus. Adjust the timer to 4 minutes. Operate the apparatus and observe the tablet while rotating. No tablets should stick to the walls of the apparatus. If so, brush the walls with talcum powders. Take the tablets out and observe. No capping should be there. Weight the tablets.
% Friability = (W1-W2) X 100 / W1

4.4.5 Drug content (Assay by HPLC)
Test solution: Dissolve 30 mg of the substance under examination in 5 ml of acetonitrile and dilute to 100.0 ml with the mobile phase.

Reference solution (a): Dissolve 30 mg of nebivolol hydrochloride RS in 5 ml of acetonitrile and dilute to 100.0 ml with the mobile phase.

Reference solution (b): Dilute 1ml of reference solution (a) to 100.0ml with the mobile phase.

4.4.6 Chromatographic system (conditions)
A stainless steel column 25cm x 4.6mm, packed with porous silica with chemically bonded phenyl groups (5 um).
Mobile phase: a mixture of 28 volumes of acetonitrile, 72 volumes of a buffer solution prepared by dissolving 3.4 g of tetrabutyl ammonium hydrogen sulphate in 1000 ml of water and 0.3 volume of diethylamine.
Flow rate: 1 ml per minute, spectrophotometer set at 220 nm.
Injection volume: 20ul.

4.4.7 Dissolution study
- Medium : 500ml 0.1M hydrochloric acid
- Volume : 900ml
- Apparatus : Paddle
- Wavelength : 233nm
- RPM : 75
- Time : 30 min
- Temperature : 37±2°c

5. RESULTS AND DISCUSSION

5.1 Preformulation Studies of Nebivolol HCL.

Table 2: Preformulation Studies of Nebivolol HCL.

S. No	Parameters	F-1	F-2	F-3	F-4	F-5
1.	Loss on drying or water content% w/w	4.31	4.37	4.31	4.34	4.35
2.	Bulk density gm / ml	0.623	0.626	0.629	0.631	0.622
3.	Tapped density gm / ml	0.821	0.838	0.838	0.841	0.832
4.	Compressibility Index %	24.31	25.29	25.34	25.32	25.30
5.	Hausner's Ratio	1.29	1.31	1.30	1.31	1.29

5.2 Pre-Compression parameter sieve analysis study

Table 3: Pre-Compression parameter sieve analysis study.

S. No	Sieve. No	% Weight Retained	Cumulative% Weight Retained
1.	Sieve No.40	11.430	14.171
2.	Sieve No.60	16.111	30.282
3.	Sieve No.80	26.529	56.811
4.	Sieve No.100	29.313	86.124
5.	Sieve No.120	4.724	90.847
6.	Base Plate	9.152	100.000

5.3 Post-Compression parameter study

Table 4: Post-Compression study.

S. No	Parameters	F1	F2	F3	F4	F5
1.	Description	White to off white colored, oblong shape tablets	White to off white colored, oblong shape tablets	White to off white colored, oblong shape tablets	White to off white colored, oblong shape tablets	White to off white colored, oblong shape tablets
2.	Average weight	181.4mg	181.4mg	181.4mg	181.4mg	181.4mg
3.	Thickness	3.5mm	3.5mm	3.5mm	3.5mm	3.5mm
4.	Hardness	6kg/cm²	6kg/cm²	6kg/cm²	6kg/cm²	6kg/cm²
5.	Disintegration time	35 sec	47 sec	40 sec	40 sec	36 sec
6.	Dissolution: Nebivolol HCL	85.37%	82.37%	81.37%	82.44%	80.45%
7.	Assay Nebivolol HCL	97.74% 2.4mg	97.73% 2.4mg	96.76% 2.4mg	94.72% 2.4mg	90.31% 2.4mg

5.4 Stability study

Table 5: Stability Study of Nebivolol HCL.

Formulation	Hardness Test	Thickness	Friability %	Disintegration Time	Mean of % dissolved
F1	6kg/cm2	3.5mm	4	35 sec	Not less than 70%

Table 6: Cumulative % drug release.

