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Formulation Development and Evaluation of Bilayer Tablet of Nebivolol Hydrochloride and Indapamide Hemihydrate

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ABSTRACT

Hypertension is chronic condition which mostly needs combination treatment for effective clinical management of the disease. Nebivolol is beta blocker agent used to reduce heart rate and hypertension while indapamide is a thiazide diuretics used to remove excess water thus to reduce hypertension. Nebivolol and Indapamide are being used in combination to treat heart failure and hypertension. In present research work, a bilayer tablet formulation containing sustained release indapamide part and immediate release Nebivolol part was prepared and evaluated. Results of the compatibility study revealed that both drugs are compatible with each other as well as with the excipients used in the formulation. Six trial batches of Sustained release Indapamide tablet were prepared using varying amount of HPMC K5, K15 and K100. Batch S6 prepared with HPMC K100 showed optimum drug release and other in vitro parameters. Immediate release layer was also prepared using wet granulation method. Amount of pregelitinised starch, SLS and Croscarmelose sodium was optimized. Among different trials, trial S6 for indapamide SR part and trial I10 for nebivolol IR part showed satisfactory *in vitro* dissolution profile so these two were selected for the preparation of bilayer tablets. Dissolution profiles of drugs in bilayer tablet were very similar to that of individual part. In vitro evaluation parameters for both individual part and bilayer tablet were found to be in specified and acceptable range. The result of stability study showed no significant change in physical and chemical parameters of the tablet; hence the formulation was found to be stable.

Key words : Bi-layer tablet, Indapamide, Nebivolol, Sustained release tablet, Immediate release tablet

INTRODUCTION

Layer tablets are composed of two or three layers of granules compressed together. Bi-layer tablets can combine two API in single dosage form with objectives of promoting patient convenience and compliance, reducing incompatibilities between API, reducing side effects and controlling release pattern of drugs to have better pharmacokinetic and better control over the disease condition1, 2, 3. Hypertension is chronic condition which mostly need combination treatment for effective clinical management of the disease4. Nebivolol is beta blocker agent used to reduce heart rate 5, 6 and hypertension while indapamide is a thiazide diuretics used to remove excess water thus to reduce hypertension7. Nebivolol and Indapamide are being used in combination to treat heart failure and hypertension8. Literature survey has revealed that indapamide Sustain Release is for effective in controlling systolic blood pressure than conventional formulation. In present research work, Bilayer tablet of nebivolol (immediate release part) and Indapamide (Sustained release) was prepared and evaluated.

MATERIALS AND METHODS

Materials and Reagents

All the chemicals and reagents used in the research study were of analytical grade. Indapamide and Nebivolol were gifted by Aurobindo Pharmaceutical ltd, Hyderbad. While Tablet formulation containing immediate release Nebivolol (5mg) and sustained release indapamide (1.5 mg) was procured from local medical store.

Preformulation Study [9, 10, 11]

FTIR Spectra

FTIR spectra was taken to analyze the drugs identity and purity and to study compatibility of drug with excipients. The Peak obtained in the FTIR spectra were compared with standard spectra of the drug to check the purity and identity.

Melting Point

The melting point of both drugs were determined by Differential Scanning colorimeter. DSC studies are also used to check the purity and compatibility between drug and excipients. Differential scanning calorimetry (DSC) measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature.

Drug-excipients Drug-Drug Compatibility Study

Excipients were mixed with drug in proportion generally used for tablet formulation. Three set of mixture were prepared, one set for initial analysis while two sets were kept at 50ºC/80 % RH for 1 month. Samples were observed visually after 1 month for changes in color and appearance and other organoleptic properties. DSC and FTIR studies were performed to evaluate any possible interaction between drug-drug and drug- excipients.

Estimation of Drugs Using RP-HPLC Method [12]

HPLC Instrumentation

Shimadzu Prominence System (SPD-20AT, Shimadzu) was used for the study. Chromatograms and data were recorded using Spinchrom CFR Software.

Preparation of Mobile Phase

After several trials, Methanol and Water in the ratio of 85:15 v/v was chosen as the mobile phase, which gave good resolution and acceptable peak parameters. Mobile phase was prepared using methanol & water in ratio 85:15 in volumetric flask. Mobile phase was filtered through a 0.45µ nylon membrane (Millipore) and degassed in an ultrasonic bath.

Preparation of Standard Solution

Preparation of Stock Solution

Standard stock solution was prepared by transferring 60 mg of Nebivolol and 20 mg of Indapamide to 100 ml volumetric flask containing mixture of 85 :15 v/v of Methanol :Water. Volume was made to 100 ml to yield concentration of 600 µg/ml of Nebivolol and 200µg/ml of Indapamide.

Selection of Analytical Wavelength

The efficiency of HPLC method based on UV spectrophotometeric determination relies on selection of appropriate detection wavelength. The standard solutions were scanned between 200 to 400 nm using UV spectrophotometer. From overlay spectra of Nebivolol and Indapamide, 280 nm was selected as detection wavelength.

Optimized Chromatographic Conditions

In present study the separation of Nebivolol and Indapamide was achieved by using column Grace C18, (250×4.6mm,5µ) with mobile phase consisting of mixture of methanol and water in the ratio of 85:15 at a flow rate 0.8 ml/min with UV detection wavelength of 280 nm at ambient temperature. The run time for Nebivolol and Indapamide was found to be 7.47 min.

Development of Calibration Curve

From stock solution of Nebivolol and indapamide, solutions were pippetted to volumetric flask, mixed and diluted to 10 ml using mobile phase correspondingly to get solutions of concentration range – 25, 50, 75, 100, 125, 150, 175, 200, 225 and 250 µg/ml of Nebivolol and 7.5, 15, 22.5, 30, 37.5, 45, 52.5, 60, 67.5 µg/ml of Indapamide. These 9 solutions were evaluated for linearity.

