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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF NEBIVOLOL HYDROCHLORIDE

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ABSTRACT

Nebivolol HCl is a highly selective beta1-adrenergic blocker that leads to vasodilation and decreased peripheral vascular resistance. The present investigation an attempt has made to prepare immediate release tablets of Nebivolol Hydrochloride by using Microcrystalline Cellulose PH101 (MCC) as diluent, Pregelatinised Starchas a binder with different superdisintegrants like Crosspovidone (CP), Crosscarmellose Sodium (CCS).The formulation development work was initiated with wet granulation. The prepared granules and tablets were evaluated for various pre and post compression parameters such as loss on drying, bulk density, tapped density, compressibility Index, Hausner's Ratio, weight variation, thickness, hardness, friability, disintegration time and dissolution studies. Among the formulations, F_7 formulation with 16mg of Crosscarmellose Sodium has given the best dissolution studies whose disintegration time was 80 seconds. Invitro Dissolution studies showed maximum (99%) release of drug within 30 min (F_7) and mechanism of drug release from the tablets was followed first order kinetics. The optimized formulation (F_7) is further selected and compared with the In-Vitro release profile of the Innovator product with various dissolution media such as Hydrochloric Acid pH 2. FTIR studies have been performed which have not shown any incompatibility with the excipients and were stable at 40ºC/75%RH & 20ºC/60% RH for a period of three months. It was concluded that Nebivolol Hydrochloride immediate release tablets were used for the treatment of hypertension.

Keywords: Nebivolol Hydrochloride, Crosspovidone, Cross Carmellosesodium, Wet granulation, immediate release tablets.

INTRODUCTION[1]:

An Oral Dosage Form is the physical form of a dose of a chemical compound used as a drug or medication intended for administration or consumption by oral route. Common oral dosage forms are tablets or capsules. Tablets are solid preparations each containing a single dose of one or more active substances with or without excipients usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated. The excipients can include binders, glidants and lubricants to ensure efficient tabletting; disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavors to enhance taste; and pigments to make the tablets visually attractive. These are included in the formulations to facilitate easy handling, enhance the physical appearance, and improve stability and aid in the delivery of the drug to the blood stream after administration.

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A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.

IMMEDIATE RELEASE TABLETS [2, 3]:

The need for new oral drug delivery system continues, due to poor patient acceptance for invasive methods, need for exploration of new market for drugs and coupled with high cost of disease management. Developing new drug delivery techniques and utilizing them in product development is critical for pharma companies to survive this century.

An immediate release dosage form allows a manufacturer to extend market exclusivity, while offering patients a convenient dosage form or dosage regimen. 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.

Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. They are also a tool for expanding

markets, extending product life cycles and generating opportunities.

Advantages of Immediate Release Tablets:

- Economical and cost effective.
- Quick onset of action.
- Suitable for industrial production.
- Improved stability and bioavailability.
- Provides some advantages of liquid dosage forms.
- Adaptable and amendable to existing processing and packaging machinery.
- Unique product differentiation

Disadvantages of Immediate Release Tablets:

Rapid drug therapy intervention is not possible. Sometimes may require more frequency of administration. Dose dumping may occur. Reduced potential for accurate dose adjustment.

MATERIALS AND METHODS:

Nebivolol HCL was obtained from PharmachemPvt Ltd, MCC PH 101 from Mingtai Chemicals,Starch & Brilliant Blue were obtained fromColorconAsia Pvt Ltd,Mannitol was obtained fromRoquetteFreres,HPMC from Dow Chemical Company & SLS,Mg Stearate were taken from Cognis (Germany), CCS,Colloidal silicon dioxide from Signet Chemicals and lastly Lactose Monohydrate was taken from DOMO Friesland Compina.

Pre compression parameters:

Bulk density:

Granular powder weighing 10 g was placed in 100ml measuring cylinder. Volume occupied by the powder was noted without disturbing the cylinder and bulk density was calculated by the following equation.

Bulk density = weight of sample / Volume of packed.

The experiment was repeated for three times.

Tapped Density:

Granular powder weighing 10g was placed in 100ml measuring cylinder. The cylinder was then subjected for the fixed number of taps until the powder bed has reached the minimum. The final volume was recorded and the tap density was calculated by the following equation.

True density = Mass of bulk sample / Volume of bulk drug on tapping

The experiment was repeated for three times

Carr's Index

Carr's compressibility was calculated for granules prepared by using the equation

[δ tap- δ bulk / δ tap] × 100

Where,δ tap= Tapped density or True density

δbulk = Bulk density.

