Journal of Biomedical and Pharmaceutical Research
Available Online at www.jbpr.in
CODEN: - JBPRAU (Source: - American Chemical Society)
NLM (National Library of Medicine): ID: (101671502)
Index Copernicus Value 2021: 83.38
Volume 12, Issue 3, May -June: 2023, 34-42

ISSN (Online): 2279-0594
ISSN (Print): 2589-8752

Research Article

Formulation and Evaluation of Bi-Layer Tablet of Nebivolol and Nateglinide

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Article Info: Received: 14-03-2023 / Revised: 19-04-2023 / Accepted: 17-05-2023
DOI: https://doi.org/10.32553/jbpr.v12i3.993
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Conflict of interest statement: No conflict of interest

Abstract:

In the present work, the Bilayered matrix type tablet were prepared by direct and wet granulation technique, in which immediate release layer (by direct compression) contains Nebivolol and extended release layer (by wet granulation) contains Nateglinide. All the developed bilayer tablets were evaluated for weight variation, friability, thickness and hardness. The percent deviation from the average weight, friability, thickness and hardness was found to be within the prescribed official limits. Release profile of Nebivolol from formulations indicate that lower MCC (Formulations CF1 and CF3) and lactose (Formulation CF3) content displayed higher release rates as compared to formulation with higher MCC and lactose content (Formulation CF2). Also the concentration of KYRON T-314 is also found to influence the release rate of the drug. It was found that formulation containing the highest concentration of superdisintegrants (Formulation CF3) has grater release then other subsequent formulations (Formulations CF1 and CF3). Similarly, the release profile of Nateglinide from formulations indicate that lower HPMC K15M(Formulation CF3) and lactose (Formulation CF3) content displayed higher release rates as compared to formulation with individual HPMC K15M, HPMC K100M, EC (Formulations CF1 and CF2) and higher lactose content (Formulations CF1 and CF2).

Introduction

In the recent years, pharmaceutical drug product manufacturers have oriented their product development activities to fixed dose combinations (FDCs) for treatments like type 2 diabetes, hypertension, pain and HIV/AIDS to advert a few. Several different approaches are been employed to deliver the FDC products to the patients such as multilayer tablets, bilayer floating tablet, compression coating, active coating and buccal/mucoadhesive delivery systems. The multilayer tablets drug delivery is gaining popularity and particularly the bilayer technology has attracted formulator's attention for the development of products for life cycle management (LCM).[1]

Objectives for designing bilayered tablets:

1. To control the delivery rate of either single or two different active pharmaceutical ingredients(s).

2. To separate incompatible APIs from each other, to control the release of one API from one layer by utilizing the functional property of other layers (such as osmotic properties).
3. To modify the total surface area available for API layer by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release.
4. To administer fixed dose combinations of different APIs.
5. Prolong the drug product life cycle; fabricate novel drug delivery system such as chewing devices, buccal/mucoadhesive delivery systems, and floating tablets for GRDDs.

Most of sustained release dosage form follows the mechanism of diffusion, dissolution or combination of both, to produce slow release of drug at predetermined rate. Hypothetically, a sustained release dosage form should release the drug by a zero-order mechanism which maintains drug plasma level time similar to intravenous infusion. Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques.(2)

The aim of present research work was undertaken to formulate bilayer tablets of Nebivolol and Nateglinide through its incorporation of an oral dosage form that is able to release Nebivolol immediately as well as sustained release of Nateglinide for 12 hrs to enhance the oral bioavailability of Nateglinide. The main objective of this work was formulation of bilayer tablets composed of two different classes of drugs by using a simple and easy-to-scale-up formulation strategy.

Material and Methods

Material:

Nateglinide and Nebivolol were obtained as gift samples from West Coast Pharmaceuticals Ltd. Ahmedabad, India. MCC, HPMC K15M and HPMC K100M were gifted by Ashland Labs, Hyderabad, India. EC, KYRON T-314 and Sodium Bi-carbonate were procured from SD Fine Chemicals, Mumbai, India. Talc and magnesium stearate were purchased from Nice Chemie Pvt. Ltd., Mumbai, India.