Sample Preparation

Accurately 20 intact tablets were weighed to determine average weight of tablets. Then tablets were finely crushed and tablet powder equivalent to 5 mg Nebivolol and 1.5 mg Indapamide was transferred into 100 ml volumetric flask. Then 50 ml mobile phase was added to flask and sonicated for 30 minute with intermittent shaking. Filter this solution through 0.45µm nylon syringe filter. Volume was made upto 100 ml to obtain solution of Nebivolol 50 µg/ml and Indapamide 15 µg/ml.

Formulation of Tablets

Formulation of Sustained Release Tablet

All the ingredients were weighed accurately and pass through # 40 mesh. Drug with diluent, polymer-HPMC was mixed to prepare blend.PVP K 30 was dissolved in solvent to prepare binder solution. Drug-excipient blend was granulated with binder solution. Prepared granules were dried in tray drier at 550C till LOD lies between 2% to 3% w/w. the dried granules were passed through # 20 mesh in Oscillating Granulator. Aerosil was weighed and passed through # 40 mesh, mixed with dried granules. The blend was lubricated with magnesium stearate. The blend was compressed by adjusting the parameters like thickness, hardness, weight and compression force.

Table 1: Composition of Sustained Release Indapamide Tablets

Ingredients	S1	S2	S3	S4	S5	S6
Indapamide	1.5	1.5	1.5	1.5	1.5	1.5
Lactose monohydrate	136.5	126.5	136.5	126.5	136.5	126.5
HPMC K4M	50	60	-	-	-	-
HPMC K15M	-	-	50	60	-	-
HPMC K100M	-	-	-	-	50	60
PVP K-30	10	10	10	10	10	10
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Aerosil	1.00	1.00	1.00	1.00	1.00	1.00
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00
Total	**200**	**200**	**200**	**200**	**200**	**200**

Formulation of Immediate Release Tablet

Nebivolol HCl and excipients like Pharmatose, pregelatinised starch was weighed and passed through # 40 mesh, mixed in cage blender. PVP K-30 and sodium lauryl sulfate were weighed and dissolved in purified water to prepare binder solution. The blend was granulated using binder solution. Granules were dried in the tray drier @ 65ºC and passed through # 20 mesh. Croscarmellose sodium, Avicel PH 102 &Aerosilwere weighed and passed through # 40 mesh. Iron oxide red was weighed and passed it through # 100 mesh& mixed with extragranular material geometrically. Blend was mixed with the dried granules in cage blender. Sodium Stearyl Fumarate was weighed and passed through # 60 mesh, blend was lubricated with it. Blend was compressed by adjusting the parameters like thickness, hardness & weight.

Optimization of Formulation

1. **Optimazation of pregelatinized starch**

Trial formulations I1 to I4 were prepared by varying amount of pre gelatinized starch to prepare granules as per the procedure stated above. Formulations were evaluated for pre compression and post compression parameters.

Table 2: Optimization of formulation for amount of pregelatinized starch

Ingredients	Quantity / Tablet (mg)			
	I1	I2	I3	I4
Nebivolol HCl	5	5	5	5
Pharmatose 200	156	144	132	120
Pregelatinized starch	0	12	24	36
PVP K 30	5	5	5	5
Sodium lauryl sulfate	0.5	0.5	0.5	0.5
Purified Water	q.s.	q.s.	q.s.	q.s.
Croscarmellose sodium	15	15	15	15
Avicel pH 102	15	15	15	15
Iron oxide red	1	1	1	1
Aerosil	1	1	1	1
Sodium stearylfumarate	1.5	1.5	1.5	1.5
Total (mg)	200	200	200	200

2. Optimization of SLS

Trial formulations I5 to I7 were prepared by varying amount of SLS to prepare granules as per the procedure stated above. Formulations were evaluated for pre compression and post compression parameters.

Table 3: Formulation Optimization for amount of SLS

Ingredients	Quantity / Tablet (mg)		
	I5	I6	I7
NebivololHCl	5	5	5
Pharmatose 200	132	131.5	131
Pregelatinized starch	24	24	24
PVP K 30	5	5	5
Sodium lauryl sulfate	0.5	1	1.5
Purified Water	q.s.	q.s.	q.s.
Croscarmellose sodium	15	15	15
Avicel pH 102	15	15	15
Iron oxide red	1	1	1
Aerosil	1	1	1
Sodium stearylfumarate	1.5	1.5	1.5
Total (mg)	200	200	200

3. Optimization of Croscarmellose Sodium

Optimization of formulation was done by varying amount of croscarmellose sodium in 4 formulation batches as given Table. Granulation was done by the process stated above. Formulations were evaluated for pre compression and post compression parameters.

Table 4: Formulation Optimization for amount of Croscarmellose

Ingredients	Quantity / Tablet (mg)			
	I8	I9	I10	I11
Nebivolol HCl	5	5	5	5
Pharmatose 200	146.5	141.5	136.5	131.5
Pregelatinized starch	24	24	24	24
PVP K 30	5	5	5	5
Sodium lauryl sulfate	1	1	1	1
Purified Water	q.s.	q.s.	q.s.	q.s.
Croscarmellose sodium	5	10	15	20
Avicel pH 102	15	15	15	15
Iron oxide red	1	1	1	1
Aerosil	1	1	1	1
Sodium stearylfumarate	1.5	1.5	1.5	1.5
Total (mg)	200	200	200	200

Preparation of Bi-layer Tablet of Nebivolol and Indapamide

Optimum batch of nebivolol immediate release and indapamide sustained release tablet was selected. As previously reported procedure, granules of nebivolol and indapamide layer were prepared separately. One by one both layers were filled in bilayer tablet machine and compressed.

Evaluation of Tablets[13]

Weight variation: 20 tablets were weighed and average weight was determined. Individual tablet weight was compared with average weight.

Thickness: Tablets were selected randomly from individual formulations and thickness was measured using Vernier caliper.

Friability: 20 tablets were weighed and transferred to friability tester. The apparatus was run for 100 revolutions at 25 rpm. Powder was collected from drum and weighed to determine % of friability.

