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Pharmaceutical Sciences **RESEARCH ARTICLE ……!!!**

SOLUBILITY ENHANCEMENT OF NEBIVOLOL BY USING SOLID DISPERSION TECHNIQUE AND FORMULATION OF FAST DISSOLVING TABLETS

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KEYWORDS:

Nebivolol, Solid dispersion, Fast dissolving tablets, *In vitro* dissolution studies.

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ABSTRACT

Nebivolol is a cardioselective β_1 receptor blocker with Nitric oxide-potentiating vasodilatory effect used in the treatment of hypertension. The major problem with this drug is its very low solubility in biological fluids, which results in poor bioavailability after oral administration. Therefore, solid dispersions of nebivolol with Guar gum and polyethylene glycol 6000 were prepared by using solvent evaporation method using different ratios with a view to increase its water solubility. *In vitro* dissolution rate of nebivolol from solid dispersion (SD) was significantly higher compared to pure nebivolol. XRD analysis indicated that crystalline drug changes into amorphous nature. FTIR analysis showed no interaction between Nebivolol, Guar gum and PEG 6000. Nebivolol solid dispersions with PEG 6000 (SD4) and Guar gum (SD8) showed maximum drug release. Thus, SD4 and SD8 were incorporated into FDTs containing super-disintegrants (Croscarmellose and sodium starch glycolate). The tablets prepared were evaluated for hardness, friability, drug content, disintegrating time, wetting time. The drug release profile was studied in Phosphate buffer pH 6.8. Among all formulations F8 (containing Guar gum SD and croscarmellose sodium) showed a maximum of 88.48 % drug release in 150 seconds and compared with conventional marketed tablet (Nebicard), which released 81.02% of drug in 45 minutes. F8 was subjected to stability studies. The formulation was found to be stable for two months at 40°C / 75% RH with insignificant change in the physical appearance and drug content.

INTRODUCTION:

Most of the new chemical entities (NCE) under development now-a-days are intended to be used as a solid dosage form that originates as an effective and reproducible route like greater stability, smaller bulk, accurate dosage and easy production. But the fact is most NCEs are poorly water soluble drugs, not well-absorbed after oral administration and the oral delivery of such drugs is frequently associated with low bioavailability and a lack of dose proportionality. In the process of absorption of drug from oral route, dissolution is the rate limiting step for lipophilic drugs. Therefore improving of dissolution is of great importance in order to ensure maximum therapeutic effect of these drugs. To overcome the problems associated with oral absorption and bioavailability issue, the solid dispersion (SD) technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous.[1] It refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. A number of drugs have been shown to improve their dissolution character, when converted to solid dispersions.[2,3] Because of its poor aqueous solubility, Nebivolol may pose dissolution related absorption problem. Hence, an attempt was made to improve the dissolution of Nebivolol through formulation of fast dissolving tablets (FDTs) containing solid dispersion of nebivolol, Guar gum and PEG 6000 using Croscarmellose sodium and sodium starch glycolate as superdisintegrants.[4,5]

MATERIALS AND METHODS

Materials

Nebivolol was obtained from Hetero Labs Ltd., Baddi. Guar Gum and PEG 6000 was obtained from S.D Fine Chemicals, Mumbai. Microcrystalline cellulose was obtained from DFE Pharma Ltd. All other chemicals were used of analytical grade and without any further chemical modification.

Methods

Formulation of Solid Dispersion (SD)

The SD was prepared by solvent evaporation method. Weighed amount of drug was dissolved in 20 ml of methanol. Then polymers (Guar gum and PEG 6000) were added in varying ratio's (D:P) 1:1, 1:2, 1:3, 1:4 respectively is shown in table 1. Methanol was completely evaporated by drying at 50°C for 5-25 min to obtain dry mass. The resultant mass was passed through 44 mesh sieve and stored in desiccators until used for further evaluation.[6]

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Table 1: Formulation batches of nebivolol solid dispersion

Solid Dispersions	Ratio	Drug + Polymer
SD1	1:1	Nebivolol + PEG 6000
SD2	1:2	
SD3	1:3	
SD4	1:4	
SD5	1:4	Nebivolol + Guar gum
SD6	1:3	
SD7	1:2	
SD8	1:1	

Evaluation of Solid Dispersion

Percentage yield

Thoroughly dried solid dispersion was collected and weighed accurately. The percentage yield was then calculated using formula given below.

$$\text{Percentage yield} = \frac{\text{Mass of solid dispersion obtained}}{\text{Total weight of drug and polymer}} \times 100$$

Estimation of drug content

Weighed quantity of SD equivalent to 10 mg of drug was added in 100 ml volumetric flask containing 5 ml of methanol. The material was mixed properly. The final volume was made up to 100 ml with phosphate buffer pH 6.8 and was spectrophotometrically analyzed at 282 nm.[7] The mean ± SD (standard deviation) values were calculated.