Methods

Characterization of Granules of SR/IR

Solubility studies of the drugs were carried out in various aqueous solutions and buffers. Drug excipient compatibility studies were done using FTIR. The granules of both the layers of IR/SR were evaluated for various precompression parameters. The angle of repose was measured by fixed funnel method. Bulk and tapped densities were determined by tapped density apparatus from which compressibility index and Hausner's ratio values were calculated.

Drug-Excipient Compatibility Studies by FT-IR

The compatibility of drugs with their respective excipients was studied by FT-IR spectroscopy. The scanning was performed 20 times at scanning speed 2 mm/sec with resolution of 4 cm−1 over the region 4000–400 cm−1. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks, and appearance of new peaks due to polymer interaction.(3)

Analytical Method Development

Construction of Calibration Curve of Nebivolol and Nateglinide:

Standard dilutions were prepared in the range of 2–10 µg/mL using 0.1 N HCl for Nebivolol and absorbance was determined at λ max f_0 (269 nm) in UV spectrophotometer (UV-1700, Shimadzu, India). Similarly standard dilutions were prepared in the range of 2–10 µg/mL using 0.01 N HCl with 0.5% w/v SLS for Nateglinide and absorbance was determined at λ max f_0 (229 nm) in UV spectrophotometer. From the values obtained, standard graph can be plotted

between concentration and absorbance values.

Preparation of Immediate Release Nebivolol Tablets

Immediate release layer of Nebivolol (NBL1–NBL9) was prepared by direct compression method. Nebivolol and other excipients like microcrystalline cellulose, Crospovidone, Croscarmellose sodium, and sodium starch glycolate and sodium lauryl sulfate were accurately weighed and sifted through sieve #40 and mixed in a polybag and these formulations are given in Table 2. The sifted powders were thoroughly mixed for approximately 5 min and again passed through sieve #40 to get uniform particle size. Magnesium stearate was added into the powder mixture for lubrication after passing through sieve #40 and 0.125% w/w of iron oxide red previously sifted to sieve #100 was added to the above mixture and blended thoroughly to ensure uniform color.[4]

Preparation of Sustained Release Nateglinide Tablets

The extended release layer was prepared by mixing the ingredients in the proper proportion and then subjected to wet granulation. Nateglinide, HPMC K100M/HPMC K15M/EC were mixed in proper proportion according to the formula developed. The binder solution was added in dry mixed material in the mortar and the wet compact mass was passed through sieve and sifted wet granules were collected and kept for drying at a temperature of 100^0C for the reported period of time. The granules were dried in tray drier and sufficient drying was conferred by taking the LOD calculation into consideration, of the dried granules. After the drying of the granule, suitable lubricant was added to the granule so as to aid the flow property. The granules were subjected to the compression using the suitable compression force.[5]

Preparation of the bilayer tablets using the optimized formulation

Three optimized formulations from each individual release were selected using the appropriate *in-vitro* dissolution and release kinetic study and were compressed into bilayer tablets. Following steps were followed during the preparation of the bilayer tablets. Initially, Nebivolol HCl containing layer was compressed using the low compression force to aid the adhesion of the second layer to be compressed. The tablets were ejected and preserved for further compression with the second layer. The granules of the second layer containing Nateglinide were transferred into the die and the initially compressed tablet of initial layer was placed over it. Final compression was done employing the suitable compression force and the tablets were preserved for the further analyzing viz. weight variation, friability, and hardness and *in-vitro* dissolution performance.