Hardness: Tablets were selected randomly from individual batch and the hardness was measured by hardness tester

Disintegration test: Disintegration time for both immediate release tablets and bilayer tablets (immediate release part only) using 6 tablets was determined.

Dissolution: The dissolution parameters used are

A) For Sustained Release Tablet

USP Dissolution apparatus : Type I (Basket)

Media : pH 6.8 Phosphate Buffer

B) For Immediate Release Tablet

USP Dissolution apparatus : Type II (Paddle)

Media : 0.1 N HCL

5 ml aliquot after specified time interval was withdrawn and analyzed it for the content of drug.

RESULTS AND DISCUSSION

FTIR Spectrophotometeric Analysis

The FTIR spectrum of both drugs were compared with reference spectrum and reported values of peaks for presence of functional group. The FTIR spectrum of drugs confirmed identity and purity of drugs.

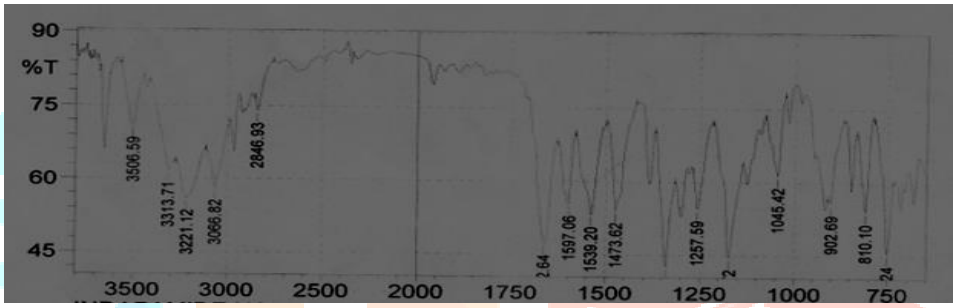

Figure 1: FTIR spectrum for Indapamide hemihydrate

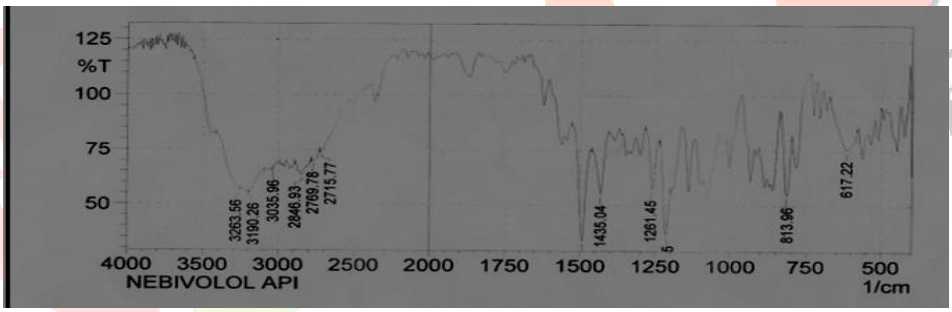

Figure 2: FTIR spectrum for Nebivolol HCl

DSC Studies

The melting point observed in DSC studies for both the drugs were matching with reference melting point of drugs respectively confirming their identity and purity.

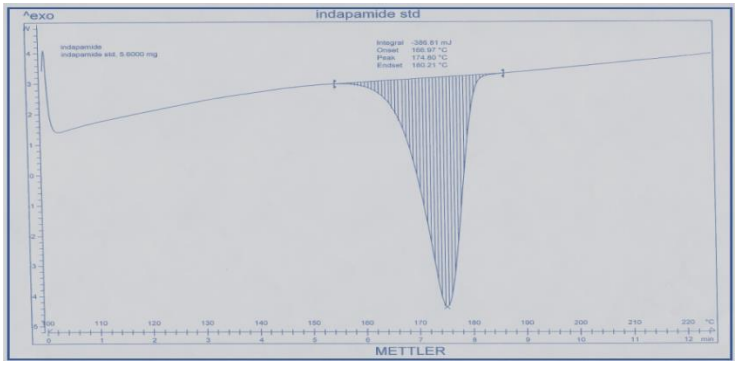

Figure 3:DSC thermogram for Indapamide hemihydrate

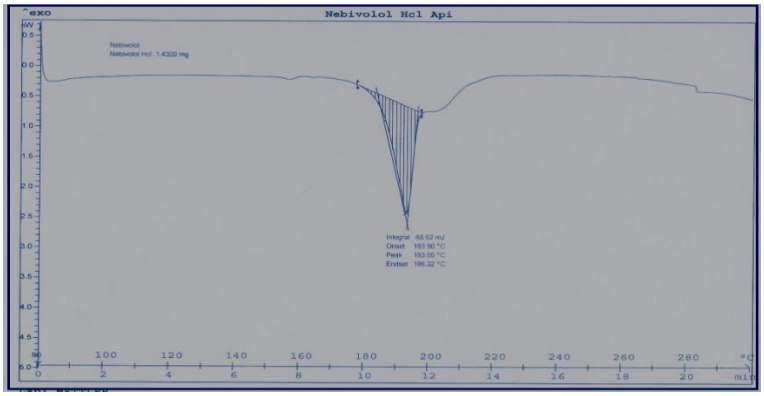

Figure 4: DSC thermogram for Nebivolol HCl

Drug -Excipients and Drug - Drug Compatibility Study

After 1 month the samples were visually observed. Both drugs were found to be compatible with all the excipients used in our formulation and with each other. There was not any type of color change or lumps formed. These samples were also evaluated for the presence of impurity by HPLC method. There wasn't presence of significant impurity in both initial samples as well as in the samples kept at 500C/80% RH for 30 Days.

Estimation of Drugs Using RP-HPLC Method

RP-HPLC method was used for the estimation of drugs in formulation. Mixture Nebivolol and Indapamide were dissolved in water and methanol. Preliminary trials were taken with different composition of mobile phase. But good separation of Nebivolol and Indapamide with sharper peaks and satisfactory system suitability parameters were observed with mobile phase- Methanol: water at composition of 85:15%. Preliminary batches also helped to optimize chromatographic conditions. System Suitability parameters were found to be in the acceptable range as showed in table and thus confirmed.

