



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Research Article

Formulation Optimization and Evaluation of Floating Bilayer Tablets of Nebivolol HCL and Nateglinide for Enhanced Gastro-Retention

Piyush Bhatt*, Manika Panday, Dr. Vinod Rana

Department of Pharmaceutics, GRD (PG) IMT, Dehradun.

ARTICLE INFO

Published: 16 Oct 2026

Keywords:

Gastro-retention, Bilayer tablets, Nebivolol HCL, Nateglinide, Sustained release, Immediate release.

DOI:

10.5281/zenodo.23425046

ABSTRACT

Bilayer tablet technology has emerged as a versatile strategy for combining immediate-release and sustained-release profiles within a single dosage form, successfully overcoming the pharmacokinetic drawbacks of conventional single-layered systems. The primary objective of this study was to formulate, optimize, and evaluate a novel gastro-retentive floating bilayer tablet featuring an immediate-release layer of Nebivolol HCL and a sustained-release floating layer of Nateglinide. Tablets were prepared via wet granulation utilizing varying ratios of matrix-forming polymers (HPMC K4M, HPMC E15, HPMC E5) and gas-generating agents (sodium bicarbonate and citric acid). Post-compression evaluations confirmed that all batches complied with USP standards for weight variation, hardness, friability, and drug content. The optimized formulation (C3) demonstrated a rapid floating lag time of 65 seconds, prolonged buoyancy exceeding 12 hours, and a biphasic drug release pattern. In vitro dissolution data followed zero-order and Korsmeyer-Peppas kinetics, indicating non-Fickian diffusion mechanisms. Accelerated stability studies in accordance with ICH guidelines confirmed that batch C3 retained its physical integrity and release characteristics.

INTRODUCTION

Drugs can enter the body via various routes, including oral, submucosal (buccal and sublingual), parenteral, transdermal, and pulmonary administration. For systemic delivery, tablets—frequently referred to as "pharmaceutical powder compacts"—are the most widely used, practical, and preferred dosage form. They offer distinct advantages, including formulation

versatility, simplicity of administration, and high patient compliance. However, the effectiveness of oral drug delivery is heavily influenced by physiological factors such as gastric emptying, gastrointestinal transit time, drug release rates, and the primary site of absorption.(1,2,3)

Conventional dosage forms often cause wide fluctuations in plasma drug concentrations, resulting in poor clinical efficacy or undesirable

*Corresponding Author: Piyush Bhatt

Address: Department of Pharmaceutics, GRD (PG) IMT, Dehradun.

Email ✉: Piyushbhatt224@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



toxicity. To address these challenges, sustained- or controlled-release systems were developed to decrease dosing frequency, maintain consistent therapeutic levels, and enhance safety by localizing medication at the site of action. (4,5)

Over the past decade, combining two or more active pharmaceutical ingredients (APIs) into a single bilayer tablet has gained significant attention. Combination therapy aims to reduce dose-dependent side effects and improve patient outcomes through lower total drug dosages. Bilayer tablets successfully overcome the drawbacks of single-layer combination tablets by physically separating incompatible APIs and facilitating distinct, biphasic release profiles—such as combining an immediate-release layer with a sustained-release layer.(6,7)

MATERIALS AND METHOD

Materials and Purpose

Sr. No.	Materials	Purpose
1	Nateglinide	Sustained release drug
2	Nebivolol HCl	Immediate release drug
3	HPMC K4M	Release retardant polymer
4	HPMC E5	Film-forming / hydrophilic polymer
5	HPMC E15	Sustained release polymer
6	Carbopol	Swelling and mucoadhesive polymer
7	Sodium bicarbonate	Gas generating agent
8	Citric acid	Floating enhancer
9	Povidone (PVP K30)	Binder
10	Dicalcium phosphate	Diluent / Filler
11	Magnesium stearate	Lubricant
12	Talc	Glidant
13	Crospovidone	Superdisintegrant
14	Purified water / IPA	Granulating fluid

IMMEDIATE RELEASE LAYER (NEBIVOLOL HCL)

Materials:

- Nebivolol HCl
- Crospovidone (superdisintegrant)
- Dicalcium phosphate
- HPMC E5
- Povidone K30
- Magnesium stearate
- Talc
- Purified water / IPA

