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Formulation And Evaluation Of Nebivolol Film Coated Tablets

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This study focuses on the formulation and evaluation of Nebivolol film-coated tablets to address the challenges associated with poor aqueous solubility and environmental susceptibility of the drug. Nebivolol, a third-generation beta-blocker with unique nitric oxide-mediated vasodilatory properties, was formulated using wet granulation followed by film coating with Opadry Yellow. Preformulation studies, including FTIR analysis, confirmed drug-excipient compatibility and chemical stability. Calibration curves in 0.1N HCl (pH 1.2) and phosphate buffer (pH 6.8) showed a linear relationship between concentration and absorbance, validating the UV spectrophotometric method for drug quantification. Micromeritic evaluations indicated good flowability and compressibility of the blends. Among the tested formulations, F5 demonstrated superior dissolution characteristics with a cumulative drug release of 98% in 120 minutes, making it the optimized formulation. The results confirm that the developed Nebivolol film-coated tablets meet pharmaceutical standards and offer improved bioavailability and patient compliance.

Keywords: Nebivolol, FTIR, Beta blockers, Excipients.

Introduction

Hypertension, commonly referred to as high blood pressure, is one of the most significant global risk factors for cardiovascular diseases (CVDs). It is often termed a "silent killer" due to its asymptomatic nature in the early stages, leading many individuals to remain undiagnosed until severe complications arise (Sundström et al., 2018). If left untreated, hypertension can cause life-threatening conditions such as stroke, myocardial infarction, heart failure, and chronic kidney disease (James et al., 2014). Managing hypertension effectively is critical in reducing morbidity and mortality rates associated with CVDs. Current therapeutic strategies involve both lifestyle modifications, such as dietary changes, regular exercise, and stress management, as well as pharmacological treatments. Among the various antihypertensive drug classes, beta-blockers remain a cornerstone in hypertension management due to their effectiveness in lowering blood pressure and reducing the risk of cardiovascular events (Williams et al., 2018).

Nebivolol is a third-generation beta-1 adrenergic blocker that distinguishes itself from traditional beta-blockers due to its highly selective action and additional vasodilatory properties. Unlike older beta-blockers, such as propranolol and atenolol, which mainly function by reducing heart rate and myocardial contractility, Nebivolol exerts a dual mechanism of action. It not only blocks beta-1 adrenergic receptors but also promotes nitric oxide (NO)-mediated vasodilation, leading to improved endothelial function and reduced peripheral vascular resistance (Ignarro et al., 2002). This nitric oxide-mediated effect has been found to contribute to superior cardiovascular protection and improved tolerability in patients with hypertension, especially in those with comorbid conditions such as diabetes or metabolic syndrome (Tzemos et al., 2001). Furthermore, Nebivolol is associated with fewer adverse metabolic effects compared to conventional beta-blockers, making it a favorable option for long-term use (Reynaud et al., 2013).

Despite its advantages, Nebivolol faces several formulation challenges that can impact its efficacy and patient compliance. One major challenge is its poor aqueous solubility. Classified as a Biopharmaceutical Classification System (BCS) Class II drug, Nebivolol exhibits low solubility but high permeability, which can hinder its bioavailability and absorption in the gastrointestinal tract (Amidon et al., 1995). To enhance its dissolution rate and bioavailability, various formulation approaches, such as the use of solid dispersions, nanoparticle technology, and inclusion complexes with cyclodextrins, have been explored (Patel et al., 2019).

Another key challenge is its susceptibility to degradation. Nebivolol is sensitive to environmental factors such as light, heat, and humidity, which can lead to loss of potency and reduced therapeutic effectiveness over time (Gowda et al., 2017). To counteract these stability issues, pharmaceutical manufacturers implement protective packaging, proper storage conditions, and formulation techniques such as the incorporation of stabilizers and antioxidants (Deveswaran et al., 2012).