Fourier Transform Infrared Spectroscopy (FTIR)

The interference study was carried out using FTIR analysis. IR spectrum of pure drug and mixture of drug- polymer i.e. PEG 6000 and Guar Gum was performed for polymer drug interaction studies between 4000-400 cm^{-1} using KBr pellet method. The results are shown in figure 1 and 2.

X-Ray Diffraction (XRD) analysis

X-ray diffraction patterns were traced for Nebivolol, solid dispersion of Nebivolol with polymers using X-ray diffractometer (X'pert pro pan analytical). The samples were analyzed using nickel filter Cu Kα radiation under the following conditions: voltage 45 kV, current 40 mA, 2θ range of 5-50°C, sampling width 0.0170° and scan set was continuous.[8] The results are shown in figure 3, 4 and 5.

***In vitro* release studies of solid dispersion and pure drug (Nebivolol)**

The *in vitro* dissolution study was carried out in the USP dissolution test apparatus type 2 (paddle). 900 ml of phosphate buffer pH 6.8 maintained at 37± 0.5°C was taken as the dissolution medium.

The speed of the paddle was set at 50 rpm. 5 ml of the dissolution medium was withdrawn at selected time intervals (15, 30, 45, 60, 75, 90 min) and the same amount was replaced with the fresh medium. The sample withdrawn was filtered and analyzed by using UV spectrophotometer at 282 nm.[9] It was performed in triplicate.

Preparation of Fast Dissolving tablets (FDTs) containing Solid Dispersion by Direct Compression method

The SD formulation which showed maximum dissolution rate was selected to formulate FDTs. The SD equivalent to 10 mg of nebivolol was taken. Then it was mixed with directly compressible diluents and superdisintegrants in the mortar pestle. Magnesium stearate and talc were passed through sieve no. 60 and mixed with the initial mixture in the mortar pestle followed by compression of the blend.[10] The formulation composition is shown in table 2.

Table 2: Formulation chart of FDTs containing solid dispersion

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
SD with PEG 6000 (1:4)	25	25	25	25	-	-	-	-
SD with Guar gum (1:1)	-	-	-	-	25	25	25	25
Sodium starch glycolate	4	6	-	-	4	6	-	-
Croscarmellose sodium	-	-	4	6	-	-	4	6
Magnesium stearate	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2
Microcrystalline cellulose	117	115	117	115	117	115	117	115
Net weight (mg)	150	150	150	150	150	150	150	150

Evaluation of FDTs containing Nebivolol SDs

Evaluation of Pre-compression Parameters

The prepared powder blend was evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio. The results obtained are mentioned in table 3.

Angle of repose

Angle of repose (θ) was determined by using funnel method. The blend was poured through a funnel. The funnel was raised vertically until a maximum cone height (h) was obtained.[11] The radius of the heap (r) was measured and angle of repose was calculated using formula:

$$\theta = \tan^{-1} (h/r)$$

Bulk density and tapped density

10 g of the granules (W) were weighed and poured through funnel into a 100 ml measuring cylinder. The initial volume occupied by the sample was recorded. The cylinder was then allowed to fall under (tapped) its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.[12] The bulk density and tapped density were calculated using formula:

$$\text{Bulk density} = W/V_o$$

$$\text{Tapped density} = W/V_F$$

Where, W = weight of granules, V_o = initial volume of the granules and V_F = final volume of the granules.

Compressibility index (Carr's index)

The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which material can be induced to flow is given by % compressibility which is calculated using formula:[13]

$$C = (\rho t - \rho b) / \rho t \times 100$$

Where, ρt is tapped density and ρb is untapped density.

Hausner's ratio

Hausner's ratio is an index of ease of powder flow.[14] It is calculated by using formula:

$$\text{Hausner's ratio} = \rho t/\rho b$$

Where, ρt = Tapped density, ρb = Untapped density.

Evaluation of Post-compression Parameters

The prepared tablets were evaluated for post-compression parameters like weight variation, hardness, % friability, disintegration time, wetting time, dispersion time, drug content and dissolution studies. The results obtained are mentioned in table 4.