Table 1: Composition of Bilayer Tablets

Formulation Code Ingredients	CF1	CF2	CF3
Nebivolol HCl	15	15	15
Nateglinide	120	120	120
MCC	15	30	22.5
HPMC K15M	10	10	10
HPMC K100M	50	---	50
EC	---	50	50
KYRON T-314	1.5	1.5	4
Sodium Bi-carbonate	40	40	40
Mag. Sterate	6.5	6.5	6.5
Talc	6.5	6.5	6.5
Lactose	385.5	370.5	325.5
Bilayer Tablet Weight	650	650	650

Evaluation of IR/SR Tablets

The prepared tablets were subjected to various evaluation tests like thickness, hardness, weight variation, friability, and drug content. Thickness of the tablets was determined by using vernier calipers. Randomly 10 tablets were selected and used for determination of thickness. Hardness is termed as the tablet crushing strength and it is the force required to break a tablet diametrically. Hardness of tablets was measured by selecting 6 tablets randomly and the hardness of each tablet was measured with Monsanto hardness tester. The hardness was noted. The hardness is usually measured in terms of kg/cm2. For weight variation test individual weight of 20 tablets was taken; then their average weight and their mean and standard deviation were calculated and compared with the standards. The weight of the tablet being made is measured to ensure that it contains predetermined amount of drug. The tablet friability is a measure of loss due to abrasion. The preweighed tablets were exposed to repeated shocks in Roche friabilator in which they are initially weighed (W 0) and kept in a tumbling and rotating apparatus drum and were subjected to fall from 6 inches height. After completion of 100 rotations, the tablets were reweighed (W) and the percent loss in weight or friability (f) was calculated. [6,7]

Drug Content

Twenty tablets were selected randomly and average weight was calculated. The tablets were crushed in a mortar and accurately weighed amount of average tablet weight was taken from the crushed blend and transferred in to a 100 mL volumetric flask. To this little amount of methanol was added to dissolve the drug and volume was made up to the mark with concerned medium. The content was shaken periodically and kept for 1 hour to allow the drug to dissolve completely. Then it was filtered and appropriate dilutions were made. Finally dilutions were observed using spectrophotometer to determine % drug content. The drug content should be within the range between 90 and 110% of standard amount.[8]

Disintegrating Time

The disintegration test is carried out in an apparatus (Electro lab, Mumbai) containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28–32 times per minute in a medium of 900 mL water which is maintained at 37 ± 2°C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh (#10) was considered as the disintegration time of the tablet.[7, 10]

***In Vitro* Dissolution Studies**

The release of drug from different batches of prepared tablets was studied using USP dissolution apparatus type II. The dissolution medium used was 500 mL of 0.1 N HCl for first 30 minutes for immediate release layer and then 900 mL of 0.01 N HCl with 0.5% w/v SLS was used up to 12 hours for sustained release layer. The temperature was maintained at 37 ± 0.5°C and the stirring rate was 50 rpm. The samples were withdrawn at regular intervals and this withdrawn volume was replaced with fresh medium. The collected samples were filtered using Whatman filter paper and observed using spectrophotometer at respective λ_{max} against a blank (respective medium).[8,9]

Evaluation of Bilayer Tablet

Evaluation parameters of bilayer tablet were performed according to I.P. specifications. Parameters such as weight variation were performed by taking average weight of 20 tablets and hardness test was performed by Monsanto hardness tester. Thickness of the tablet was measured using vernier caliper. Friability test was performed by taking 6

tablets in Roche friabilator and % friability was calculated. In vitro drug release studies of bilayer tablets were carried out uv using USP dissolution apparatus type II in 500 mL of 0.1 N HCl for first 30 minutes and in 900 mL of 0.01 N HCl with 0.5% SLS up to 12 hours. Samples were collected at regular intervals of time and filtered. The medium in bowl was discarded after 30 minutes and replaced with another medium which was preferred for dissolution of sustain release layer. The collected samples were filtered and observed in UV spectrophotometer.[9, 11]

Kinetic Data Analysis

The drug release kinetic studies were carried out for bilayer tablets of Nebivolol and Nateglinide and were evaluated using the linear regression method:

- Zero order kinetic models—cumulative % of drug released versus T;
- First order kinetic model—log cumulative percent drug remaining versus T;
- Higuchi's model—cumulative percent drug released versus square root of T;
- Korsmeyer equation/Peppa's model—log cumulative percent drug released versus log T.

