SOLID DISPERSION TECHNIQUE FOR FORMULA DEVELOPMENT AND IN VITRO EVALUATION OF NEBIVOLOL HYDROCHLORIDE TABLETS WITH IMPROVED DISSOLUTION

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ABSTRACT

The goal of the study is to create and assess Nebivolol Hydrochloride tablets using the solid dispersion technique, as well as to carry out a stability analysis for the formulation that has been optimised. Direct compression was used to create twelve separate batches of immediate release tablets. To get the ideal formulation and give it immediate release properties, several concentrations of super disintegrants were used. The completed tablets' post-compression properties, such as friability, hardness, drug content, weight fluctuation, and swelling index, were evaluated after pre-compression parameters for the powder mixture were examined. Every 30 minutes, an in vitro dissolution study was conducted. 10 ml of samples were taken every five minutes at the predetermined intervals. 10 ml of samples were taken at the predetermined intervals (every 5 minutes), and their contents were then measured for the presence of nebivolol hydrochloride using a UV-Visible spectrophotometer at 282 nm. After post-compression evaluation, formulation F2 was put through a stability study to create an optimised formulation. All of the physicochemical parameters, including the angle of repose (20°12'), Carr's index (16.07), Hausner's ratio (1.14), weight variation, hardness (3.58 Kg/cm2), friability (0.3%), thickness (2.79 mm), disintegration time (21 sec), dissolution (98.5% at 30 minutes), and drug content (99. Analysis using infrared spectroscopy indicated that there is no interaction between the pharmacological excipients. Analysis of stability studies Results obtained using formulation F2 were satisfactory. Thus, this study

demonstrated that the use of a solid dispersion technique and the subsequent formulation of Nebivolol Hydrochloride into a tablet can both improve the drug's ability to dissolve.

Keywords: Nebivolol Hydrochloride, Solid Dispersion, Evaluation, *In-vitro* dissolution study, Stability study.

INTRODUCTION

Oral route of drug administration is the almost favoured transmit of drug delivery due to convenience and easy of ingestion. A solid dosage form is appropriate along with well-known aid of taking medication. Hence, patient compliance and drug treatment are usually more effective with orally administered medications than other routes of administration [1]. At least 40% of the new chemical molecules tested are drugs having poor aqueous solubility. Many methods are available to improve dissolution rate, solubility characteristics, including salt formation, micronization, and addition of solvent or surface-active agents. Solid dispersion techniques one of the most promising and extensively Performed approach to improve the dissolution rate of insoluble compounds. According to scalability, its change over to solid dosage forms such as tablets, capsules, implants, and to taste masking strips are some favours afforded by Solid dispersion technique [2] . Nebivolol hydrochloride, chemically 1,1'-(bis(6-fluoro-3,4-dihydro-2h-1-benzopyran-2-yl)-2,2' aminoethanols a unique highly effective adrenergic blocker [1] Nebivolol hydrochloride reduces heart rate, rate of Myocardial contractility and systemic blood pressure. Blockers are useful prophylactic agents in stable and unstable types of anginas. Nebivolol hydrochloride is preferable in patients with bronchi spasm, diabetes, peripheral vascular disease, or Raynaud's phenomenon [3]. Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments.

The present approach to immediate release drug delivery systems (IRDDS) aims to enhance patient compliance by developing an appropriate dosage form for administration. Almost 35–50% of the general population, including children and elderly patients, suffer from dysphagia, which leads to a high incidence of non-compliance and ineffectiveness.The swallowing problems are very common in young individuals because of their poorly developed muscular and nervous systems) [4]. Adult patients with difficulty swallowing conventional dosage forms could be struggling with mental illness, have tremors in their extremities, be inflexible, be developmentally disabled, have poor dietary habits, experience nausea, be travelling, or be placed on a water embargo.The swallowing problems are also common in some cases such as motion sickness, sudden episodes of allergic attack or coughing and due to the lack of water [5]**.** The study revealed that solubility of nebivolol was enhanced by preparing solid dispersion technique with Poly ethylene glycol (PEG 6000). The characterization of optimized formulation was done by Post compression evaluation of tablets. The drug-excipients interaction was investigated by FTIR. Thus, the purpose of the current study was to formulate and evaluate the Nebivolol hydrochloride using Solid dispersion technique with various excipients.