Patient compliance is another crucial factor in the effectiveness of Nebivolol therapy. Conventional oral dosage forms, such as tablets and capsules, may present difficulties for certain patient populations, including the elderly and those with dysphagia (swallowing difficulties) (Nunn & Williams, 2005). Consequently, alternative dosage forms, such as orally disintegrating tablets (ODTs) and liquid formulations, have been investigated to improve patient adherence and ease of administration (Saurabh & Harsoliya, 2011).

Film coating is a widely employed pharmaceutical technology that plays a crucial role in overcoming many of the challenges associated with solid dosage forms. A film-coated tablet consists of a thin polymeric layer applied to the tablet surface, offering multiple benefits (Felton, 2013).

One of the primary advantages of film coating is improved stability. The coating acts as a protective barrier, shielding the active pharmaceutical ingredient (API) from environmental factors such as moisture, heat, and light, which could otherwise lead to degradation and loss of potency (Zhang et al., 2018). Additionally, film coatings enhance the palatability of oral medications by masking unpleasant tastes and odors, which can improve patient adherence, particularly in pediatric and geriatric populations (Ishida et al., 2008).

Another significant advantage is controlled drug release. Modified-release film coatings, such as enteric

coatings and sustained-release formulations, allow for precise drug release kinetics, ensuring consistent plasma drug concentrations and minimizing fluctuations that could lead to side effects (Wen et al., 2010). This is particularly beneficial for drugs like Nebivolol, where maintaining stable plasma levels is essential for optimal therapeutic outcomes.

Moreover, film coatings enhance the aesthetic appeal and branding of pharmaceutical products. By incorporating specific colors, imprints, and unique finishes, manufacturers can improve product differentiation and reduce medication errors, ensuring patients receive the correct medication (Markl & Zeitler, 2017).

Methodology

Materials

The following materials were used in the formulation of Nebivolol film-coated tablets:

Active Pharmaceutical Ingredient (API): Nebivolol Hydrochloride

Excipients: Microcrystalline Cellulose (MCC), Lactose Monohydrate, Polyvinylpyrrolidone (PVP K30), Cross-linked Sodium Carboxymethylcellulose (Croscarmellose Sodium), Magnesium Stearate, and Talc

Coating Agents: Hydroxypropyl Methylcellulose (HPMC), Titanium Dioxide (Coloring Agent)

Solvents: Purified Water and Isopropyl Alcohol

Finding Nebivolols absorption maxima (λ-max)

Nebivolol standard solutions (10 µg/ml) were prepared in 0.1 N HCl, pH 6.8, and pH 7.4 phosphate buffer. The prepared solutions were scanned using a UV spectrophotometer to determine the absorption maxima (λ-max) (Patel, N et.al 2012)

Nebivolol Standard Plot Preparation in 0.1N HCl (pH 1.2)

A stock solution of Nebivolol was prepared at a concentration of 100 µg/ml by dissolving 10 mg of Nebivolol in 100 ml of 0.1 N HCl. This stock solution was appropriately diluted to obtain graded solutions in the 10–80 µg/ml range. The absorbance of each solution was measured using a UV spectrophotometer at a wavelength corresponding to its absorption maxima (λ-max). The results are presented in the following table and figure, highlighting its pharmacological relevance and potential for physicochemical improvement. (Patel, N et.al 2012)

Preparation of Standard Plot in Phosphate Buffer (pH 6.8)

A stock solution of Nebivolol was prepared by dissolving 10 mg of Nebivolol in 100 ml of pH 6.8 phosphate buffer, resulting in a concentration of 100 µg/ml. This stock solution was appropriately diluted to obtain graded solutions in the 10–80 µg/ml range. The absorbance of each solution was measured using a UV spectrophotometer at a wavelength corresponding to its absorption maxima (λ-max). (Patel, N et.al 2012)

Preformulation Study of Nebivolol

Preformulation investigations were carried out to determine the physical and chemical properties of Nebivolol before formulation development. The characteristics of the selected model drug play a crucial role in influencing the formulation's loading efficiency, compatibility, pharmacokinetic response, and overall formulation strategy.

Preformulation studies serve as essential steps in developing a stable, safe, and effective dosage form. The drug was evaluated based on the following parameters.