Results and Discussion

Compatibility of the drug with excipients and drug-drug interaction was determined by FTIR spectral analysis. This study was carried out to detect any changes on chemical constitution of the drug after it is combined with the excipients. The scanned graphs and the results of interaction study were pictured in the Figure 1. The I.R. spectra of mixture of drug and polymer indicated that there is no interaction between drug and polymers, hence polymers and drug were chosen for further investigations.

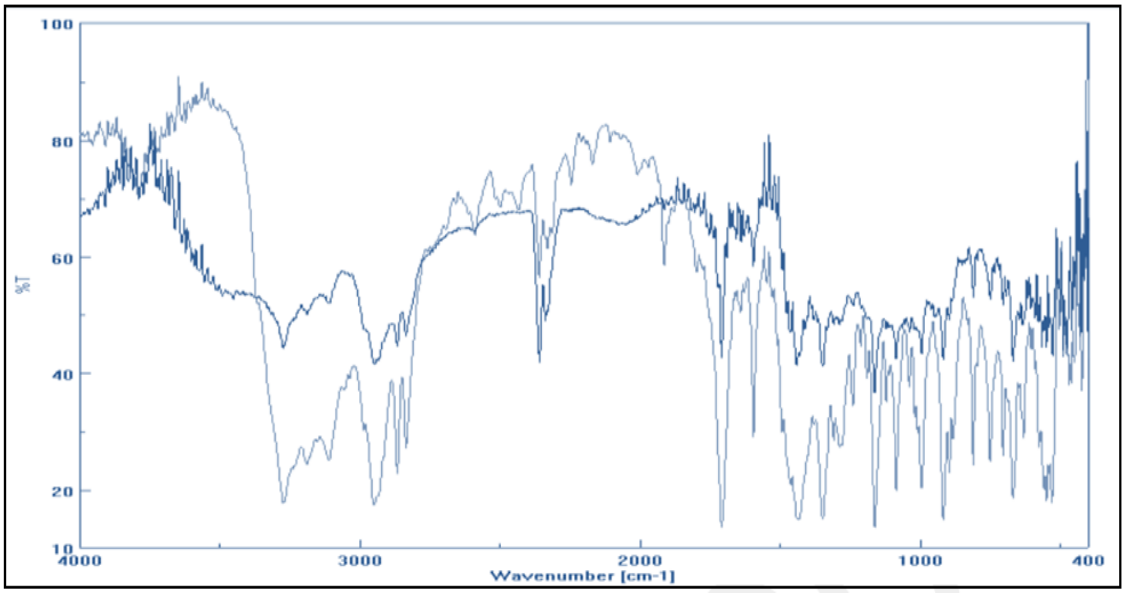

Figure 1: FTIR of Nebivolol and Nateglinide (Blend)

Determination of λ_{max} and preparation of Standard Curve:

10µg/ml solution of drug was prepared in respective solvents and using Shimadzu UV-Visible double beam spectrophotometer (UV 1800), the sample solution was scanned and the peak with distinguishable peak area was selected. λ_{max} of Nebivolol was found to be 269.0 nm and that of Nateglinide was found to be 229.0 nm.