MATERIALS AND METHODS

Nebivolol Hydrochloride Pure drug was generous gift from Zydus Pharma Ltd, Hosur, India. Isabgol were obtained from Fourrts India Pvt. Ltd., Tamil Nādu, India. PEG 6000 and HCl were gifted from Micro Labs Pvt. Ltd., Hosur. Microcrystalline cellulose, Sodium alginate, Talc, Aerosol was obtained from Tristar Formulations, Pondicherry. Sodium starch glycolate, Cross povidone were obtained from Medo Pharm Pvt.Ltd. Aspartame was gifted from Bangalore antibiotics& Biological, Salem. Methanol is obtained from Bafna Pharma, Chennai. Immediate release tablets were prepared by Direct compression method. Nebivolol was mixed with the required quantities of disintegrants, Micro crystalline cellulose (60%), and Aerosol by geometric mixing. The powder blend was then lubricated with Talc (2.0%) and mixed for about 3 minutes. Finally, this mixture was compressed on a 16-station rotary tablet machine (Cadmach, Ahmedabad, India) using a 6 mm standard flat-face punches [6,7].

Characterization of Solid dispersions of Nebivolol Hydrochloride with PEG 6000

Drug content

Around 10mg of drug equivalent of Physical mixture and solid dispersion was weighed accurately and transferred to 50ml volumetric flask along with 20 ml methanol and sonicated for 15 minutes and volume was made up with methanol. Further dilution from this stock solution was carried and the outcomes were assessed using an ultraviolet spectrophotometer calibrated at 282 nm.

Dissolution Studies:

Nebivolol powder, solid dispersion (SD), and physical mixture (PM) dissolution examinations were conducted using the USP type II paddle apparatus with 900 ml of 0.1 N HCl as the dissolution medium at 37 0.5 °C and a paddle rotation speed of 50 rpm.The SD or PM equivalent to 10 mg of Nebivolol hydrochloride was weighed using a Digital balance and added into the dissolution medium. At the specified times (every 10 min for 2hours), 10 ml samples were withdrawn by using syringe filter (0.45 μm) and then assayed for Nebivolol content by measuring the absorbance at 282 nm using a UV-Visible spectrophotometer. Fresh medium (10ml), which was pre warmed at 37°C was added to the dissolution medium after each sampling to maintain its constant volume throughout the test.

Fourier transform IR spectroscopy:

Fourier-transform infrared (FT-IR) spectra were obtained by using Bruker Alpha FTIR. The samples (NEBIVOLOL HYDROCHLORIDE, SD and PM) are formerly grounded and blended thoroughly with (KBr) potassium bromide, an infrared transparent matrix, at 1:5 (Sample/KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press.

Pre-compression Study of Powder Blend

Loss on drying:

Determined by using 1gm of powder by drying in an oven at 100°C to 105°C for 3 hours. Mixed and accurately weighed the substance to be tested. Tare a glass stopper, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Weighed the empty bottle (W1). Put the sample in bottle, replace the cover, and accurately weighed the empty bottle with contents (W2). By gentle, sidewise shaking, distributed the sample as evenly as practicable to a depth of about 5 mm. Placed the loaded bottle in the drying chamber. Dried the sample at the specified temperature in desicator before weighing. Weighed the bottle (W3).The difference between successive weights should not be less than 0.3%.

The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W2-W3)}{(W2-W1)} \times 100$$

Where,
W1 = Weight of empty weighing bottle
W2 = Weight of weighing bottle + sample
W3 = Weight of weighing bottle + dried sample

Bulk Density and Tapped Density:

An accurately weighed quantity of the powder (w) was carefully poured into the graduated cylinder and the volume (v_0) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus (Bulk density apparatus) the density apparatus was set for 500 taps and after that, the volume (v_f) was measured and continued operation till the two consecutive readings were equal.