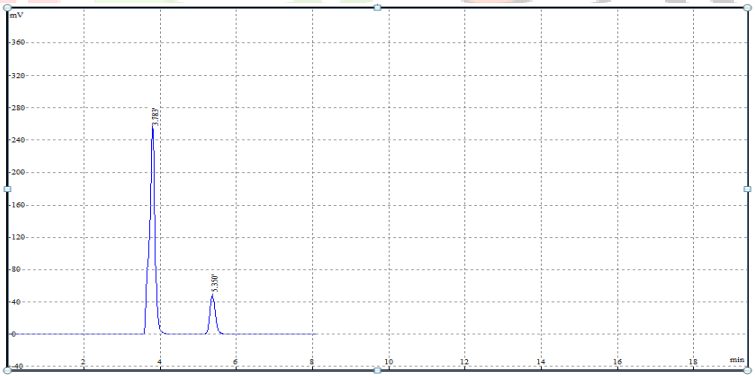

Figure 5: Chromatogram For Standard Solution of Nebivolol and Indapamide

Table 5: Evaluation of System Suitability parameters

Name of Drug	RT(min)	Resolution	Th.Plate	Asymmetry factor
Nebivolol	3.753	6.40	4833	1.07
Indapamide	5.334	0.00	6579	1.17

Development of Calibration Curve

Solutions of Nebivolol and Indapamide were prepared as per concentration range mentioned in the table 6 and 7. Responses at various respective concentrations were found to be linear. The linear regression equation for Nebivolol was y = 32.73x – 9.592 with correlation coefficient 0.9999 and for Indapamide was y = 30.41x – 0.050 with correlation coefficient 0.999.

Table 6: Linearity data for Nebivolol

Sr No	Concentration µg/ ml	Mean area ± SD	% RSD
1	25	810.25 ± 6.58	0.78
2	50	1642.56 ± 5.97	0.56
3	75	2471.11 ± 15.23	0.43
4	100	3289.2 ± 19.44	0.52
5	125	4127.57 ± 26.31	0.73
6	150	4919.26 ± 22.62	0.65
7	175	5734.33 ± 32.02	0.68
8	200	6521.42 ± 29.45	0.64
9	225	7364.87 ± 21.59	0.77

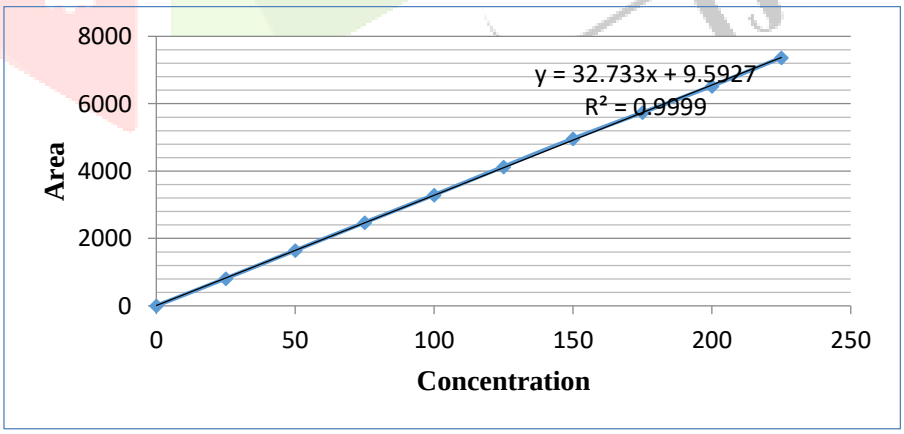

Figure 6: Calibration curve for Nebivolol

Table 7: Linearity data for Indapamide

Sr No	Concentration µg/ ml	Mean area ± SD	% RSD
1	7.5	225.15 ± 1.58	0.66
2	15	458.25 ± 4.71	0.64
3	22.5	673.88 ± 5.13	0.79
4	30	906.14 ± 6.44	0.72
5	37.5	1157.27 ± 12.41	0.77
6	45	1382.62 ± 14.32	0.69
7	52.5	1594.53 ± 20.21	0.41
8	60	1821.66 ± 19.45	0.82
9	67.5	2044.82 ± 18.89	0.85

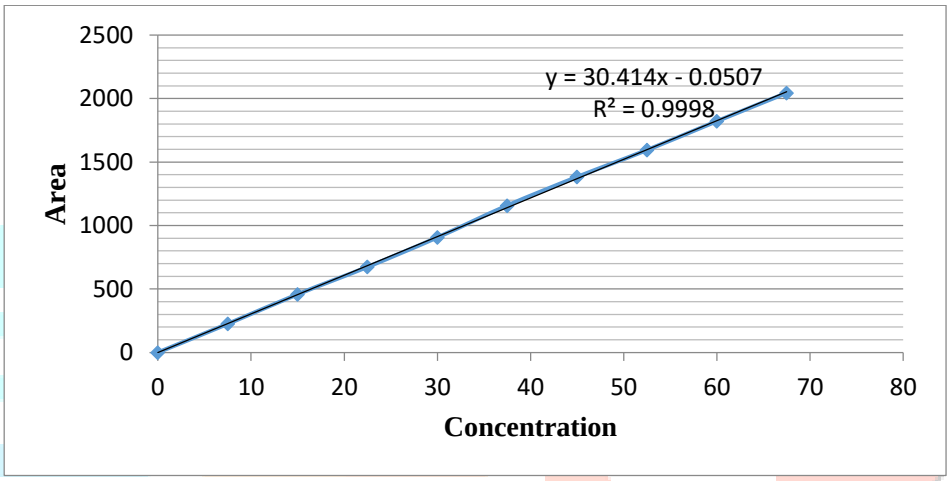

Figure 7: Calibration curve for Indapamide

Evaluation of Tablets

A. Evaluation of Sustained Release Indapamide Ttablet

Evaluation of Pre-compression Parameters of Sustained Release Tablet

Table 8: Pre-compression Parameters (Granules evaluation)

Batch No.	Angle of Repose	Bulk Density(g/ml)	Tapped Density(g/ml)	Carr's Index(%)	Hausner Ratio
S1	28.50	0.57	0.63	9.82	1.13
S2	27.67	0.52	0.63	10.34	1.12
S3	29.35	0.56	0.65	10.24	1.13
S4	28.23	0.56	0.64	10.50	1.13
S5	28.33	0.51	0.63	9.93	1.12
S6	26.17	0.51	0.64	10.07	1.13

From the values of angle of repose, Hausner ratio and Carr's Compressibility Index, it was concluded that granules of the above batches have good flow property.