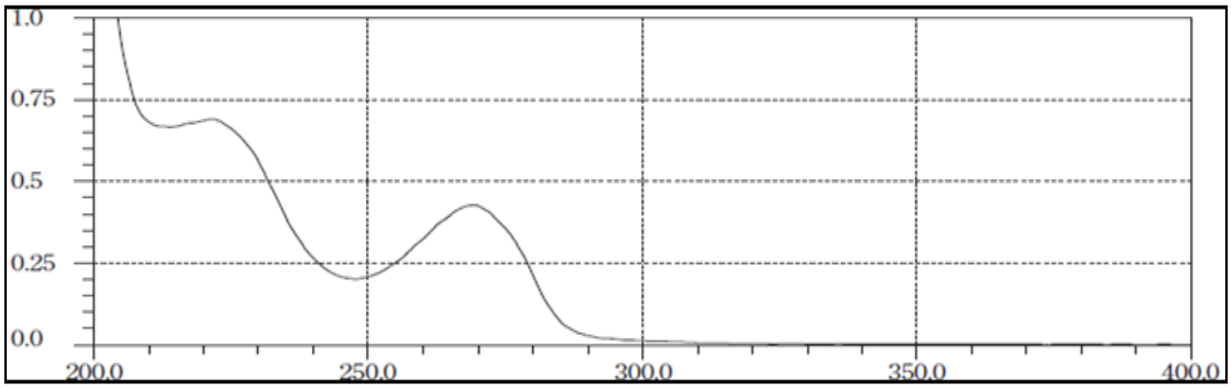

Figure 2: Wavelength scan graph of Nebivolol in 0.1N HCl (pH 1.2)

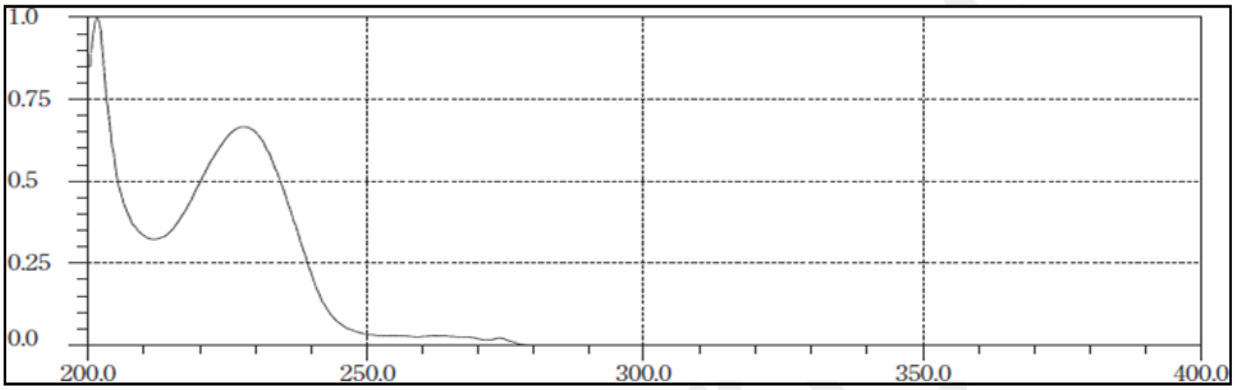

Figure 3: Wavelength scan graph of Nateglinide in Phosphate Buffer (pH 7.4)

Evaluation of Powder Blend of the best Formulations:

The powder blends of best formulation batches were evaluated for the bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio. Formulations FP1, FP3 and FP8 for Nebivolol and Formulations FG1, FG3 and FG9 for Nateglinide were evaluated. Results are presented in table.

Table 2: Pre-compression Parameters of Nebivolol Powder Blend

Formulation code	Angle of Repose (θ)	Bulk Density (g/cm3)	Tapped Density (g/cm3)	Carr's Index	Hausner Ratio
FP1	25.4	0.624	0.722	13.573	1.157
FP3	29.8	0.553	0.642	13.862	1.160
FP8	28.3	0.628	0.724	13.259	1.152

Table 3: Pre-compression Parameters of Nateglinide granules

Formulation code	Angle of Repose (θ)	Bulk Density (g/cm^3)	TappedDensity (g/cm^3)	Carr's Index	HausnerRatio
FG1	34.3	0.380	0.438	13.242	1.153
FG3	28.0	0.384	0.439	12.528	1.143
FG9	27.5	0.392	0.444	11.711	1.132

The results of pre-compression parameters showed that all the powder blends have good flow property and compressibility which are essential for the preparation of the tablets from the powder blend.