Purpose:

- This layer should break quickly.
- Fast Disintegration
- Rapid Nebivolol release

SUSTAINED FLOATING LAYER (NATEGLINIDE)

Materials:

- Nateglinide
- HPMC K4M
- HPMC K15M
- Carbopol
- Sodium bicarbonate
- Citric acid
- Povidone K30



- Magnesium stearate
- Talc
- Purified water / IPA

Purpose:

- HPMC → slow release
- Sodium bicarbonate + citric acid → floating
- Controlled Nateglinide release
- Floating behaviour
- Prolonged gastric residence

FORMULATION:

IMMEDIATE RELEASE LAYER (NEBIVOLOL HCL)

1. DISPENSING:

Weigh the All Raw Materials (API + Excipients)

- Nebivolol HCl
- Crospovidone
- Dicalcium Phosphate
- HPMC E5
- Povidone K30
- Magnesium Stearate
- Talc

2. SIFTING:

Sifting of Raw Materials through suitable sieve (#40/#60)

- Nebivolol HCl

- Crospovidone,
- Dicalcium Phosphate
- HPMC E5

3. DRY MIXING / BLENDING:

Mix:

- Drug
- Polymer
- Diluent

4. PREPARE BINDER SOLUTION:

Dissolve povidone in:

- Purified Water or
- IPA

5. WET GRANULATION:

Add Binder solution slowly to powder mix.

Mix until:

- Until uniform Dough-like wet mass form

6. WET SCREENING:

Pass wet mass through sieve #16 or #22

Wet granules formed.

7. DRYING

Dry granules:

- Tray dryer or
- Hot air oven

Temperature:



- 40–50°C

Until proper moisture removal.

8. MILLING/ SIZING:

Pass dried granules through sieve #20.

Uniform granules obtained

9. BLENDING:

Final Blending for uniform distribution Add:

- Magnesium stearate
- Talc

Mix gently

SUSTAINED FLOATING LAYER (NATEGLINIDE)

1. DISPENSING:

Weigh the All Raw Materials (API + Excipients)

- HPMC K4M
- HPMC K15M
- Carbopol
- Sodium Bicarbonate
- Citric Acid
- Povidone
- Magnesium
- Talc

2. SIFTING:

Sifting of Raw Materials through suitable sieve (#40/#60)

- Nateglinide

- HPMC K4M

- HPMC K15M

- Carbopol

- Sodium Bicarbonate

- Citric Acid

3. DRY MIXING / BLENDING:

Mix:

- Nateglinide
- HPMC K4M
- HPMC K15M
- Carbopol
- Sodium Bicarbonate
- Citric Acid

4. PREPARE BINDER SOLUTION:

Preparation of Binder Solution (Povidone in IPA / Purified Water)

5. WET GRANULATION:

Add Binder solution slowly to powder mix.

Mix until:

- Until uniform Dough-like wet mass form

6. WET SCREENING:

Pass wet mass through sieve (#16/#20)

7. DRYING



Dry granules:

- Tray dryer or
- Hot air oven

Temperature:

- 40–50°C

Until proper moisture removal.

8. MILLING/ SIZING:

Pass dried granules through sieve #20.

Uniform granules obtained

9. BLENDING:

Final Blending for uniform distribution Add:

- Magnesium stearate
- Talc

Mix gently.

COMPRESSION STAGE OF BILAYER GASTRO-RETENTIVE FLOATING TABLET

The floating Bilayer tablet was prepared by sequential compression technique.

- Preparation of Immediate Release Granules and Sustained Floating Granules
- Transfer of Prepared Granules to Separate Hopper Compartments

- Filling of Immediate Release Layer (Nebivolol HCl Layer) into Die Cavity
- Light Compression / Pre-compression of First Layer
- Addition of Sustained Floating Layer (Nateglinide Layer) over First Layer
- Final Compression using Bilayer Tablet Compression Machine
- Formation of Bilayer Floating Tablets
- Tablet Ejection from Die Cavity
- Collection and Visual Inspection of Tablets
- Evaluation of Bilayer Tablets

COMPRESSION PRINCIPLE

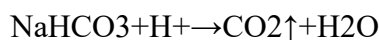
FIRST LAYER:

Immediate release layer is lightly compressed.