Method: A quantity of 5 gm of powder weighed and transferred to a measuring cylinder and observed the volume occupied by the sample

The bulk density and tapped density were calculated using the following formulas.

Bulk Density = W/V_0
Tapped Density = W/V_f
Where, V_0= Initial volume,
V_f = final volume

Angle of Repose:

Angle of repose of powder was determined by the funnel method. Accurately weighed powder was taken in the funnel. Height of the funnel was attuned in such a way the angle of the funnel just touches the apex of the powder. The powder blend was allowed to flow through the funnel freely on to the surface.

Method:

The funnel method was employed to determine the angle of repose. The height of the funnel has been modified so that the tip barely brushes the top of the mix. A correctly weighed blend is allowed to move freely through the funnel on top. The powder cone's height and diameter were measured, and the following equation was used to figure out the angle of repose.

Diameter of the powder cone was measured, and angle of repose was calculated using the following equation.

$Ø = \text{Tan}^{-1} h/r$
Where, h = height of file
R = radius of the base of the pile
Ø = angle of repose

Measurement of Powder Compressibility and Hausner's ratio

The compressibility Index and Hausner's ratio are measures of the property of a powder to be compressed. As such, they measure the relative importance of inter particulate interactions. In a free flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorly flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the Hausner ratio.

The compressibility index and hausner ratio are calculated by measuring the values for bulk density (P_{bulk}) and tapped density (P_{tapped}) as follows:
Compressibility index = $P_{tapped} - P_{bulk}/P_{tapped}$ 100
Hausner's ratio = P_{tapped} / P_{bulk}

Table No:1 Scale of flowability

Compressibility index (%)	Flow character	Hausner's Ratio
≤ 10	Excellent	1.10-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

Preparation of Standard Curve:

The spectrophotometry is the basis of the calibration curve. At 282nm, the highest absorption was noted. In the concentration range of 10–50 g/mL, it conformed to Beer's law.

Drug-Excipients Compatibility Study by FTIR

One of the most common techniques in the pharmaceutical industry to determine the purity of pharmaceuticals is infrared spectroscopy. Bruker's alpha spectrometer was used to record Fourier transform infrared spectra. Pellets of wood were prepared for sampling using KBr powder. The scanning field of view was 400-4000 cm.

FORMULATION OF IMMEDIATE RELEASE TABLETS OF NEBIVOLOL HYDROCHLORIDE:

The formulation table's proportions were used to create several Nebivolol hydrochloride Immediate release tablets. The preliminary materials went via sieve #60. Separately weighed before mixing was the nebivolol Solid dispersion. [9, 10].

Table No:2 All formulation prepared according to the following formulation Table

INGREDIENTS	Quantity in mg per tablets											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1:5 Solid dispersion equivalent to 20 mg Nebivolol	120	120	120	120	120	120	120	120	120	120	120	120

Microcrystalline Cellulose	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0	60.0
Mannitol	49.0	49.0	49.0	49.0	49.0	49.0	49.0	49.0	49.0	49.0	49.0	49.0
Isphagol mucilage	9.0	12.0	-	-	-	-	-	-	-	-	-	-
Isphagol powder			9.0	12.0								
Isphagol husk Powder	-	-	-	-	9.0	12.0	-	-	-	-	-	-
Cross povidone	-	-	-	-	-	-	9.0	12.0				
Starch Glycolate Sodium	-	-	-	-	-	-	-	-	9.0	12.0		
Calcium Carboxy Methyl Cellulose	-	-	-	-	-	-	-	-	-	--	9.0	12.0
Sodium Stearyl Fumarate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Talc	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Aerosol	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Aspartame	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Orange flavour	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Total weight (mg)	250	250	250	250	250	250	250	250	250	250	250	250

Evaluation of post-compression evaluation of Tablets

Weight Variation Test

The twenty tablets were selected arbitrarily from every formulation and weighed independently to check for weight using Shimazu weighing balance.

Uniformity of Thickness

Thickness of tablets was measured by Vernier calliper.

Hardness Test

The hardness of the tablets was determined using Monsanto hardness tester.