Hausner ratio

Tapped density and bulk density were determined and the Hausner ratio was calculated by the following formula,

Hausner ratio = δ tap / δ bul

Where, δ tap= Tapped density or True density

δbul = Bulk density.

Angle of Repose

It is the maximum angle that can be obtained between the free standing surface of the granule heap and the horizontal plane. The angle of repose can be calculated by the following formula,

θ = tan- h/r

Where, h = height of the pile, r = radius of plane surface occupied by the powder.

PREPARATION OF IMMEDIATE RELEASE TABLETS:

Tablets containing 21.76mg of Nebivolol Hydrochloride were prepared by Wet Granulation method and the various formulae used in the study are shown in table 4&5. The drug, diluents (MCC and Lactose monohydrate, Mannitol) and disintegrants (Cross Carmellose Sodium, Cross Povidone) were properly mixed together (in a plastic container). A binder solution was prepared by dispersing granulating agent, HPMC, SLS in water. Granulation of the above mixture is done until end point is obtained (dough mass). Pass the mass via mesh 12 and keep in a tray dryer to dry out granules. Remove the dried granules from oven and pass via mesh 16 to get optimum sized granules. Aerosil and Magnesium Stearate were passed through mesh number 40, mixed and blended with initial mixture in a plastic container. The tablets were prepared by wet granulation method by using 9mm flat punches &compression is done by using rotary CADMACH punching machine, a 20 station rotary compression machine.

Table 1: Formulation Development

INGREDIENTS	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)	F9(mg)
Nebivolol HCL	21.76	21.76	21.76	21.76	21.76	21.76	21.76	21.76	21.76
Microcrystalline Cellulose ph 101	46	46	46	46	44	43	43	44	46
Mannitol-60	30	36	45	56	60	65	72	68	68
Pre-Gelatinized starch	48	45	48	50	54	54	60	56	56
Brilliant blue FCF	0.4	0.6	0.6	0.7	0.8	0.8	0.9	0.8	0.8
Cross Carmellose Sodium	11	12	13	13	12	16	16	15	14
HPMC E 15 CPS	3	3.35	4.4	5	5	4	6	5	4
Crosspovidone	-	3	4.5	5	2	1	-	-	-
Magnesium stearate	10	10	10	10	12	12	12	12	12
Colloidal silicon dioxide	0.72	0.9	0.95	0.9	0.9	0.95	1.2	1.2	1.2
Lactose Monohydrate	72	62.4	46	30	28	22	8.0	14	15
Sodium Lauryl Sulphate	-	0.8	0.9	0.9	-	0.5	0.7	0.2	0.6
Polysorbate 80	-	-	-	-	2.3	1.0	-	1.2	1.4
Total Weight	**242.8**	**241.81**	**242.11**	**239.26**	**242.76**	**241.51**	**240.56**	**239.66**	**241.76**

Evaluation of blends [4]:

Prior to the compression of both granules into tablets, the granules were evaluated for properties like Angle of repose, Bulk Density, Tapped density, Carr's index and Hausner's ratio.

Evaluation of tablets[5]:

Thickness:

Thickness was determined for twenty pre-weighed tablets of each batch using a digital vernierscale (Mitutoyo- Digi) and the average thickness was determined in mm.

Hardness:

Hardness or crushing strength is the force required to break a tablet in diametric compression. Hardness of the tablets is determined by Monsanto hardnesstester which consists of a barrel with a compressible spring. The pointer moving along the gauze in the barrel at which thetablet a fracture indicates the hardness of the tablet. Six tablets from each batch were taken randomly and their hardness was determined.

Friability:

This test is performed to evaluate the ability of a tablet to withstand abrasion in packing, handling and transporting purpose. Twenty sample tablets were rotated at 25rpm for 4 minutes by a USP-type Roche friabilator, then reweighed after removal of fines and the percentage weight loss was calculated according to the following formula. The tablets were found to pass the friability test, if the percentage weight loss was found tobe less than 1%.

% Friability= (W0-W)/W0 ×100

Where W0=initial weight of twenty tablets

W= weight of 20 tablets after 100 revolutions

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 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.The disintegration time that patients can experience for oral disintegrating tablets ranges from 5 to 30 sec.

Dissolution study:

Dissolution study was carried out by using USP Type II dissolution apparatus. The dissolution was carried out in pH 2 buffer solution as dissolution medium. 5ml sample where collected at 10, 20, 30 and 45 minutes time intervals and after proper dilution they were analyzed at 269 nm against the blank pH 7.2 buffer solutions using an Eli co UV Double beam Spectrophotometer.