SECOND LAYER:

Sustained floating layer is added and final compression is applied to obtain bilayer tablet.

Floating Mechanism After Compression



List of Materials Used in the Formulation of Gastro-Retentive Floating Bilayer Tablets of Nebivolol HCl and Nateglinide

Sr. No	Ingredients	Function	C1	C2	C3	C4	C5	C6	C7	C8	C9
Sustained Release Floating Layer											
1	Nateglinide	Active drug	60	60	60	60	60	60	60	60	60
2	HPMC K4M	Release retardant / matrix forming polymer	50	100	150	–	–	–	150	100	50



3	HPMC E15	Release modifier / matrix forming polymer	150	100	50	50	100	150	–	–	–
4	HPMC E5	Low viscosity release modifier	–	–	–	150	100	50	50	100	150
5	Sodium Bicarbonate	Gas generating agent	100	100	100	100	100	100	100	100	100
6	Citric Acid	Floating enhancer / acidifying agent	50	50	50	50	50	50	50	50	50
7	Dicalcium Phosphate	Diluent	40	40	40	40	40	40	40	40	40
Total Weight of SR Layer (mg)			450	450	450	450	450	450	450	450	450
Immediate Release Layer											
8	Nebivolol HCl	Active drug	5	5	5	5	5	5	5	5	5
9	Crospovidone	Superdisintegrant	10	10	10	10	10	10	10	10	10
10	Dicalcium Phosphate	Diluent	30	30	30	30	30	30	30	30	30
11	Magnesium Stearate	Lubricant	3	3	3	3	3	3	3	3	3
12	Talc	Glidant	2	2	2	2	2	2	2	2	2
Total Weight of IR Layer (mg)			50	50	50	50	50	50	50	50	50
Total Tablet Weight (mg)			500	500	500	500	500	500	500	500	500

POST-COMPRESSION EVALUATION OF BILAYER TABLETS

1. GENERAL APPEARANCE:

For a tablet to be accepted by customers, its overall "elegance," visual identity, and general look are crucial. includes the tablet's dimensions, shape, colour, taste, odour, surface texture, physical defects, and the consistency and readability of any identifying markings...^(08,09)

2. SIZE AND SHAPE:

The compressed tablets' dimensions and form were assessed using a magnifying lens.^(08,09)

3. TABLET THICKNESS:

Tablet thickness is a crucial feature for both counting with filling equipment and duplicating look. Certain filling machines use the tablets' consistent thickness as a counting mechanism. A micrometer was used to measure the thickness of ten pills.⁽¹⁰⁾

4. FRIABILITY TEST:

The Roche friabilator was used to assess the tablets' friability. The percentage (%) is used to express it. Twenty pills were put into a friabilator after being first weighed (w₀ initial). The friabilator was run up to 100 revolutions or at 25 rpm for four minutes. Once more, the pills were weighed (w).⁽¹¹⁾

Percentage of Friability:

Initial weight = Final Weight (After Friability) / Initial Weight X 100

Limit: Percentage friability of tablets less than 1% is considered acceptable.

5. WEIGHT VARIATION TEST:

The average weight of twenty randomly chosen pills was calculated. None of the individual weights differ from the average weight by more than twice the percentage, and no more than two deviate by more than the percentage shown in the



table. The table displays the approved USP limits for tablet percentage variation. ^(12,13)

6. SWELLING STUDIES:

The tablet's swelling property was assessed by submerging it in 900 ml of 0.1 N HCl at 37 ± 2 °C in the dissolving test device. By regularly removing the tablets from the dissolving media, the weight and volume that the matrix tablets attained over time were ascertained. After the pills were lightly blotted with tissue paper to eliminate any remaining test liquid, they were weighed on an analytical scale. Taking into account a right circular cylinder shape, the thickness and diameter of the tablets were measured to determine their volume. The tablet density during the dissolving research was computed using the determined weight and volume. The equation was used to express swelling properties as a percentage of water absorption (WU%). ^(14,15)

$$\text{WU \%} = \frac{\text{Wt. of swollen tablet} - \text{Initial wt. of tablet}}{\text{Initial wt. of tablet}} \times 100.$$

7. HARDNESS (Crushing Strength):

The hardness of a tablet determines how resistant it is to capping, abrasion, or breaking during handling, storage, and transit. When a coil spring's force is applied diametrically to a tablet, the Monsanto hardness tester calculates the force needed to shatter the tablet. The diametrically applied force needed to shatter the pill is measured using the Strong-Cobb Pfizer and Schleuniger device. Determinations of hardness, which is now more accurately referred to as crushing strength, are made during tablet manufacture and are used to assess if the tablet machine's pressure has to be adjusted.