FTIR Analysis:

FTIR studies were conducted to assess the compatibility of the pure API with excipients used in the formulation. The analysis was performed by preparing KBr pellets of the drug and the optimized formulation, followed by scanning in the 4000–400 cm^{-1} range using an FTIR spectrophotometer. The obtained spectra were analyzed to detect any possible interactions or changes in functional groups. This study helps ensure the stability and compatibility of the drug with excipients before formulation development. (Gowda, D. V et. al 2010)

Physical Observation of Nebivolol

A small quantity of Nebivolol powder was placed on a white background sheet, and its physical state (e.g., powder, granules) and texture (e.g., fine, coarse) were observed and recorded. The sample was examined under natural daylight to determine its color (e.g., white, off-white, light yellow).

For odor evaluation, a small amount of the powder was transferred to a clean glass container, and the air above the container was gently wafted towards the nose to observe and document any characteristic odor (e.g., characteristic, odorless).

For taste assessment, a small amount of Nebivolol was dissolved in distilled water, and a small portion of the solution was tasted to record its taste profile (e.g., bitter, tasteless).

Determination of Solubility of Nebivolol

The solubility of Nebivolol was determined in distilled water, 0.1N HCl, and phosphate buffer (pH 6.8). An excess amount of the drug was added to a 25 ml volumetric flask containing 25 ml of the respective solvents. The flasks were agitated using a wrist shaker at room temperature for 24 hours over a period of two days.

Aliquots were withdrawn at specific intervals and filtered through Whatman filter paper. The filtrates were appropriately diluted with the respective solvents and analyzed using a UV spectrophotometer to determine the solubility of Nebivolol in each medium. (Patel H A 2011)

Partition Coefficient of Nebivolol

The partition coefficient of Nebivolol was determined using a 1:1 mixture of octanol and water in a separatory funnel. A known amount of Nebivolol was added to the mixture, which was then shaken vigorously for a specific duration to ensure thorough mixing of the two phases. The mixture was allowed to stand undisturbed until complete separation of the layers occurred.

The aqueous and octanol layers were carefully separated, and the concentration of Nebivolol in each layer was measured using a UV spectrophotometer. The partition coefficient (P) was calculated using the ratio of the concentration of Nebivolol in octanol to its concentration in water. (Shakeel, F. et. al. 2008)

Melting Point Determination of Nebivolol

The melting point of Nebivolol was determined using the capillary fusion method. A small quantity of the drug was placed in a capillary tube sealed at one end. The capillary tube containing the drug was then inserted into a melting point apparatus.

The temperature at which Nebivolol began to melt and transition into a liquid state was recorded as the melting point range. (Rechnitzer, L. A., & Tevebaugh, A. D. 1960).

Micromeritic Properties of Drug

1. Bulk Density (g/cm^3):

A specific amount of Nebivolol powder was weighed and transferred into a graduated cylinder without tapping. The volume (V_0) occupied by the powder was recorded. Bulk density was calculated using the formula: (Dawood, A et. al. 2021)

$$\text{Bulk Density} = \frac{\text{Weight of powder (g)}}{\text{Initial volume } (V_0)\ (\text{cm}^3)}$$

2. Tapped Density (g/cm^3):

Using the same sample in the graduated cylinder, the cylinder was mechanically tapped 100 times or until no further volume change was observed. The final volume (Vf) after tapping was recorded. Tapped density was calculated using the formula: (Patel, D. M.et.al. 2012)

$$\text{Tapped Density} = \frac{\text{Weight of powder (g)}}{\text{Final volume (Vf) (cm}^3\text{)}}$$

3. Hausner Ratio (HR):

The Hausner Ratio was determined using the equation: (Dawood, A et. al. 2021)

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

4. Carr's Index (CI):

The compressibility index (Carr's Index) was calculated using the formula: (Patel, D. M.et.al. 2012)

$$\text{Carr's Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

5. Angle of Repose (θ):

A sheet of paper was placed on a flat surface, and a funnel was fixed at a specific height (H) above the surface. Nebivolol powder was allowed to flow freely through the funnel to form a conical pile. The height (H) of the cone and the radius (R) of the base were measured, and the angle of repose was calculated using the formula: (Aulton, M. E. et.al. 2018)

$$\theta = \tan^{-1}\left(\frac{H}{R}\right)$$

These parameters were evaluated to assess the powder flow properties of Nebivolol.