Friability Test

The friability of tablets was determined by using Roche Friabilator (Electro lab, Mumbai, India). It is expressed in percentage. Variability of tablets less than 1% is considered acceptable.

Disintegration Time

Six tablets from each formulation's disintegration time have been evaluated using a USP disintegration device. Six tablets were used in the disintegration test, which was conducted in 900 ml of buffer pH 6.8 at 37 °C. One tablet was placed in each tube, a disc was placed on top, and the disintegration time was recorded.

Water Absorption Ratio

Water absorption ratio is a crucial factor when assessing whether or not disintegrants would enlarge in the presence of a small amount of water. Weight of the tablet both before and after the test.

Formula used is Water absorption = [(A – B)/B] x 100%

ASSAY OF NEBIVOLOL HYDROCHLORIDE TABLETS:

Standard Preparation

Accurately measured 50 mg of nebivolol hydrochloride were added to a 100 ml volumetric flask and thoroughly dissolved in methanol. the amount of 0.1 N hydrochloric acid created up to 100 ml. Following that, 0.1 N hydrochloric acid was used to dilute 10 ml of that solution to 100 ml. After that, 0.1N hydrochloric acid was used to dilute 1 ml of that solution to 10 ml.

Sample Preparation

15 tablets were crushed, and 10 mg of Nebivolol hydrochloride were dissolved in 0.1 N of hydrochloric acid, which was then thoroughly mixed and produced up to a volume of 100 ml. 10 ml of the filtered solution were diluted to 100 ml. From there, 1 ml was taken and diluted to 10 ml. A UV/Visible spectrophotometer was used to detect absorbance at 282 nm.

Dissolution study of prepared tablets:

Dissolution studies were carried out using USP type II (paddle apparatus) at 50 rpm 0.1 N Hydrochloric acid was used as dissolution medium. Temperature was maintained at 37 ± 0.5 ^{0}C. Aliquots of dissolution media were withdrawn at specific time intervals, and it was filtered. The same quantity of fresh media was replaced. The filtered solution was used to

determine the drug content. The absorbance was measured at 282 nm by UV/Visible spectrophotometer. The test was carried out for 30 minutes [13].

Accelerated Stability Studies

Selected formulation was subjected to stability studies as per ICH guidelines. The following conditions were used for stability testing. 40^0C / 75 % RH analyzed every month for a period of three months as per ICH guidelines [14].

Pre-compression Parameter:

Immediate release tablets of Nebivolol Hydrochloride were prepared by direct compression method using Isabgol, Cross Povidone, as natural super disintegrants in different concentrations. Twelve formulations were prepared. The powder blend of twelve formulations F1 to F12 were evaluated for Bulk density, tapped density, Carr's index and Hausner's ratio, Angle of repose, which showed the pre compressed blend, has good flow property.

RESULTS AND DISCUSSION

Table No: 3 Calibration Data for Formulated NEBIVOLOL HYDROCHLORIDE

Sl. No.	Concentration	Absorbance
1	10	0.123
2	20	0.280
3	30	0.436
4	40	0.614
5	50	0.782