Formulations	Immediate release of Drug	Time (mins)	Limit	Amount of drug release	Cumulative %drug release
F1	NEBIVOLOL HCL	30 mins	NLT70%	2.13mg	85.37%

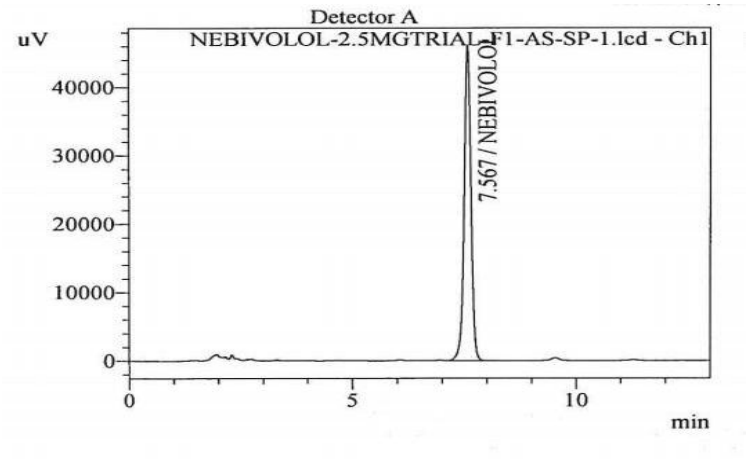

Fig. 3: Assay for Standard (HPLC).

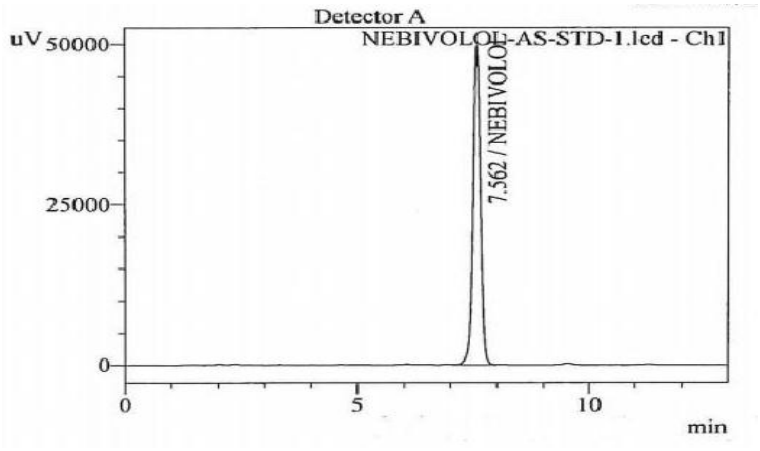

Fig. 4: Assay for Sample (HPLC).

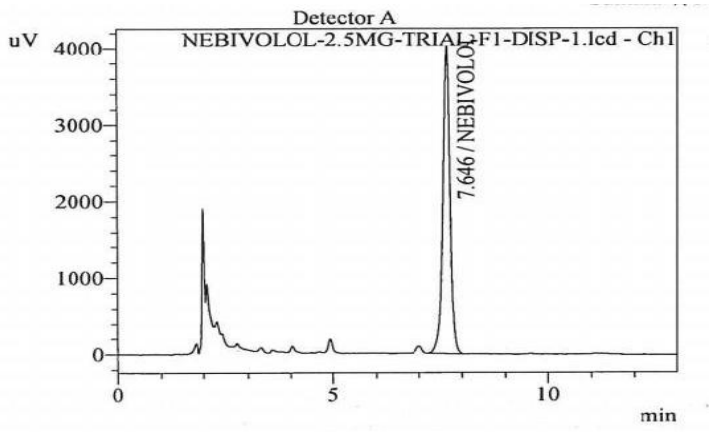

Fig. 5: Dissolution Graph (HPLC).

Table 7: Dissolution Rate of Nebivolol HCL.

Time (mins)	Drug Release In %
10	62.87
20	76.45
30	85.37
40	96.21

6. CONCLUSION

The study on the formulation and evaluation of a fixed-dose combination tablet of Nebivolol HCL for the management of high blood pressure focused on developing an immediate-release (IR) formulation. Nebivolol HCL 2.5 mg was used as the active ingredient in the immediate-release layer, which was prepared using Croscarmellose sodium through a direct compression technique. The powder blends for the formulation met the pharmacopeial specifications, with good flow and compressibility.

The formulation F1, which exhibited the highest in vitro release (85.37%) of Nebivolol HCL within 30 minutes, was selected for tablet preparation. This formulation is expected to improve patient compliance by offering a fixed-dose combination tablet with an enhanced dosing frequency and bioavailability, which is crucial in managing high blood pressure effectively.

The dissolution profile and stability studies for the formulated tablet adhered to ICH guidelines in the initial two months, with further studies currently ongoing. Following successful stability studies, bioequivalence trials should be conducted. If the results of these trials are positive, the developed product could be introduced to the market, potentially offering a more convenient treatment option for patients managing hypertension.

This study highlights the potential benefits of fixed-dose combination tablets in enhancing therapeutic outcomes for hypertension, particularly through improved formulation design and patient adherence.

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