Drug-Excipient Compatibility Study

The compatibility between Nebivolol and excipients was evaluated using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). These studies were performed to ensure no significant interactions occurred that could affect the stability and efficacy of the formulation.

Formulation of Nebivolol Film-Coated Tablet

Multiple batches were prepared to develop Nebivolol core tablets with the desired mechanical strength, friability, weight uniformity, content uniformity, and appearance. Wet granulation was used for the formulation of the Nebivolol film-coated tablet.

The required raw materials were accurately weighed using a precision weighing balance. Microcrystalline Cellulose (MCC), Nebivolol Hydrochloride, and Croscarmellose Sodium (CCS) were sifted using a 16# mesh sieve. Polyvinylpyrrolidone (PVP K30) was dissolved in an appropriate volume of filtered water and stirred until a clear binder solution was formed.

The sifted materials were blended for 10 minutes in a rapid mixer granulator (RMG). The prepared binder solution was then sprayed onto the dry mixed materials at an atomizing pressure of 1.0 to 2.0 kg/cm² over a period of 3–4 minutes to form a wet mass.

The wet mass was granulated and dried, followed by sieving through a 40# mesh to obtain uniform granules. The dried granules were then lubricated with Talc, Sodium Stearyl Fumarate, Microcrystalline Cellulose, and Croscarmellose Sodium. The final blend was mixed in a double-cone blender for 10 minutes to ensure uniformity. (Liew, K. B. et. al 2022) (Chaudhar S. P. et.al. 2015)

Preparation of Opadry Yellow Dispersion Solution for Nebivolol Tablets2015

In a mixing tank, 1000 mL of filtered water and 140 mg of Opadry Yellow were blended continuously for approximately 45 minutes to achieve uniform dispersion.

Before the coating process, the liquid suspension was passed through a 250-micron filter to remove any undissolved particles. During the coating application, the dispersion was continuously agitated to maintain uniformity and prevent settling of the coating materials. (Phutane, P. K et.al. 2023)

Film Coating of Nebivolol Tablets

The compressed Nebivolol tablets were transferred into a coating pan for the film coating process. The tablets were coated using the Opadry Yellow dispersion solution, ensuring uniform application.

The coating process was continued until the tablets achieved a 3 to 3.5% weight gain, which was set as the coating parameter. The coated tablets were then dried at an optimized temperature to ensure a smooth, uniform, and defect-free film while maintaining tablet integrity.

The coating parameters and conditions were maintained as per Table 2 for consistency across all batches.

Table 1 Composition of formulations F1 to F5 (in grams)

Sr. No.	Name of Ingredient and Supplier	F1	F2	F3	F4	F5
1	Nebivolol Hydrochloride	5	5	5	5	5
2	PVPK-30 (Polyvinylpyrrolidone)	18	20	19	18.5	19.5
3	Croscarmellose Sodium	75	80	73	71	74
4	Opadry Yellow	25	24	26	27	27
5	Sodium Stearyl Fumarate	19	21	18	19	20
6	Talc	16	17	17	17	17
7	Microcrystalline Cellulose (MCC)	85	78	82	80	76
Total	Tablet Weight (mg/tab)	250	250	250	250	250

Result & Discussion:

Figure1 FTIR of Pure Nebivolol

Figure 2 FTIR of Nebivolol Optimized formulation

The FTIR spectrum of pure Nebivolol displayed characteristic peaks corresponding to functional groups such as N-H stretching, C-H stretching, and C=O vibrations, confirming its structural integrity. In the optimized formulation, the FTIR spectrum retained the major peaks of Nebivolol without significant shifts or new peak formations, indicating the absence of major drug-excipient interactions. This confirms that Nebivolol remains chemically stable in the formulation, ensuring its compatibility with the selected excipients.