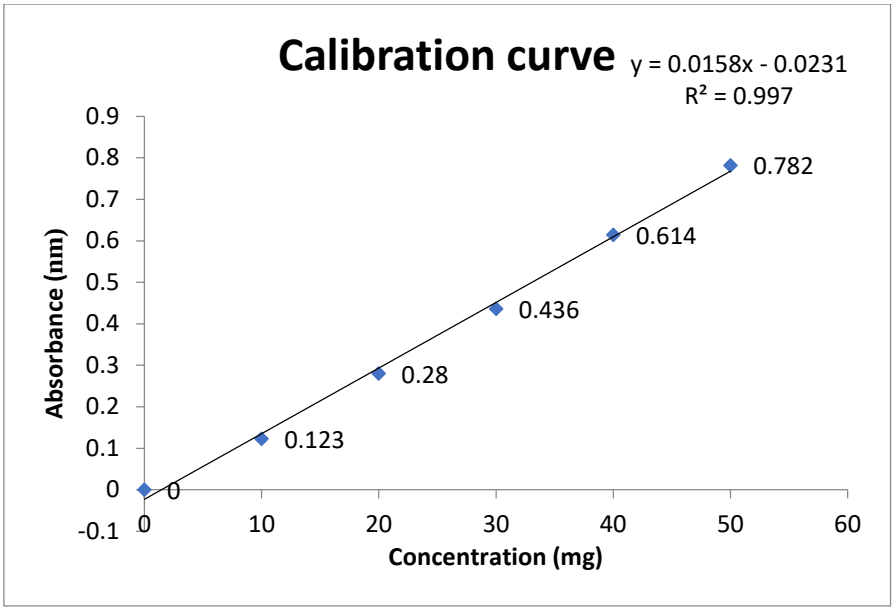


Figure No: 1 Standard plot for Nebivolol hydrochloride in 0.1N HCL

Drug-Excipients Compatibility Study by FTIR

The FTIR spectra obtained for the pure API and API – excipient mixture was compared and there is no presence or absence of any peaks which indicates there is no incompatibility between the API and excipients used.

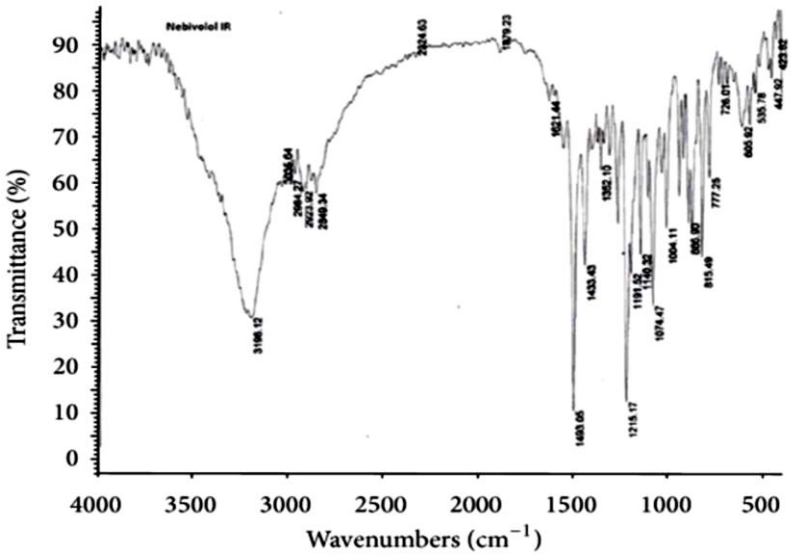


Figure No: 2 FTIR Spectra for NEBIVOLOL HYDROCHLORIDE

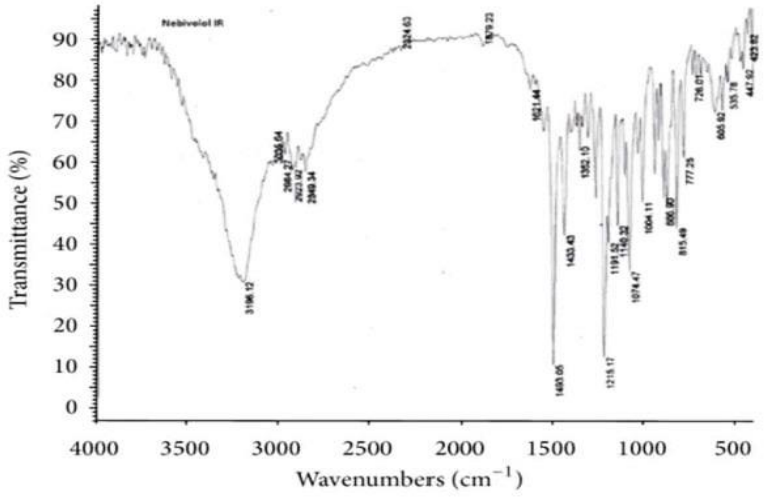


Figure No: 3 FTIR Spectra of NEBIVOLOL HYDROCHLORIDE and Excipient Mixture.