Weight variation: Twenty tablets were selected at a random from each formulation and average weight was determined. Then individual tablets were weighed and compared with the average weight.[15]

Tablet thickness: The thickness of tablet was determined by using screw guage. Average thickness and standard deviation of each formulation was determined.[16]

Hardness: Five tablets were randomly selected from each batch and hardness of tablets was determined by using Monsanto hardness tester.[17]

Friability: Friability of tablets was determined by using Roche Friabilator. Ten preweighed tablets were placed in chamber and subjected to 100 revolutions for 4 minutes. After these revolutions tablets were dedusted using a soft muslin cloth and reweighed.[18] The friability was calculated by using formula:

$$F = (W_0 - W) / W_0 \times 100$$

Where, W_0 is the weight of tablets before test, W is the weight of the tablet after the test.

Wetting time and Water absorption ratio: A piece of tissue paper folded double was placed in a Petri plate (internal diameter 6.5 cm) containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. For measuring water absorption ratio, the weight of the tablet before keeping in a petridish was noted (w_b). The wetted tablet from the petridish was taken and reweighed (w_a).[19] The water absorption ratio, R can be determined by using formula:

$$R = 100 (w_a - w_b) / w_b$$

***In vitro* dispersion time**

In vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 50 ml Phosphate buffer pH 6.8. The time required for complete dispersion of tablets was measured and the mean ± SD (standard deviation) values were calculated.[20]

% drug content determination

Five tablets were crushed in a glass mortar pestle. Then weight of powder equivalent to 10 mg Nebivolol was taken and dissolved in 100 ml of Phosphate buffer pH 6.8 in the volumetric flask. The flask was shaken for 4 h in a mechanical shaker. The solution was filtered through whatmann filter paper and analyzed at 282 nm using a UV-visible double beam spectrophotometer. Each sample was analyzed in triplicate.[21]

***In vitro* disintegration time**

Disintegration time of prepared tablets was determined in disintegration test apparatus. One tablet from each formulation was placed in each tube and the basket rack was positioned in a 1 litre beaker containing phosphate buffer pH 6.8 maintained at temperature 37± 2°C. The tablet should remain 2.5 cm below the surface of the liquid. The time taken for complete disintegration of the tablets with no particulate matter was noted[22] and the mean ± SD (standard deviation) values were calculated.

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***In vitro* Drug dissolution studies**

The dissolution profile of FDTs of nebivolol was carried out in a beaker containing 30 ml of Phosphate buffer pH 6.8 as a dissolution medium, maintained at 37 ± 0.5°C. The medium was stirred at 100 rpm. Aliquots (5 ml) of the dissolution medium were withdrawn at 15, 30, 45, 60, 75, 90, 105, 120, 135 and 150 sec time intervals and the same amount was replaced with the fresh medium. Samples were analyzed by using UV spectrophotometer at 282 nm. The percentage of the drug dissolved at various time intervals was calculated and plotted against time.[23] Then, the release profile of FDTs was compared with that of conventional marketed tablets.

Stability Study

The stability study of formulation (F8) was carried out at 40°C / 75% RH for two months. The tablets were wrapped in the aluminium foil and stored in a stability chamber at accelerated conditions.[24] The drug content was checked at regular time intervals of 15, 30, 45 and 60 days respectively and was evaluated for physical appearance. The results of drug content are shown in table 5.

RESULTS AND DISCUSSION

Evaluation of Solid Dispersions

Percentage Yield

The yield obtained was in the range of 66.7-91.2%. The maximum percentage yield was obtained in SD4 and SD8 with 89.57% and 91.2% respectively.

Estimation of drug content

The drug content obtained was in the range of 91.11±0.16 to 96.84±0.35 %. Maximum drug content was obtained in SD4 and SD8 solid dispersion with 93.46±0.22 % and 96.84±0.35 % respectively.

Fourier Transform Infrared Spectroscopy (FTIR)

It was observed that there is no interaction between drug and polymers shown in figure 1 and 2.