Table 2 solubility of Nebivolol in different solvents

Solvent	Solubility (mg/mL)
Distilled Water	~0.02 mg/mL
0.1N HCl	~0.85 mg/mL
Phosphate Buffer (pH 6.8)	~0.34 mg/mL

Table 3 Table Calibration curve for Nebivolol using 0.1N HCL

S. No	Concentration (µg/ml)	Absorbance
1	0	0.000

2	10	0.230 ± 0.012
3	20	0.442 ± 0.007
4	30	0.653± 0.014
5	40	0.882± 0.05
6	50	1.106± 0.022

(Mean ± SD, n = 3)

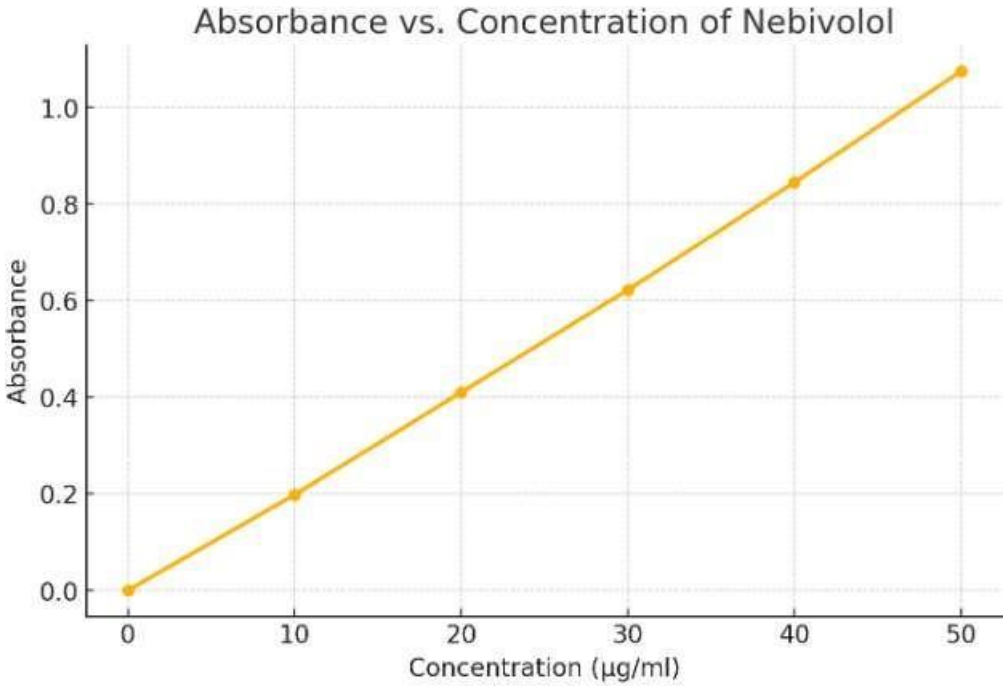


Figure 3 Standard curve of Nebivolol using 0.1N HCl (pH1.2)

The line graph illustrates the relationship between concentration (µg/ml) of Nebivolol and its absorbance measured using a UV spectrophotometer. The absorbance values show a linear increase with rising concentration, indicating that Nebivolol follows Beer-Lambert's law within the studied range. This suggests that the method is suitable for quantitative analysis, as the absorbance remains proportional to concentration. The consistency of the readings confirms the accuracy and reliability of the spectrophotometric method for Nebivolol estimation.