A. Evaluation of Post-compression Parameters of Sustained Release Tablet

Table 9: Post-compression parameters of SR tablets

Trials	Avg. Tab Wt. (mg)	Thickness (mm)	Hardness (Kg/cm2)	Friability %
S1	200 ± 1.4	2.15 ±0.01	**6.1**	**0.18**
S2	200 ± 1.7	2.15 ±0.01	**6.1**	**0.17**
S3	200 ± 1.5	2.15 ±0.01	**6.1**	**0.17**
S4	200 ± 1.4	2.15 ±0.01	**6.1**	**0.15**
S5	200 ± 1.3	2.15 ±0.01	**6.1**	**0.16**
S6	200 ± 1.4	2.15 ±0.01	**6.1**	**0.15**

Post compression parameters of sustained release tablet formulation batches were found to be in specified and acceptable range.

***In-vitro* Drug release- Sustained Release Tablets**

Cumulative percent release of Indapamide from different tablet formulation is given in Table. It was observed that dissolution rate was retarded with the increase polymer concentration and viscosity.

Table No 10: In vitro drug release for sustained release tablet containing Indapamide

Time in hr	% Cumulative Drug Released						
	Markted form.	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**
0.5	5.30 ± 0.51	13.36±0.92	11.33±0.29	11.09±0.58	9.65± 0.63	8.16± 0.74	7.01± 0.36
1	13.50 ± 0.88	27.35±1.27	24.93±1.48	19.25±1.44	17.90±2.04	18.05±1.02	15.8± 0.68
2	22.50± 0.94	38.57±1.11	34.09±2.19	32.55±1.57	30.96±1.00	27.25±2.12	24.4± 0.86
4	35.60± 0.67	53.95±2.54	48.52±1.99	42.98±2.56	40.27±1.40	37.5± 2.28	36.2± 1.67
6	48.00± 1.21	60.12±1.89	57.15±1.52	56.79±1.41	55.8± 1.88	53.06±1.87	47.6±1.78
8	60.30± 1.68	74.18±1.66	70.57±2.04	66.35± 0.7	65.66±2.54	62.89±2.51	59.22±2.49
12	77.80± 1.81	88.52±2.08	86.90±1.51	81.5± 1.97	79.29±1.59	79.18±1.48	76.18±1.58
16	91.40± 2.09	99.9±1.10	99.11±1.59	95.27±2.13	93.24±1.57	92.87±2.41	90.47±1.85
20	98.90± 1.98			101.23± 2.54	102.03± 3.33	100.32 ± 3.22	98.26 ± 4.11
24	102.20± 1.56						101.32 ± 3.04
F1 Value (Difference Factor)		29	22	15	14	9	3
F2 Value (similarity factor)		44	50	59	60	69	86

The drug release was found to be slower for formulation S6. The comparison of dissolution profile of marketed formulation and trial formulation was done by calculating F1 (difference factor) and F2 (similarity factor) value calculation. It was observed that formulation S6 was most similar in dissolution

profile as that of marketed formulation. There was significant difference observed in t60% value for different batches of tablet formulations. The time was found to be highest for S6 batch among the trial batches.

Table No 11: Time to release 60% of the drug from sustained release tablet

Time	S1	S2	S3	S4	S5	S6
t_{60}% in min	358	371	412	423	470	485

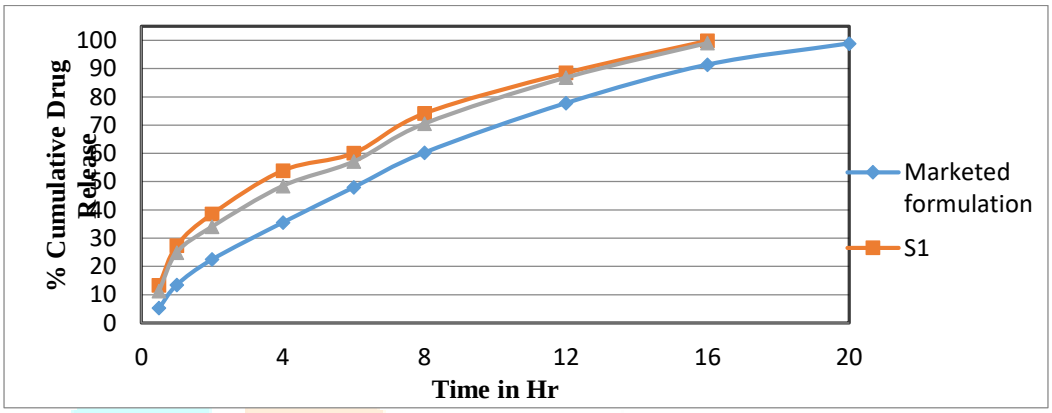

Figure 8: Dissolution profile of S1 and S2 in comparison with marketed formulation