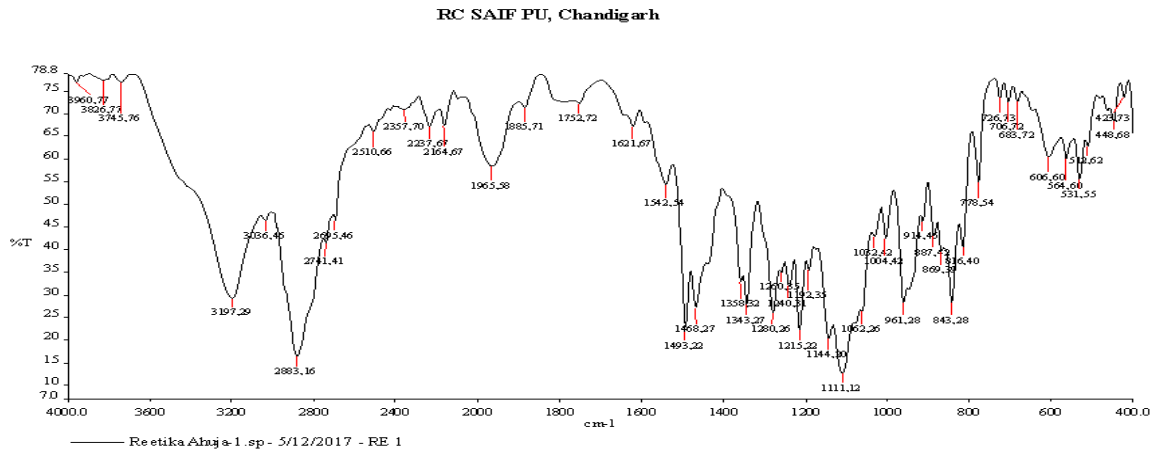

Figure 1: IR spectra of mixture Nebivolol + PEG 6000

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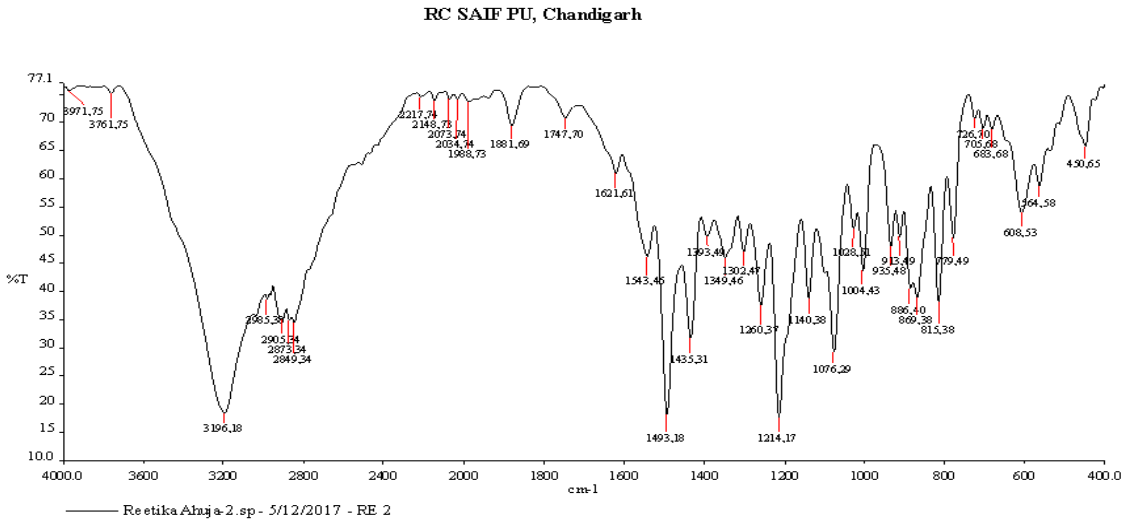

Figure 2: IR spectra of mixture Nebivolol + Guar Gum

X-Ray Diffraction (XRD) analysis

It was observed that the intensity of sharp peaks in the diffractograms of solid dispersions reduced considerably indicating the reduced crystallinity of the drug in all the cases of solid dispersions when compared to pure drug. This may be due to conversion of the drug to amorphous state from crystalline state as shown in figure 3 and 4.