If the tablet is too soft, it might not be able to resist handling during further processing, such as

coating or packaging and shipping operations; if it is too hard, it might not dissolve in the time needed to fulfill the dissolving standards. A crushing strength of 4 kg is typically regarded as the minimum for acceptable tablets, and the force needed to shatter the tablet is measured in kilograms. While hypodermic and chewable tablets are typically significantly softer (3 kg) and certain extended release tablets are substantially harder (10–20 kg), oral pills typically have a hardness of 4–10 kg. Hardness often rises with regular tablet storage and is influenced by the form, chemical makeup, and binding agent. ⁽¹⁶⁾

8. DISINTEGRATION TEST:

Tablet disintegration time is typically measured using a disintegration test device. One pill is put in each tube for the disintegration time, and the basket arch is placed in a 1-liter beaker with water at $37^\circ\text{C} \pm 2^\circ\text{C}$. The basket assembly is moved up and down using a typical motor-driven mechanism. All tablets must dissolve and all particles must pass through the 10 mesh in the allotted period in order to meet USP standards. ^(17,18)

9. DISSOLUTION STUDIES:

Since the usual stomach emptying duration is around two hours, drug release investigations are conducted using USP dissolution test equipment I at 100 rpm, $37 \pm 0.5^\circ\text{C}$, and pH 1.2 buffer (900 ml) (i.e., 0.1 N HCl) for two hours. The experiment was carried out for an additional ten hours when pH 6.8 phosphate buffer (900 ml) was substituted for the dissolving medium. A UV spectrophotometer with a multi-component mode of analysis is used to examine the samples removed during the dissolution test. ^(19,20)

10. STABILITY STUDY:



According to ICH criteria for expedited research, the bilayer tablets are packaged appropriately and kept under the following circumstances for a certain amount of time. After 15 days, the tablets were taken out and examined for drug content and physical characteristics such as hardness, friability, dissolution, and visual flaws. The kinetics of deterioration are ascertained by fitting the collected data into first-order equations. The Arrhenius equation is used to visualize accelerated stability data in order to calculate the shelf life at 25°C.^(21,22)

Study	Storage Condition	Minimum time period covered by at submission
Long term study	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate study	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated study	40°C ± 2°C/75% RH ± 5% RH	6 months

RESULT AND DISCUSSION

PREFORMULATION STUDIES:

Preformulation studies are an essential initial step in the development of pharmaceutical dosage forms. These studies involve the systematic investigation of the physical, chemical, and physicochemical properties of drug substances before formulation development. The primary objective of preformulation is to generate relevant information regarding the drug's characteristics, stability, solubility, compatibility, and processing behaviour to facilitate the development of a safe, effective, and stable pharmaceutical formulation. Various parameters, including organoleptic properties, particle size, melting point, solubility, pH, flow properties, bulk density, tapped density, compressibility index, and Hausner's ratio, may be evaluated depending on the nature of the drug and the intended dosage form. Furthermore, drug-excipient compatibility studies are performed to identify potential interactions that could affect the stability, performance, or quality of the final product. The findings obtained from preformulation studies help in selecting suitable excipients, establishing appropriate manufacturing procedures, and optimizing formulation composition. Therefore, preformulation studies provide a scientific foundation for subsequent formulation development and evaluation.