Comparative dissolution studies of prepared solid dispersion:

The prepared solid dispersions (different ratio of PEG used) were compared with the pure API and physical mixture to evaluate their drug release, and the results were as follows, the solid dispersion SD 5 gives maximum release due to the higher concentration of PEG when compared with others and is further selected for formulation into a tablet.

Table No: 4 Comparative dissolution studies of prepared solid dispersion

TIME (MINS)	API	PM	SD1	SD2	SD3	SD4	SD5
0	0	0	0	0	0	0	0
10	2.04	3.17	10.09	14.79	13.17	16.34	18.69
20	3.17	7.12	21.65	22.14	22.36	23.25	22.43
30	3.69	11.25	36.24	29.36	32.54	28.36	29.37
40	4.54	13.25	39.54	33.25	36.22	31.25	38.15
50	9.73	16.32	41.25	38.64	39.35	36.25	50.36
60	12.31	20.21	46.25	44.52	44.32	41.89	61.63
70	16.43	26.89	49.85	55.41	49.65	45.69	68.27
80	19.89	30.25	51.25	61.23	51.32	49.58	72.54
90	21.09	33.26	55.87	66.84	54.36	51.69	85.69
100	23.17	39.36	61.98	72.65	66.52	67.35	91.34
110	26.47	41.89	71.56	79.59	78.98	75.98	96.91