Stability studies:

The optimized formulation was subjected for stability studies at accelerated conditions of a temperature 400 C and a relative humidity of 75% and at initial , 1st , 2nd and 3rd monthfor their physical appearance, hardness, disintegration time, drug content, friability, thickness and %drug release.

Difference and Similarity Factor[6]:

Results obtained from the dissolution profile were fitted into equations (1) and (2) to determine the difference and similarity factors of the various batches compared to standard. Difference and similarity factors are model independent approach used to estimate the dissimilarity factor (f_1) and similarity factor (f_2) to compare the dissolution profile of optimized formulation (F_7) with innovator product. The difference between the reference and test curve at each time point and is a measurement of the relative error between two curves. The FDA suggested that two dissolution profiles were declared similar if f_2 value between 50 – 100 and f_1 was 0 – 15. The results are given in table -11.

f1= {[Σ t=1n |Rt-Tt|] / [Σ t=1n Rt]} ×100 -- Equation (1)

f2 = 50 + log {[1+ (1/n) Σt=1 * n (Rt-Tt) 2]-0.5 *100 --- Equation (2)

Where,

f1 = difference factor

f2 = similarity factor

n = time points

Rt = cumulative percentage dissolved at time t for the reference

Tt = cumulative percentage dissolved at time t for the test.

Solubility Studies:

The solubility of Nebivolol Hydrochloride was determined in various aqueous solutions and buffer (Hydrochloride pH 2)The solubility study was conducted by taking excess amount of the drug in 10 ml of the solution and the solutions were kept in the water-bath shaker for 72 hours. Then the solution was filtered and diluted with sufficient amount of the same solvent. The absorbance of the solution was determined at 269nm.

RESULTS AND DISCUSSION:

Immediate release tablets of Nebivolol Hydrochloride were prepared by wet granulation method using Crosscarmellose, Crosspovidone, as super disintegrants in different concentration. Nine formulations were prepared. The powder blend of nine formulations F1 to F9 were evaluated for Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio, which showed the pre compressed blend, has good flow property. The results are shown in [Table 2].

The values of different physical tests are given in [Table 3]. The tablets obtained had drug contents in the range of 98 to 101%. This is within the acceptable limit. Hardness of tablet was found in the range of 6.3(0.05) to7.1 (0.01) 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 with ,Crosscarmellosewas found to be 80 seconds. Among all the formulations F7 was showing promising results as the DT was 80 second. In-vitro drug release studies were performed with all formulations. The results are accordingly tabulated in [Table 4], [Fig-1, 2]. The

percentage drug release for the formulation F7 was found to be 97.85% respectively at the end of 45 minutes. Formulation F7 prepared with crosscarmellose was found to be the optimised formulation.The optimized formulation F7 wasselected for accelerated stability studies and the tablets possessed the same parameters even after the stressed conditions, indicates good stability properties of formulation [Table.5, 6].and results of optimized batch were displayed in [Table 7] [Fig-3]

Release kinetic studies have also been performed wherein it has been proved that the drug follows first order release with a regression factor of 0.895 [Table 8]. [Fig-4, 5]
Solubility studies were also carried out and results were displayed in [Table 9]. And lastly [Table 10] displays difference and similarity factors along with the standard graph. [Table 11]. [Fig-6]

Table 2: Evaluation of Pre-compression Parameters

Formulation	Bulk Density (gm /ml) (±SD), n=3	Tapped Density (gm/ml) (±SD), n=3	Hausner's Ratio	Carr's Index (%) (±SD), n=3	Angle of Repose (θ) (±SD), n=3
F1	0.291(0.01)	0.331(0.02)	1.13(0.1)	12(0.1)	26.12(0.0)
F2	0.314(0.0)	0.376(0.03)	1.18(0.01)	16.4(0.02)	27.14(0.1)
F3	0.298(0.02)	0.347(0.02)	1.16(0.03)	16.2(0.02)	26.85(0.01)
F4	0.326(0.03)	0.384(0.0)	1.17(0.04)	15.1(0.1)	30.12(0.02)
F5	0.286(0.03)	0.342(0.02)	1.19(0.0)	14.5(0.03)	28.47(0.02)
F6	0.301(0.02)	0.35(0.1)	1.16(0.03)	14.(0.02)	26.96(0.01)
F7	0.285(0.1)	0.324(0.02)	1.13(0.01)	12(0.05)	25.22(0.02)
F8	0.290(0.3)	0.338(0.03)	1.16(0.02)	14.2(0.0)	26.41(0.1)
F9	0.294(0.02)	0.344(0.04)	1.17(0.01)	14.5(0.2)	25.8(0.02)