Table : Preformulation Characteristics of Nebivolol HCl and Nateglinide

Sr.no.	Parameter	Nebivolol HCl	Nateglinide
1.	Colour	White to off-white	White to pale white
2.	Odour	Odourless	Odourless
3.	Appearance	Crystalline powder	Crystalline powder
4.	Taste	Slightly bitter	Slightly bitter
5.	Particle Size (µm)	85.4 ± 2.1	112.7 ± 3.4
6.	Angle of Repose (°)	27.4	29.8
7.	Bulk Density (g/mL)	0.42	0.39
8.	Tapped Density (g/mL)	0.49	0.47
9.	Compressibility Index (Carr's Index) (%)	14.28	17.02
10.	Hausner's Ratio	1.16	1.2
11.	Flow Property	Good	Fair to good
12.	Moisture Sorption Capacity (%)	2.1 ± 0.1	2.1 ± 0.1

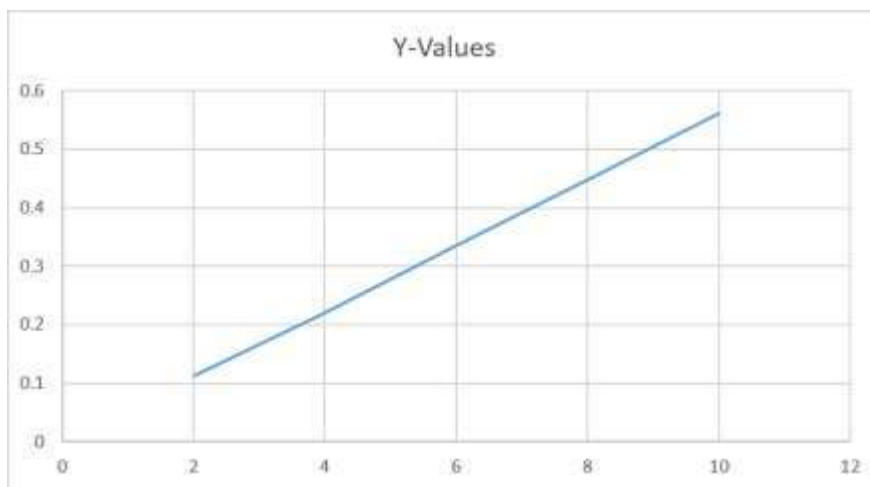


CALIBRATION CURVE:

Solvent: 0.1 N HCl λ_{max} : 281 nm

Nebivolol HCl Calibration Curve

Concentration ($\mu\text{g/ml}$) – Absorbance



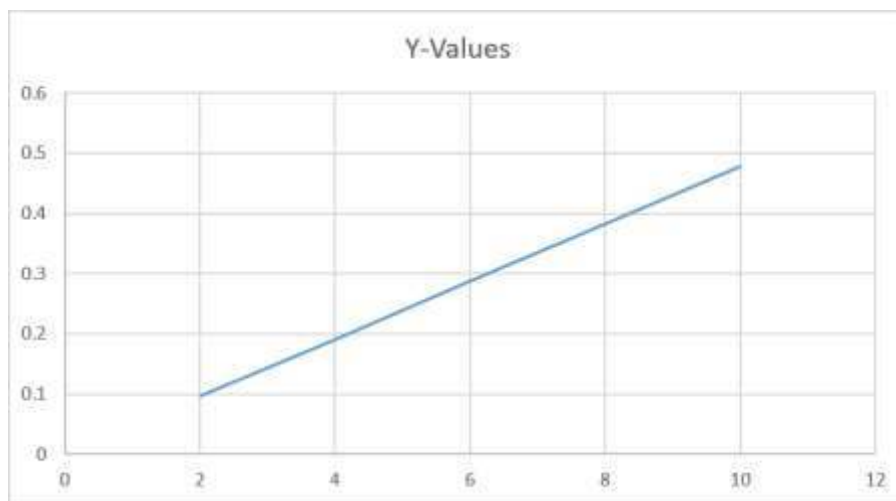
Regression equation: $y = 0.056x + 0.001$