120	30.09	43.4	73.7	81.85	82.05	87.65	98.5

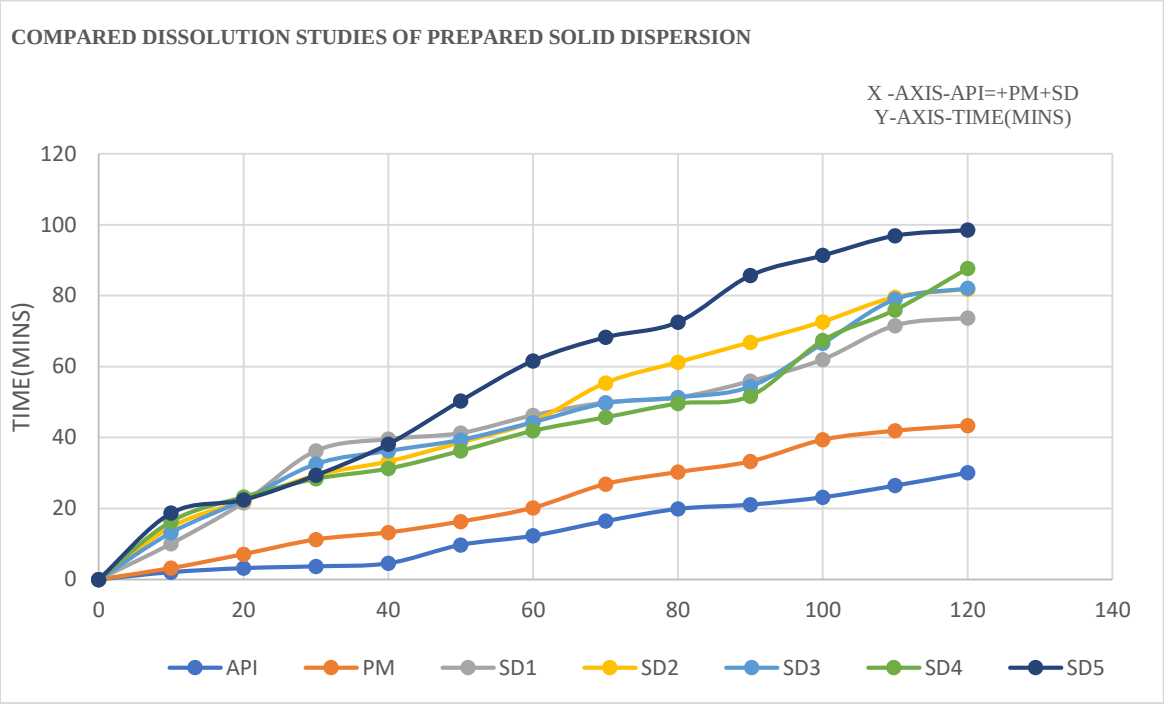


Table No: 5 Evaluation of Pre-compression Parameters

Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Bulk density	0.560	0.572	0.510	0.515	0.520	0.538	0.527	0.550	0.576	0.556	0.536	0.520
Tapped Density	0.657	0.650	0.656	0.670	0.653	0.650	0.660	0.650	0.654	0.655	0.653	0.657
%Compressibility	16.36	16.07	22.64	21.15	20.75	20.37	17.64	16.66	17.39	18.18	18.86	I7.64
Hausner's Ratio	1.195	1.14	1.29	1.26	1.26	1.25	1.21	1.40	1.14	1.22	1.33	1.21

Post-compression Parameter

The tablets obtained had drug contents in the range of 98.2 to 99.9 %. This is within the acceptable limit. The hardness of tablets was found in the range of 3.0 to 3.9 kg/cm^2.Friability was found to be below 1%, which indicates good mechanical strength of the tablets. The disintegration time (DT) for the formulation prepared was within 35 seconds. Among 12 different formulations F2 was showing promising results as the Disintegration within 21 seconds.

Table No: 6 Evaluation of Pre-compression Parameter of Nebivolol Hydrochloride granules

Sr. No	Parameter	Formulation Code											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Weight Variation Test	231.3 ± 2.0	233.6± 0.17	242.1±0.10	253.7±0.13	236.2±0.11	242.3±0.11	244.3±0.13	264.3± 0.17	254.3 ±0.13	246.7 ±0.16	266.5 ±0.18	236.3±0.18
2	% Friability	0.36	0.30	0.31	0.40	0.38	0.30	0.33	0.31	0.34	0.42	0.35	0.33
3	Thickness (mm)	2.78 ± 0.03	2.79 ± 0.02	2.65 ± 0.04	2.60 ± 0.03	2.71 ± 0.04	2.71 ± 0.03	2.72 ± 0.01	2.78± 0.05	2.74± 0.03	2.73± 0.04	2.71± 0.03	2.65 ± 0.04
4	Hardness (Kg / cm^2)	3.54 ± 0.12	3.58 ±0.13	3.98 ±0.21	3.46 ±0.17	3.18 ±0.15	3.06 ±0.17	3.24 ±0.2	3.26 ±0.23	3.03 ±0.19	3.38 ±0.17	3.14 ±0.21	3.08 ±0.19
5	Disintegration Time(sec)	23.33 ± 2.1	21.00 ±1.5	27.33 ±2.3	23.66 ±2.0	25.66 ±2.5	26.00 ±3.0	26.00 ±2.5	24.66 ±2.1	28.00 ±2.2	26.66 ±3.1	34.66 ±2.1	34.66 ±2.2
6	Wetting time (sec)	50.66 ± 1.9	47.66 ±1.5	63.00 ±2.3	66.33 ±2.2	63.33 ±2.0	57.67 ±2.1	54.33 ±1.9	52.66 ±2.3	52.00 ±2.2	53.33 ±2.7	65.33 ±2.6	63.00 ±2.3
7	Uniformity of Dispersion	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
8	Water absorption ratio(%)	65.41	65.38	73.87	74.01	66.02	67.37	65.32	65.31	66.17	66.98	74.12	73.65