Table 3: Evaluation of Post Compression Parameters

Formulation	Weight Variation Test (mg) (±SD), n=3	Hardness (kg/cm^2) (±SD), n=3	Friability (%) (±SD), n=3	Thickness (mm) (±SD), n=3	Content Uniformity (±SD), n=3	Disintegration Time (min) (±SD), n=3	Assay (%) (±SD), n=3
F1	242.8(0.1)	6.4(0.08)	0.56(0.0)	2.6(0.1)	99.28(0.0)	2' (0.14)	97.56(0.01)
F2	241.81(0.2)	6.3(0.05)	0.68(0.1)	2.6(0.1)	97.16(0.1)	1'55'' (0.25)	97(0.02)
F3	242.11(0.1)	6.5(0.03)	0.69(0.2)	2.8(0.0)	101.1(0.0)	1'42''(0.14)	97.8(0.02)
F4	239.76(0.01)	6.6(0.02)	0.66(0.2)	2.75(0.1)	97.68(0.3)	1'50'(0.35)	98.4(0.2)
F5	242.76(0.2)	6.7(0.1)	0.67(0.1)	3.0(0.1)	99.41(0.1)	1'38''(0.12)	97.2(0.2)
F6	241.51(0.03)	6.9(0.12)	0.65(0.0)	2.8(0.2)	98.19(0.0)	1'48''(0.23)	98.2(0.01)
F7	240.56(0.04)	6.8(0.0)	0.48(0.0)	3.2(0.0)	99.8(0.2)	1'20''(0.1)	99(0.01)
F8	239.66(0.03)	7.1(0.01)	0.65(0.2)	2.6(0.2)	99.5(0.1)	1'40'' (0.42)	98.75(0.02)
F9	241.76(0.04)	6.8(0.02)	0.62(0.2)	2.59(0.3)	99.6(0.1)	1'35''90.11)	98(0.01)

Table 4: Dissolution Profiles of Immediate Release Tablets in HCL Buffer (pH 2)

Formulation	Time (Min)			
	10min	20min	30min	45min
F1	62(0.01)	75(0.01)	86(0.01)	95(0.35)
F2	54.9(0.01)	84.47(0.03)	93.34(0.02)	93.72(0.3)
F3	49.88(0.0)	76.88(0.02)	89.84(0.01)	91.28(0.05)
F4	36.9(0.02)	60.42(0.01)	75.98(0.6)	91.67(0.3)
F5	56(0.02)	62(0.02)	76(0.1)	85.7(0.03)
F6	38.31(0.01)	47.5(0.01)	73.02(0.2)	90.51(0.05)
F7	80.00(0.02)	85(0.01)	93.85(0.03)	97.85(0.4)
F8	54.77(0.03)	89.35(0.03)	93.34(0.02)	93.47(0.5)
F9	38.82(0.01)	60.42(0.02)	84.21(0.0)	94.75(0.4)
Innovator	71.3(0.01)	76(0.02)	86(0.02)	96.2(0.3)

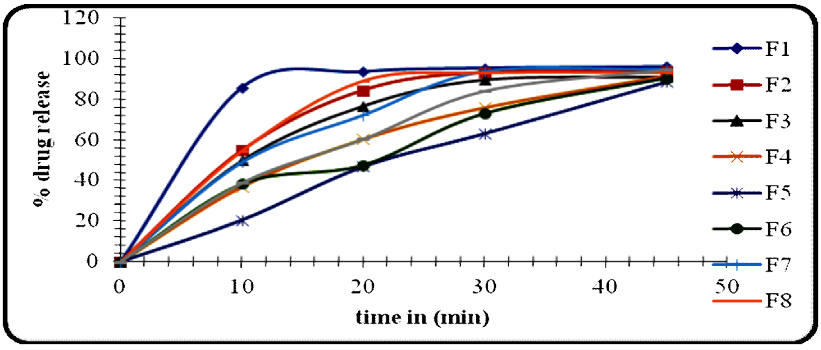

Fig 1: Cumulative % drug released for all formulations (F1-F9)