Solvent: Phosphate Buffer pH 6.8 λ_{max} : 210 nm

$R^2 = 0.999$

Concentration ($\mu\text{g/ml}$) – Absorbance

Nateglinide Calibration Curve



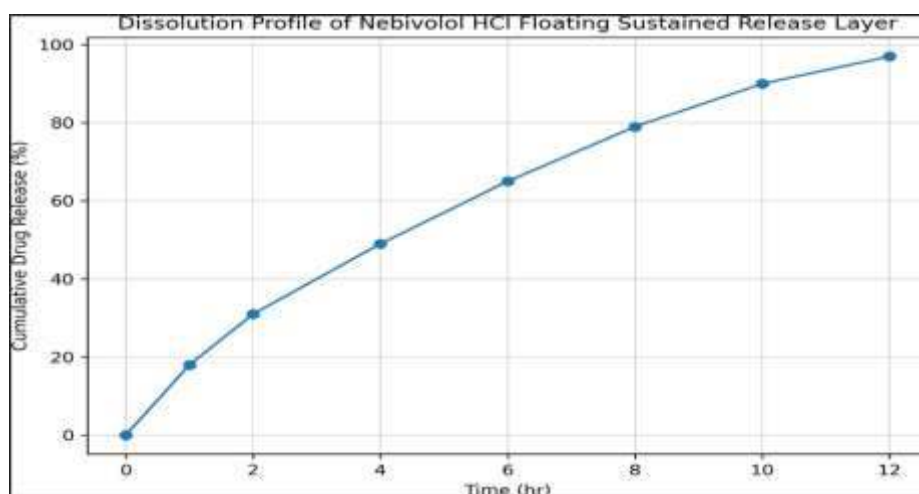
Regression equation: $y = 0.0478x + 0.0003$

The purpose of the dissolving research was to assess the bilayer gastro-retentive floating tablet formulation's drug release behaviour.

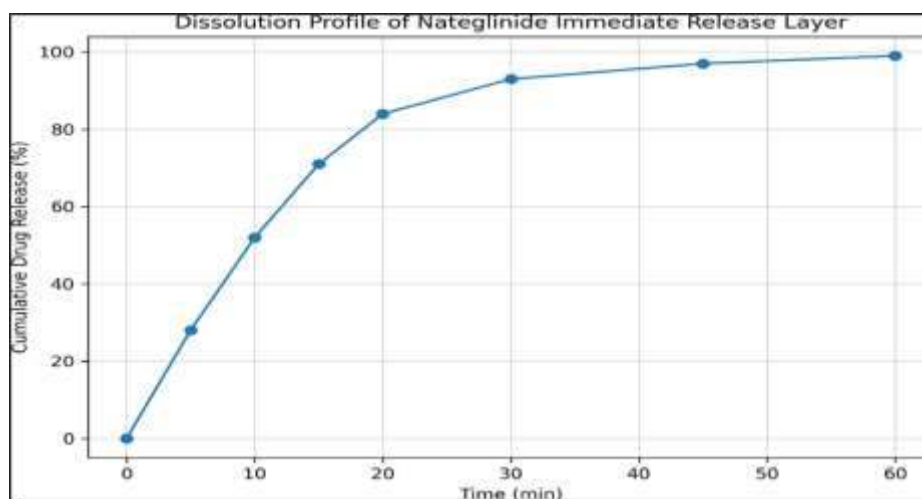
$R^2 = 0.999$

Dissolution Profile Study

1. Nateglinide Immediate Release Layer



2. Nebivolol HCl Floating Sustained Release Layer



Floating Behavior Study

The floating lag time and total floating time in 0.1 N HCl were used to assess the floating behavior of gastro-retentive bilayer tablets. Better gastro-retentive function is indicated by a longer floating duration and a lower floating lag time.

Batch	Floating Lag Time (sec)	Total Floating Time (hr)
F1	92	7.5
F2	78	8.0
F3	65	8.8
F4	58	9.5
F5	46	10.2
F6	39	11.0
F7	32	11.5
F8	28	12.0
F9	24	12.0