Table 4 Calibration Curve of Nebivolol Using Phosphate Buffer (pH 6.8)

S. No	Concentration (µg/ml)	Absorbance
1	0	0.000
2	10	0.247 ± 0.003
3	20	0.458 ± 0.009
4	30	0.652 ± 0.012
5	40	0.848 ± 0.011

6	50	1.052 ± 0.009

(Mean ± SD, n = 3)

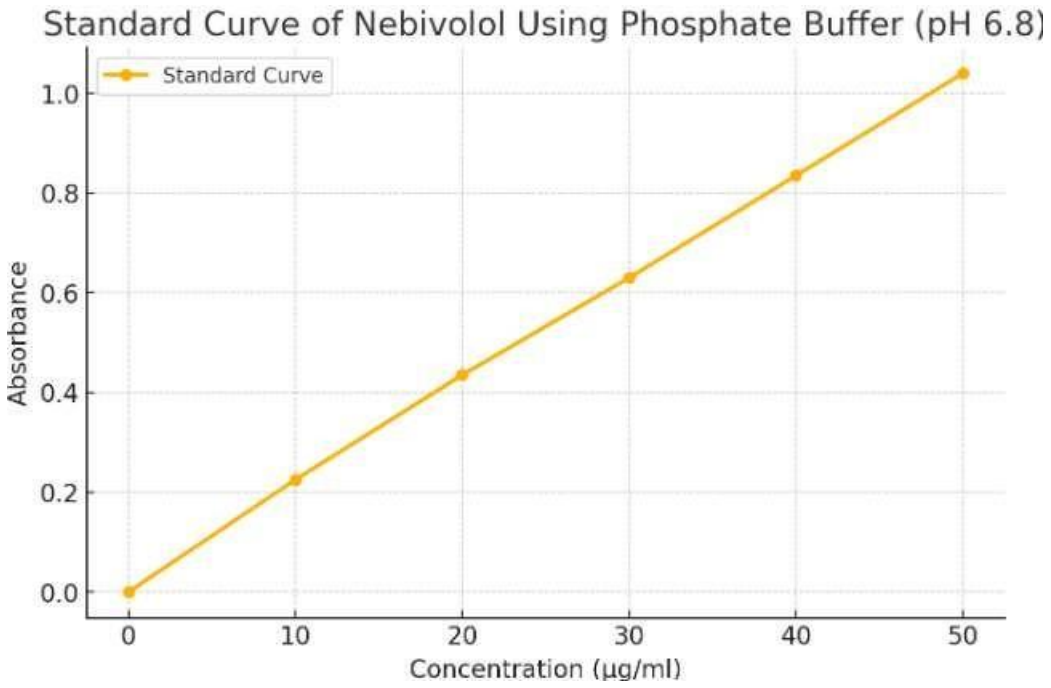


Figure 4 Standard Curve of Nebivolol Using Phosphate Buffeer (6.8)

The standard curve of Nebivolol in phosphate buffer (pH 6.8) demonstrates a linear relationship between concentration (µg/ml) and absorbance. The absorbance values increase proportionally with increasing drug concentration, indicating adherence to Beer-Lambert's law. This confirms the accuracy and reliability of the UV spectrophotometric method for the quantitative analysis of Nebivolol in phosphate buffer. The linearity of the curve ensures that this method can be effectively used for drug estimation in pharmaceutical formulations.

Table 5 Organoleptic Properties of Drug

S.No.	Drug	Test	Specification	Observation
1.	Nebivolol	Colour	A off-white crystalline powder.	A white to off-white crystalline powder.
2.	Nebivolol	Odour	Odourless	odourless