Evaluation of Bilayer tablets:

Table 4: Physical Properties of formulations CF1 to CF3

Formulationcode	Hardness(kg/cm^2)	Friability (%)	Thickness(mm)	Weight Variation (mg)
CF1	6.5	0.61	3.16 ± 0.16	652 ± 0.31%
CF2	5.5	0.65	3.40 ± 0.09	656 ± 0.21%
CF3	6.5	0.63	3.21 ± 0.21	655 ± 0.30%

All the developed bilayer tablets were evaluated for weight variation, friability, thickness and hardness and the results are given in table. The percent deviation from the average weight was found to be within the prescribed official limits. Hardness of bilayer tablets was found to be in the range of 5.5 to 6.5 Kg/cm^2 and the friability of all the developed bilayer tablets was found to be in the range of 0.61 to 0.65 %, fulfilling the official requirements (not more than 1%). Thickness of bilayer tablets was found to be in the range of 3.16 to 3.40 mm.

Table 5: Drug content of formulations CF1 to CF3:

Formulationcode	Percent drug content ± SD	
	Nebivolol	**Nateglinide**
CF1	98.69 ± 0.014	95.43 ± 0.063
CF2	97.07 ± 0.024	96.57 ± 0.039
CF3	98.38 ± 0.014	94.94 ± 0.036

Drug content estimation data for all the optimized batches are given in table. It was found to be in the range of 97.07 to 98.69% for Nebivolol and 94.94 to 96.57% for Nateglinide with low values of standard deviation indicates uniform drug content in the bilayer tablets developed.

***In-vitro* Dissolution Study of Optimized Formulations:**

All the formulations of the Bilayer tablets were subjected to *In-vitro* dissolution study and the data was generated and various release kinetic models were implicated.

Release profile of Nebivolol from formulations indicate that lower MCC (Formulations CF1 and CF3) and lactose (Formulation CF3) content displayed higher release rates as compared to formulation with higher MCC and lactose content (Formulation CF2). Also the concentration of KYRON T-314 is also found to influence the release rate of the drug. It was found that formulation containing the highest concentration of superdisintegrants (Formulation CF3) has grater release then other subsequent formulations (Formulations CF1 and CF3). In short, it can be concluded that formulation CF3 has the maximum release rate, releasing 93.56 % of drug in 50 mins. Similarly, the release profile of Nateglinide from formulations indicate that lower HPMC K15M (Formulation CF3) and lactose (Formulation CF3) content displayed higher release rates as compared to formulation with individual HPMC K15M, HPMC K100M, EC (Formulations CF1 and CF2) and higher lactose content (Formulations CF1 and CF2). In short, it can be concluded that formulation CF3 has the maximum release rate, releasing 89.33 % of drug in 720 mins.

Kinetic Models (correlation coefficient R^2):

Table 6: Drug kinetic of Bilayer Formulation Nebivolol (IR Layer)

FormulationCode	Zero order	First order	Higuchi model	Korsmeyer-peppas
	R^2	R^2	R^2	R^2
CF1	0.974	0.950	0.949	0.982
CF2	0.983	0.908	0.961	0.961
CF3	0.975	0.922	0.953	0.974

Table 7: Drug kinetic of Bilayer Formulation: Nateglinide (MR Layer):

FormulationCode	Zero order	First order	Higuchi model	Korsmeyer- peppas
	R^2	R^2	R^2	R^2
CF1	0.788	0.969	0.931	0.921
CF2	0.805	0.973	0.939	0.914
CF3	0.853	0.983	0.960	0.912

For Nebivolol formulations, the kinetic data of all the formulations are shown in table 5.50. The kinetic data of CF3 formulation have shown good fit in Zero Order Kinetic Release Model which indicated the best linearity. The release kinetic data for all the Nateglinide formulations is shown in table 5.51**.** The kinetic data of CF3 formulation showed good fit in First Order Kinetic Release Model.

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