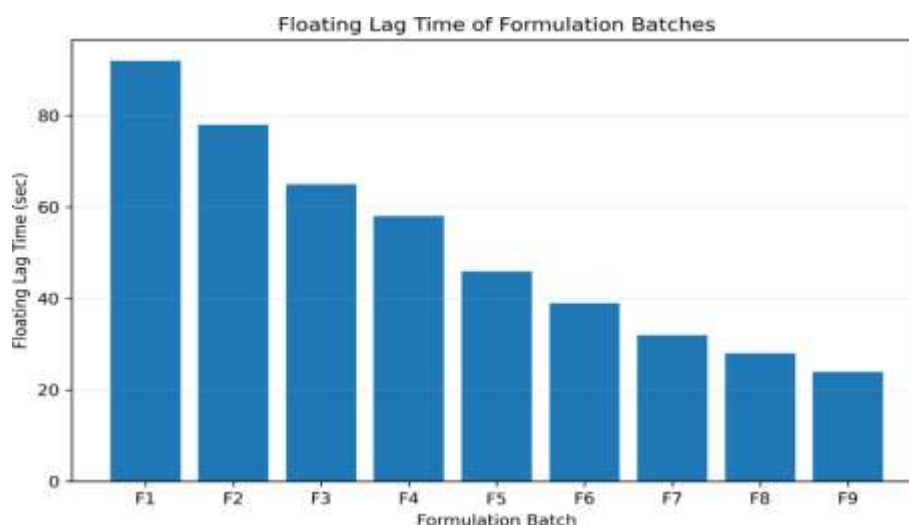


Figure. Floating Lag Time

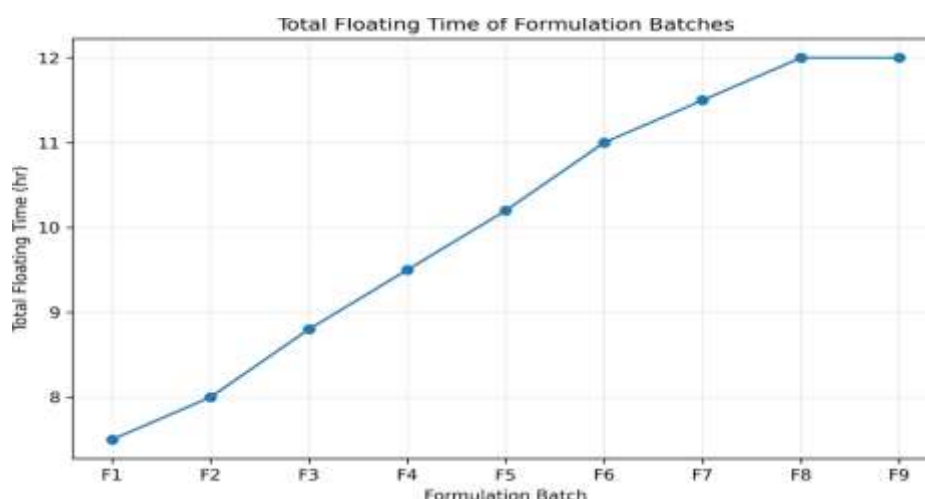


Figure. Total Floating Time

Interpretation

Over the course of the formulation batches, the overall floating time grew while the floating lag time gradually reduced. This might be because of increased polymer concentration and effective gas production from citric acid and sodium bicarbonate. The batch that was optimized demonstrated quick buoyancy and continued to float for up to 12 hours.

CONCLUSION

Bilayer tablets including both an immediate release layer and a sustained release layer were successfully produced for nateglinide and

Nebivolol. It was discovered that release adhered to zero, Krossmayer-Peppas models. Every formulation batch that was examined for physical characteristics such as drug content, hardness, friability, and weight fluctuation was determined to be within the USP standards. The enhanced formulations were found to be stable across all stability parameters. No discernible change in drug release was seen during stability tests, suggesting that formulation batch C3 was stable under the selected conditions for three months. The medication release profile was improved by the optimized formulation C3. An intriguing polymer mixture for making SR matrix tablets is a combination of HPMC K4M and HPMC E5.