Table 6 Partition Coefficient of Telmisartan

S. N	Drug	Partition Coefficient (logP)

1	Telmisartan	2.22± 0.10

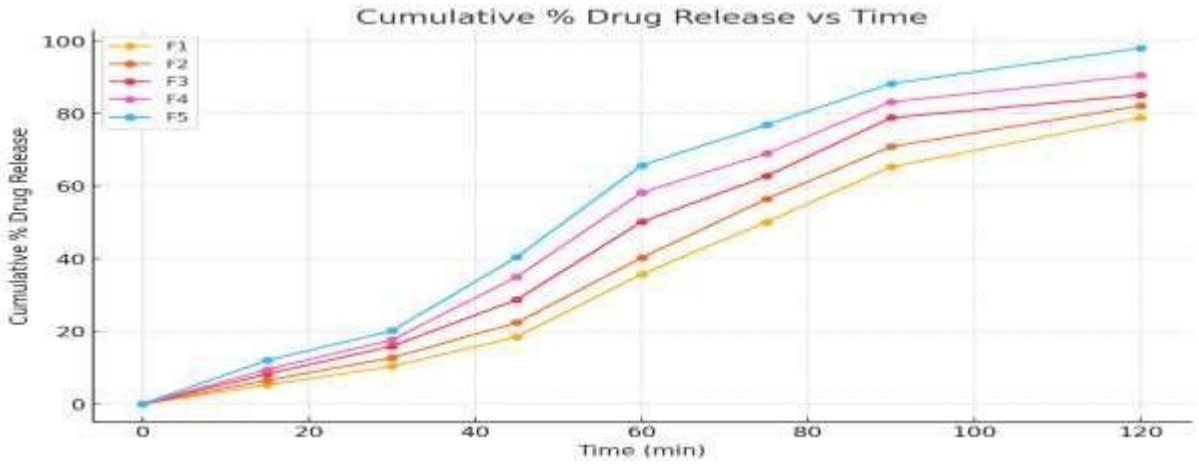
Table 7 Micromeritic Properties of Drug

Formulation Code	Bulk Density (gm/cm³)	Tapped Density (gm/cm³)	Hausner Ratio (HR)	Carr's Index (CI)	Angle of Repose (θ)
F1	0.45±0.02	0.58±0.03	0.88±0.12	12.20±0.25	26°·7'±0.90
F2	0.48±0.04	0.63±0.05	0.91±0.15	15.00±0.30	27°·5'±0.70
F3	0.43±0.03	0.61±0.04	1.02±0.11	13.75±0.35	28°·0'±0.50
F4	0.51±0.05	0.70±0.06	1.08±0.14	14.50±0.20	28°·9'±0.60
F5	0.46±0.02	0.65±0.03	1.04±0.13	14.10±0.25	29°·1'±0.45

The flow properties of formulations F1 to F5 were evaluated through parameters such as bulk density, tapped density, Hausner ratio, Carr's index, and angle of repose. The Hausner ratio values (0.88–1.10) and Carr's index (12.20–15.00%) indicate acceptable compressibility and flowability. The angle of repose values (26°·7'–29°·1') suggest that the formulations exhibit good to excellent flow properties. These results confirm that the prepared blends are suitable for tablet compression.

Table 8 % Cumulative Drug Release

Time in min	F1	F2	F3	F4	F5
0	0.00	0.00	0.00	0.00	0.00
15	5.25	6.50	8.25	9.50	12.00
30	10.35	12.75	15.90	17.65	20.15
45	18.50	22.40	28.75	35.00	40.50
60	35.75	40.25	50.15	58.25	65.75
75	50.12	56.45	62.75	68.95	76.85
90	65.30	70.90	78.85	83.20	88.25
120	78.85	82.15	85.10	90.50	98.00



Cumulative % of Drug Release

The graph illustrates the cumulative % drug release of formulations F1 to F5 over time. Formulation F5 demonstrated the highest release rate, reaching 98% at 120 minutes, indicating superior drug release characteristics. The other formulations, F1 to F4, showed progressively lower release profiles, with F1 having the slowest release. These differences may be attributed to variations in excipient composition,

which influenced the dissolution rate. The results suggest that F5 is the optimized formulation for achieving rapid and complete drug release.

Conclusion:

The study confirmed the successful formulation and evaluation of Nebivolol tablets with optimized properties. FTIR analysis validated the chemical stability of Nebivolol in its formulation, ensuring compatibility with excipients. The calibration curves in 0.1N HCl (pH 1.2) and phosphate buffer (pH 6.8) demonstrated a linear relationship between concentration and absorbance, confirming the reliability and accuracy of the UV spectrophotometric method for drug estimation.

The micromeritic properties indicated that all formulations (F1 to F5) possessed good flowability and compressibility, making them suitable for tablet compression. Among the formulations, F5 exhibited the highest cumulative drug release (98% at 120 minutes), making it the optimized formulation with superior dissolution and release characteristics. This suggests that F5 is highly effective for achieving rapid and complete drug release, meeting the desired pharmaceutical standards.

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