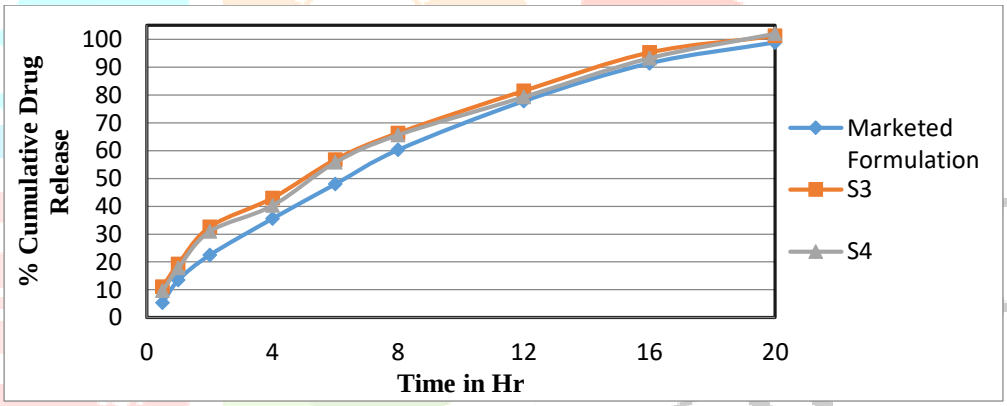

Figure 9: Dissolution profile of S3 and S4 in comparison with marketed formulation

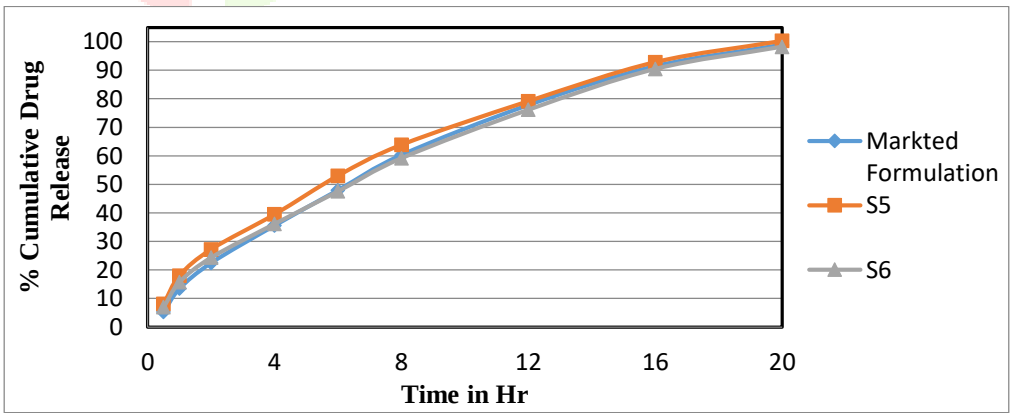

Figure 10: Dissolution profile of S5 and S6 in comparison with marketed formulation

Model Fitting of *In-vitro* Dissolution Data

The release pattern of all the formulations was studied using PCP Disso v2.0.8.5 software. All the formulations were fitted to zero order release, first order release, Higuchi matrix model, Hixson and Crowell powder dissolution model and Korsmeyer- peppas model. None of the formulations followed first-order kinetics, which was confirmed by the poor correlation coefficient values. All formulations best fitted both Higuchi matrix model (R2 =0.9210 –0.9961) and Korsemeyer and Peppas equation (R2 =0.9751-0.9965). S6 tablet Formulation showed the best release pattern with highest R2 value of 0.9962 in Higuchi matrix model. The value for diffusional exponent n was found between 0.5 (suggesting Fickian diffusion controlled drug release) and 1.0 (swelling-controlled drug release). For all formulations, the value of n was in the range 0.4978-0.6377 indicating non-Fickian anomalous transport wherein the drug release mechanism was controlled by both diffusion and polymer swelling.

B. Optimization and Evaluation of Immediate Release Tablet of Nebivolol HCl

1. Optimization of Pregelatinized Starch

Evaluation of pre compression parameter

Granules of I3 batch showed optimum flow and compression properties. Evaluation of post compression parameters of tablet formulations showed that increase in amount of pregelatinized starch increased hardness of tablets. Disintegration time and % friability were decreased with increase in concentration of starch in tablet formulations. Thus tablet formulation I3 was selected for further optimization of formulation.

2. Optimization of Sodium Lauryl Sulphate

It was observed that addition of SLS has no significant effect on the flow properties and compressibility of granules. Post compression parameters of tablet formulation batches were found to be in specified range and acceptable. I6 batch showed optimum disintegration time, increasing SLS amount further did not significantly change disintegration time.

3. Optimization of Croscarmellose

It was observed that batches I8 to I11 have acceptable flow properties and compressibility of granules. Disintegration time was found to be decreasing with increase in croscarmellose sodium concentration (I8, I9 and I10 batch). Higher disintegration time for I11 batch could be attributed to formation of viscous gel layer at higher concentration thus forming thick barrier for penetration of disintegrating medium.

Table 12: Optimization of croscarmellose sodium amount- precompression parameters

Batch No.	Angle of Repose	Bulk Density(g/ml)	Tapped Density(g/ml)	Carr's Index(%)	Hausner Ratio
I8	**29.66**	**0.53**	**0.60**	**11.66**	**1.13**
I9	**29.61**	**0.53**	**0.59**	**10.16**	**1.11**
I10	**29.51**	**0.53**	**0.60**	**11.66**	**1.13**
I11	**29.87**	**0.62**	**0.70**	**11.42**	**1.12**

Table 13: Optimization of Croscarmellose sodium Post compression parameter evaluation

Batch No.	Avg. Tab Wt. (mg)	Thickness (mm)	Hardness (Kg/cm2)	Avg Disintegration Time (min)	Friability (%)
I8	200 ± 1.8	2.22 ±0.02	5.5	3 min 58 Sec	0.17
I9	200 ± 1.9	2.22 ±0.01	5.5	3 min 29 Sec	0.18
I10	200 ± 1.9	2.22 ±0.01	5.4	3 min 13 sec	0.19
I11	200 ± 1.7	2.22 ±0.01	5.4	3 min 16 sec	0.19

***In-Vitro* Drug Release- Immediate Release Tablet- I8 to I11 formulation**

Percent Cumulative drug release was evaluated for various trial batches prepared using varying concentration of Croscarmellose in comparison to marketed immediate release tablet of Nebivolol HCl. The Drug release for I8 and I9 batch was slow as compared to marketed product. In- vitro drug release of Nebivolol HCl from I10 and I11 batch was comparable to release profile of marketed formulation. Similarity factor f1 and f2 calculation showed that formulation I10 and I10 were very similar in drug release as compared to reference immediate release tablet of Nebivolol HCl. But Tablet formulation batch I11 showed more disintegration time than I10. So batch I10 was selected for further stability testing and development of bilayer tablet.