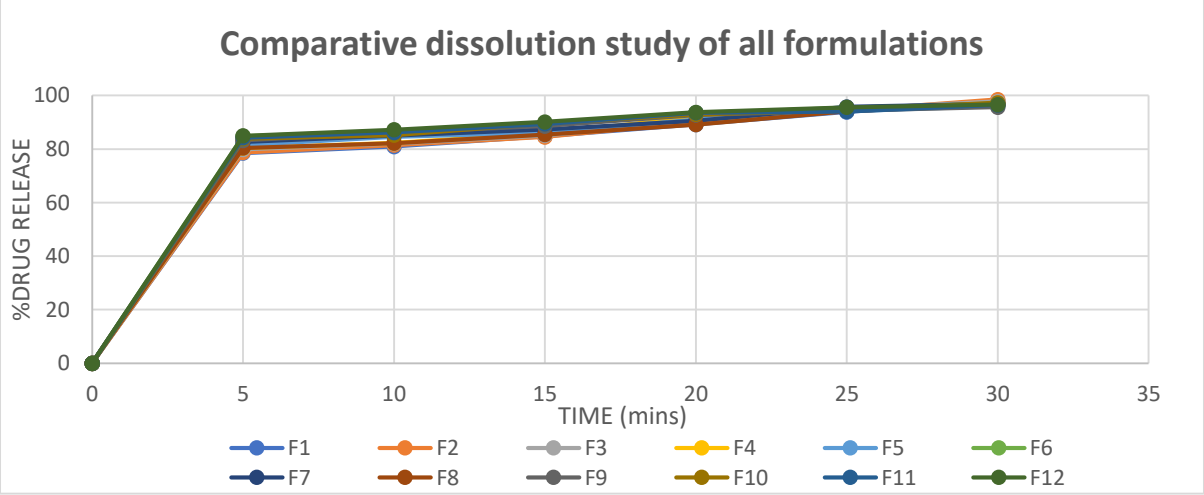
9	Assay(%)	99.2	99.8	98.6	98.4	98.2	98.7	98.6	99.7	99.8	99.9	99.9	98.4

Dissolution study of Nebivolol hydrochloride tablets:

In-vitro drug release studies were performed for all formulations. The results are accordingly tabulated. The percentage drug release for the formulation F2 was found to be 98.5 % respectively at the end of 30 minutes. Formulation F2 prepared with Isabgol mucilage was found to be the optimized formulation. The optimized formulation F2 was selected for accelerated stability studies and the tablets possessed the same parameters even after the stressed condition, indicating good stability properties of formulation, and results of optimized batch were displayed.

Table No 7*: In-vitro* drug release of all formulations

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
5	78.47	78.75	79.84	80.39	81.49	84.78	82.59	80.39	83.21	83.84	84.21	84.91
10	80.94	81.49	82.04	82.31	84.51	86.7	85.06	82.16	86.16	85.16	86.21	87.24
15	84.78	84.51	85.06	85.88	86.15	89.17	87.25	85.43	88.57	89.57	89.37	90.17
20	89.17	90	90.54	91.92	90.99	93.29	90.54	89.1	92.73	92.93	93.53	93.73
25	93.84	94.39	94.93	94.39	94.11	95.4	95.76	94.12	94.41	94.47	94.01	95.61
30	97.95	98.5	97.78	96.23	96.05	96.98	96.85	96.68	95.63	97.34	96.45	96.59



Accelerated Stability Studies at 40°C/75%RH

Based on the Post compression evaluation and in-vitro drug release studies, Formulation (F2) was selected as ideal, and was subjected to accelerated stability study as per ICH guidelines and then evaluated and the results obtained were tabulated as follows

Table No: 8 Accelerated Stability Studies at 40°C/75%RH

Sl. No.	Parameter	Initial	30 days	60 days	90 days
1.	% Friability	0.274	0.271	0.270	0.273
2.	Hardness (Kg/cm^2)	3.0	2.7	3.1	3.2
3.	Drug Content (%)	100.01	99.13	98.51	98.21
4.	In-vitro Disintegration Time (Sec)	21	24	25	29

CONCLUSION

From the above results, it can be concluded that by Formulating as a solid dispersion and subsequent formulation as immediate release tablets, enhances the dissolution of Nebivolol hydrochloride which may lead to improved bioavailability and effective therapy. Based on the *in-vitro* dissolution studies, formulation F2was found to be promising and showed a disintegration time of 21 sec. It can be concluded that immediate release tablets of Nebivolol Hydrochloride with enhanced dissolution can be successfully formulated by employing the direct compression method with the help of solid dispersion techniques.

ACKNOWLEDGMENT:

Authors are grateful to Department of Pharmaceutics, Sri Shanmugha College of Pharmacy, Sankari, Salem, Tamil Nadu, India.

CONFLICTS OF INTEREST: Nil

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