REFERENCES

- Manjula, A., Selvam, P., Nirmal, R and Shakilabanu, S. In vitro evaluation studies of cross-linked chitosan microspheres containing rabeprazole sodium. *Int J Pharm Sci Res* 2011, 2(6):1513-
- Abdul, S., Poddar, S. S. A flexible technology for modified release of drugs: multi layered tablets. *J. Control. Release* 97, published 2004, 393–405.
- Rohilla, A., Dahiya, A., Rohilla, S., Khan, M. U. Gastroretentive dosage forms: Review on floating drug delivery systems. *Int Res J Pharm*, 2011; 2(5):72-78.
- Nilawar, P.S., Wankhade, V.P., Badnag, D. B. An emerging trend on bilayer tablets. *Int J Pharm & Pha Scie Res* 2013; 3(1): 15-21.
- Reddy, P.T., Rao, D.V., Kumar, R. K. Bi-layer technology- an emerging trend: a review. *Int. J. Res. Dev. Pharm. L. Sci.* 2013, 2(3): 404-411.
- Mohideen, S., et al. Development and evaluation of two layered tablet of glimepiride and metformin hydrochloride for the treatment of hyperglycemia. *Int J Bio.* 2011; 2(1): 31-35.
- Chien, Y. W. Fundamentals of controlled-release of drug administration in: J. Swarbrick (Ed.), *Novel Drug Delivery System* Marcel Dekker, New York, 1982, pp. 465–574.
- Singh, B.N., Kim, K.H. Floating drug delivery systems an approach to oral controlled drug delivery via gastric retention. *J Control Release*. 2000; 63: 235-259.
- Shirwalkar, A.A., Kumar, S.M., Jacob, S. Recent developments in floating drug delivery systems for gastric retention of drugs, an overview. *Indian drugs*. 2006;43(9): 697-704.
- Bagde, S.B., Bakde, B.V., Channawar, M.A. Chandewar AV. Formulation and evaluation of bilayer tablet of Metoprolol succinate and Ramipril. *Int J Pharm Pharm Sci*. 2011;3(4):174-178.
- Pandey, S., Niraj, Gupta, M.M., Chauhan, B. S. Bilayer Tablets: Recent Trends In Oral Drug Delivery With Present And Future Prospects. *Int J Uni Pharm & Bio Sci*. 2013; 2(3):360-378.
- Noor, A.V., et al. Formulation design, characterisation and in vitro evaluation of bilayered tablets containing Telmisartan and Hydrochlorthizide. *Int J Biopharm.* 2013; 4(1): 1-9.
- Bakka, A., Teja, G. K. Design And Evaluation Of Bilayered Tablets To Treat Respiratory Tract Infections , *Int J Pharm Pharm Sci*. 2013; 5(1):250-255.
- Chaudhari, S., Bawaskar, M., Shirsat, A. Formulation And Evaluation Of Bilayer Floating Tablet Of Carvedilol Phosphate. *J Drug Del & Ther.* 2012;2(5):9-19.
- Kasid, I., Saleem, M.A., Rozeena, P., Nikhat, P., Aijaz, A.S. Development Of Bilayer Tablets Of Lisinopril Gliclazide: In Vitro And In Vivo Evaluation. *Der Pharmacia Lettre*. 2013;5 (2):54-62.
- Podczeck, F., Drake, K.R., Newton. J.M., Haririan, I. The strength of bilayered tablets. *Eur J Pharm Sci* . 2006; 29:361–366.
- Patidar, R., Choukse, R., Agrawal, S., Patidar, A. Formulation and Development of Bilayer Tablet Containing Telmisartan and Indapamide. *IJDDHR*. 2012; 2(4): 516-520.
- Indhumathi, D., Mastan, V.S., Priyadharshini, N., Damodharan, N. Formulation And Evaluation Of Bilayer Tablet Of Conventional Release Paracetamol And Modified Release Diclofenac Sodium. *IJRPB*. 2013;1(5): 676 - 678.
- Purohit, R., Naruka, P.S., Chauhan, C. S., Bhatt, D. Formulation, Development And Evaluation Of Bilayer Tablet Of Nebivolol And Indapamide. *IAJ P R*. 2013; 3 (7):5105-5117.
- Mohan, A., Vaishali, T. Formulation And Evaluation Of Immediate Release And Sustained Release Bilayer Tablets Of Tramadol Hydrochloride, *AJADD* .2013 ;1(4):435-442.
- Sharma, A., Deb, P., Dash, S. Bilayer Tablet And Duredas Technology – A Review. *IJPBS*. 2013; 3 (2):554-563.
- Chitra, K.S., Nalini., G, Sachin, S.N. International Journal Of Pharmaceutical,



Chemical And Biological Sciences. IJPCBS
.2013; 3(1): 107-112.

HOW TO CITE: Piyush Bhatt, Manika Panday, Dr. Vinod Rana, Formulation Optimization and Evaluation of Floating Bilayer Tablets of Nebivolol HCL and Nateglinide for Enhanced Gastro-Retention, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 10, 2731-2743. <https://doi.org/10.5281/zenodo.23425046>