Table 14: Dissolution profiles

Time in min	% Cumulative Drug Release				
	Mkted formulation	I8	I9	I10	I11
5	23.81	6.96	10.93	19.32	19.46
10	51.81	21.85	36.87	45.71	46.94
15	69.96	43.2	49.28	67.62	68.63
30	84.68	59.34	64.32	83.49	83.81
45	93.79	70.51	79.53	92.8	92.34
60	99.8	86.8	91.8	98.71	98.12
90	99.83	94.61	97.36	99.78	99.32
F1 Difference factor		18.23	16.25	2.16	2.19
F2 similarity factor		39.65	17.33	89.36	89.25

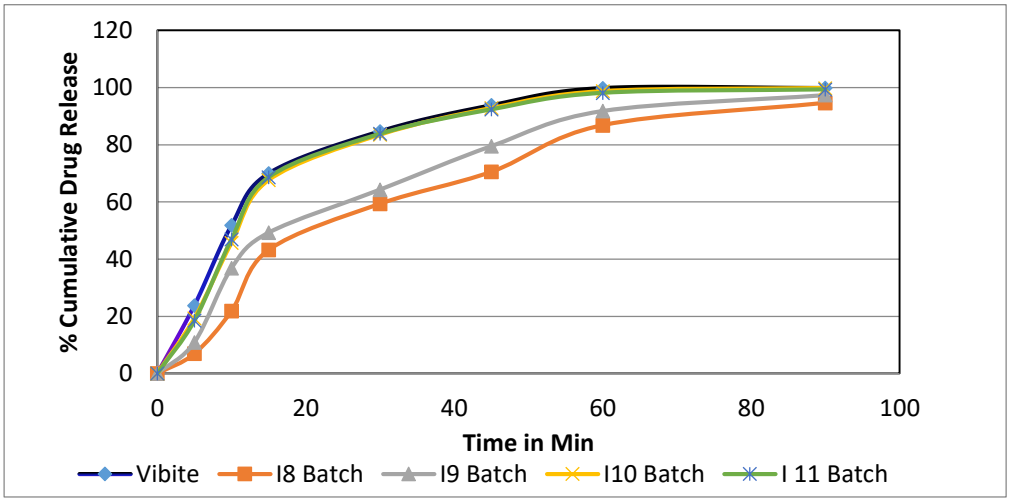

Figure 11: In vitro drug release of Nebivolol HCl from trial formulations

Evaluation of Bilayer Tablet

Optimized batch of Indapamide SR tablet (S6) and Nebivolol IR tablet (I10) was used for the preparation of bilayer tablet.

Table 15: Post-compression parameters of bilayer tablets

Trial	Avg. Tab Wt. (mg)	Thickness (mm)	Hardness (Kg/cm2)	Disintegration Time (IR Part) (min)	Friability (%)
F1	400.00	4.40-4.45	7.1	3 min 16 sec	0.23

***In- vitro* drug release from Bilayer Tablets**

Dissolution test was performed separately for both Sustained Release Part & Immediate Release Part. Dissolution profiles for both Indapamide SR Part and Nebivolol IR Part are given in the following tables. There was no significant change observed in the dissolution profile from the bilayer tablets as compared to that of individual tablets.

Table 16: Dissolution profiles of indapamide SR part from bilayer tablet in PBS pH 6.8

Time in hr	*% Cumulative Drug Release*	
	Mkted Formulation	*F1*
0.5	5.30± 0.51	7.38± 0.22
1	13.50± 0.88	17.2± 0.78
2	22.50± 0.94	25.4± 0.36
4	35.60± 0.67	37.1± 1.65
6	48.00± 1.21	49.8±1.88
8	60.30± 1.68	60.25± 2.01
12	77.80± 1.81	76.68±1.38
16	91.40± 2.09	91.07± 1.80
20	98.90± 1.98	98.75 ± 2.11
24	102.20 ± 1.77	100.82 ±2.04
F1 Value		3
F2 Value		90

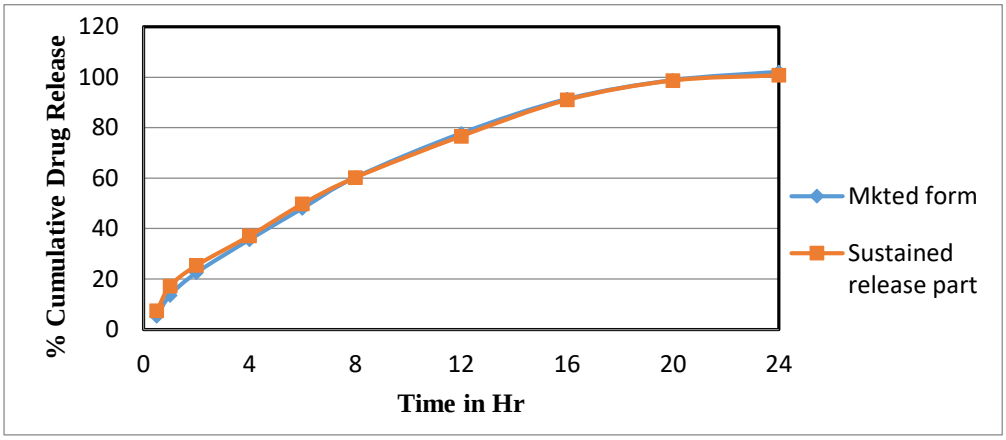

Figure 12: Cumulative % drug release from indapamide SR part of bilayer Tablet and Marketed SR tab