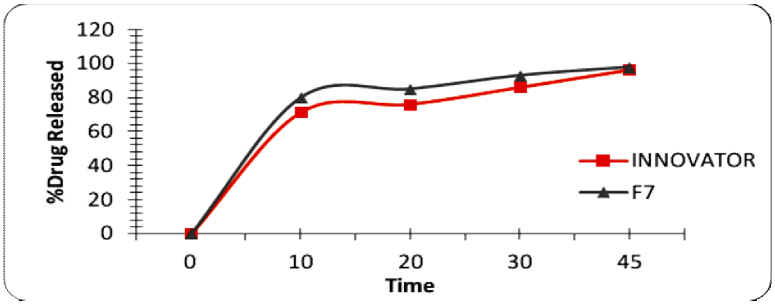

Fig 2: Release Study of Optimized Batch with Innovator

Table 5: Accelerated Stability Studies at 25°C/60%RH

S. NO	PARAMETERS	LIMITS AS PER SPECFICATIONS	25^0 C ± 2^0 C/60% ± 2% R.H			
			Initial	1 Month	2 Month	3 Month
1	Organoleptic Properties	Light Blue Coloured Round Tablets	Light Blue Coloured Round Tablets	No Change	No Change	No Change
2	Hardness	6.8	6.8	6.8	6.6	6.5
3	Friability (%)	0.2	0.18	0.16	0.19	0.2
4	Thickness (mm)	2.8	2.8	2.8	2.8	2.8
5	Disintegration Time (min)	1’32’’	1’30’’	1’32’’	1’29’’	1’33’’
6	Average Weight (mg)	241.72	241.56	241.62	241.68	241.72
7	Water Content (%)	2.12	1.98	1.99	2.03	2.12

Table 6: Accelerated Stability Studies at 40°C/75%RH

S. No	PARAMETERS	LIMITS AS PER SPECFICATIONS	40^0 C ± 2^0 C/75% ± 2% R.H			
			Initial	1 Month	2 Month	3 Month
1	Organoleptic Properties	Light Blue Coloured Round Tablets	Light Blue Coloured Round Tablets	No Change	No Change	No Change
2	Hardness	6.8	6.8	6.8	6.6	6.5
3	Friability (%)	0.18	0.16	0.19	0.2	0.18
4	Thickness (mm)	2.8	2.8	2.8	2.8	2.8
5	Disintegration Time (min)	1’30’’	1’32’’	1’29’’	1’33’’	1’30’’
6	Average Weight (mg)	241.56	241.62	241.68	241.72	241.56
7	Water Content (%)	1.98	1.99	2.03	2.12	1.98
8	Drug Content	Not < 90 % Not > 110 %	96.31	96.96	96.22	96.00
9	Drug Release in Hydrochloric Acid pH 1.2	Not < 85 %	98.2	97.5	98.0	99.00

Table 7: Stability Results of Optimized Batch (F7)

Time (min)	% Drug Release			
	Initial	1st month	2nd month	3rd month
0	0	0	0	0
10	80	79.6	77	76.5
15	85	84.9	84.5	84
20	93	93	92.9	92
30	97.85	97.0	96	95

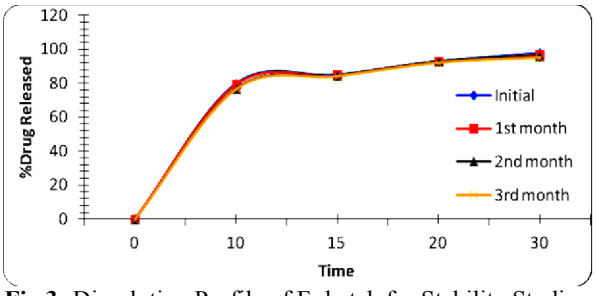

Fig 3: Dissolution Profile of F_7 batch for Stability Studies

Table 8: Mechanism and Release Kinetics of Nebivolol HCL from Tablets and from Innovator

S. No	FORMULATION	ZERO ORDER		FIRST ORDER	
		K_0	R^2	K_1	R^2
1	**F_1**	0.0447	0.6107	0.0006	0.7008
2	**F_2**	0.0273	0.5880	0.0009	0.8257
3	**F_3**	0.0568	0.5392	0.0007	0.7080
4	**F_4**	0.0507	0.5997	0.0006	0.8969
5	**F_5**	0.0535	0.5816	0.0007	0.8080
6	**F_6**	0.0465	0.5247	0.0005	0.8978
7	**F_7**	0.0278	0.5147	0.0007	0.9975
8	**F_8**	0.0479	0.5147	0.0007	0.9975
9	**F_9**	0.0475	0.7863	0.0005	0.8748
10	**Innovator**	0.0305	0.8054	0.0007	0.8975