Dissolution Summary of Nebivolol IR Part from Bilayer Tablet

Table 17: Dissolution Profiles of Nebivolol IR part from Bilayer Tablet in 0.1 N HCl

Time in min	*% Cumulative Drug Released*	
	Mkted formulation	F1
5	23.81	19.20
10	51.81	45.00
15	69.96	64.90
30	84.68	80.50
45	93.79	93.10
60	99.8	98.20
F1 Value		3
F2 Value		88

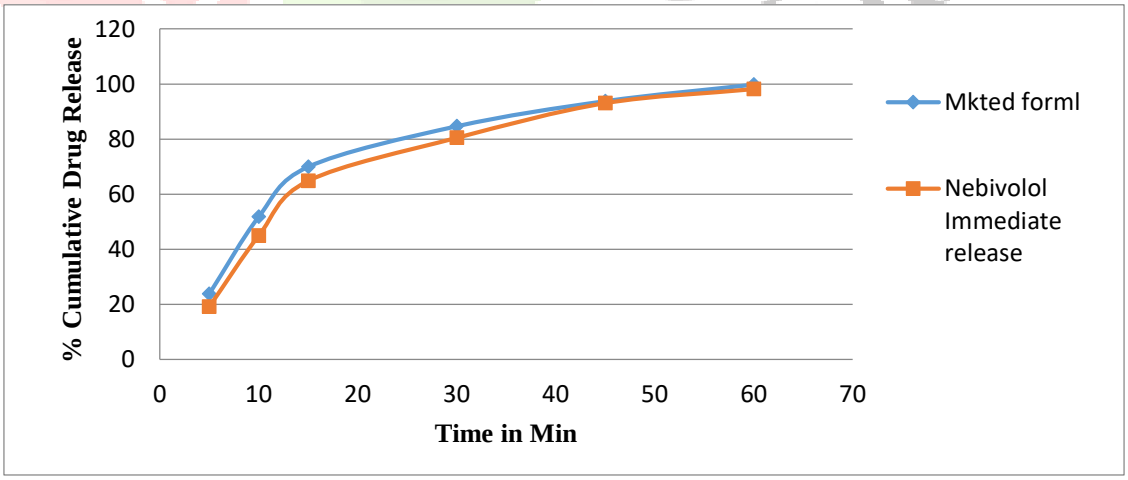

Figure 13: Cumulative percent drug release form nebivolol IR part of bilayer Tablet and Marketed immediate release tablet

Stability Studies

From the stability study conducted at 40°C ± 2°C / 75% RH ± 5 % RH, it revealed that the product was stable during its storage at 40°C/75%RH for 12 Weeks (3 months).

CONCLUSION

Nebivolol and Indapamide are being used in combination to treat heart failure and hypertension. Literature survey has revealed that indapamide Sustain Release is for effective in controlling systolic blood pressure than conventional formulation. In present research work, Bilayer tablet of Nebivolol (immediate release part) and Indapamide (Sustained release) was prepared, optimized and evaluated successfully.

REFERENCES

1. Divya A, Kavitha K, Rupesh M, Dakshayani S, Singh SD (2011). Bilayer tablet technology: an overview, Journal of Applied Pharmaceutical Sci, 1(8): 43-47.
2. Arunkumar S, Srinivas L, Satyavati D, Emmanuel C (2019). Formulation and evaluation of Bilayer matrix tablet of nebivolol hydrochloride and valsartan, J Drug Delivery and Therapeutics, 9(4-s): 82-93.
3. Dineshmohan S, Ryakala H, Ramesh A, Gupta VR (2015). Formulation,in vitro evaluation of bilayer tablets of Nebivolol hydrochloride and Nateglinide for the treatment of diabetes and hypertension, Journal of Drug Delivery,1:1-14.
4. Chandira RM, Thakor P, Kumudhavalli MV, Bhowmik D, Jayakar B (2012), Formulation evaluation and development of sustained release tablets of indapamide and immediate release blend of Ramipril in capsules, J Drug Delivery Res., 1(1): 17-26.
5. Boregowda SS, jayaramu RA, Varma ARD, Kalegowda C (2014). Development of fast dispersing tablets of nebivolol: Experimental and computational approaches to study formulation characteristics, Brazilian J Pharm Sci. 50(4): 955-64.
6. Doina D, Ardelean S, Khalaf Z, Ardelean M, Lupuleasa D (2015). Delivery of nebivolol hydrochloride from immediate release tablets, Vasile Gold is Seria Stiintelevietii, 1: 47-50.
7. London GM (2004). Efficacy of Indapamide 1.5 mg sustained release in lowering of systolic blood pressure, J of human Hypertension, ;18:S9-S14.
8. Hossain AM, Alam S, Paul P (2013). Development and evaluation of sustained release matrix tablets of indapamide using methocel K15M CR. J App Pharm Sci., 3(5): 85-90.
9. Reddy PS, Alagarsamy V, Bose PS, Damineni S, Sruthi V (2019). Development and evaluation of Indapamide effervescent floating tablets using different HPMC grade polymers, Int J Pharm Sci Rev Res, 57(2): 122-129.
10. Rajesh Babu V, Nikhat SR (2017). Formulation and evaluation of indapamide sustained release matrix tablets, IJPSR, 8(3): 1255-1259.
11. Siriah TM, Puranik PK (2018). Formulation Optimisation and evaluation of self emulsifying immediate release tablet of nebivolol HCl using 3^2 factorial design, Int J Drug Del, 10(2): 11-18.
12. Gavandare SL, Pathan AK, Nirmal SA. Development and validation of RP HPLC method for estimation of Nebivolol and Indapamide in tablet dosage form. J
13. Sharma V, Swetanshu (2019). Formulation, optimization and evaluation of bilayer tablet of antihypertensive drug, J Drug Del therapeutics, 9(4): 704-708.