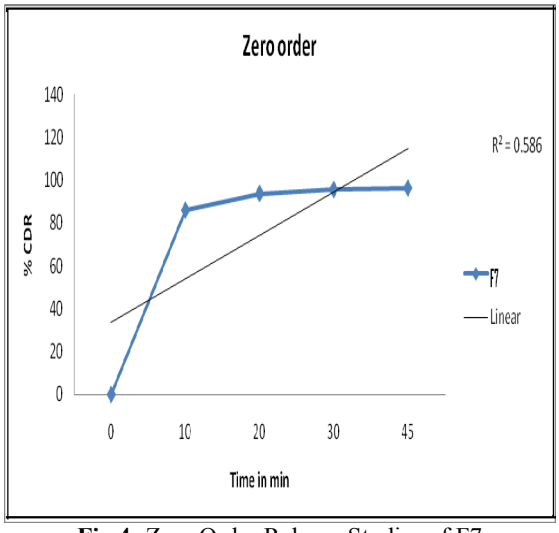

Fig 4: Zero Order Release Studies of F7

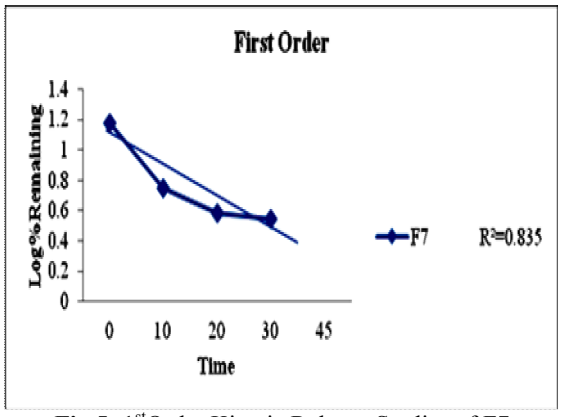

Fig 5: 1st Order Kinetic Release Studies of F7

Table 9: Solubility study data of Nebivolol Hydrochloride in Various Solvents and Buffers

S. No	NAME OF SOLVENT/BUFFER	Concentration (mg/ml)* (±SD), n = 3
1	Water-	0.0017(0.001)
2	Hydrochloric acid buffer pH 1.2	1.2234(0.159)
3	Phosphate buffer pH 6.5	0.0012(0.000)
4	Acetate Buffer pH 4.8	0.1690(0.026)
5	PEG	0.9102(0.003)
6	DSMO	0.4567(0.002)
7	Methanol	0.0814(0.001)

Table 10: Difference and Similarity Factors of Nebivolol HCL Immediate Release Tablets

S. NO	FORMULATION	DIFFERENCE FACTOR (f_1)	SIMILARITY FACTOR (f_2)
1	F_1	10	62
2	F_2	11	59
3	F_3	13	52
4	F_4	12	69
5	F_5	11	57
6	F_6	9	68
7	F_7	6	60
8	F_8	10	69
9	F_9	8	65
10	Innovator	5	59

Table 11: Calibration Curve Data for Nebivolol HCL

S. No	Concentration (mcg/ml)	*Absorbance at 269nm Mean (±SD), n=3
1	0	0.00 ± 0.00
2	2	0.068 ± 0.009
3	4	0.143 ± 0.012
4	6	0.212 ± 0.009
5	8	0.282 ± 0.008
6	10	0.356 ± 0.016
7	12	0.428 ± 0.014

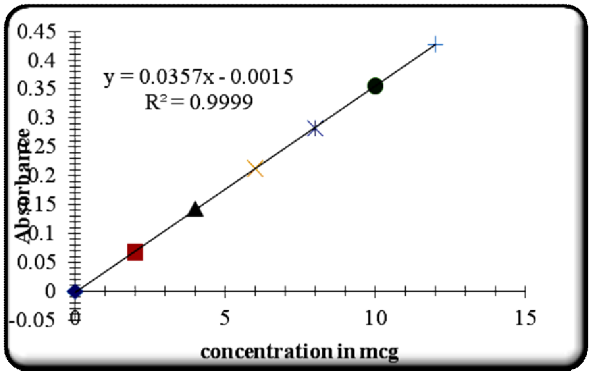

Fig 6: Standard Curve Of Nebivolol HCL

CONCLUSION:

Based on the results obtained from the pre and post compression studies along with the FTIR studies, Difference and similarity factors & release studies it has been proved that the dissolution has been improved with faster disintegration time by using the superdisintigrent cross carmellose sodium.

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