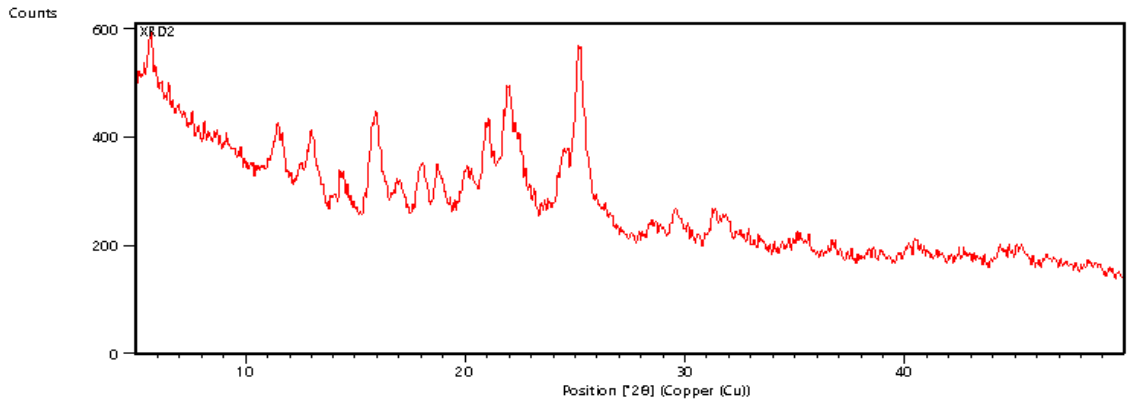

Figure 3: XRD of Nebivolol SD with guar gum

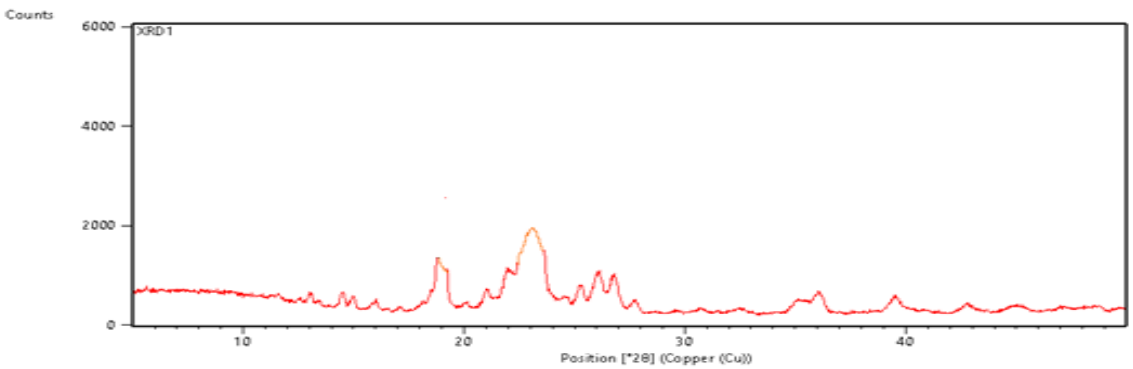

Figure 4: XRD of Nebivolol SD with PEG 6000

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***In vitro* release studies of solid dispersion and pure drug (Nebivolol)**

From the data, it was observed that maximum amount of drug released was obtained in SD4 and SD8 solid dispersion with 75.32% and 83.34% respectively in 90 min, whereas the pure drug released maximum 27.34 % of drug in 90 min. The graph is shown in figure 5. Hence, formulations SD4 and SD8 were selected for further formulation study of Fast Dissolving Tablets.

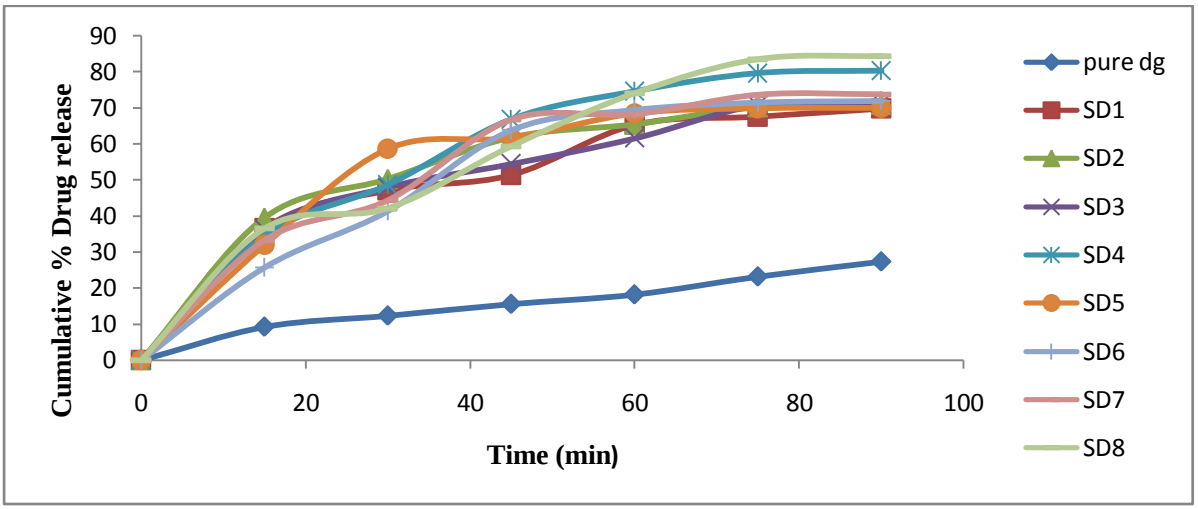

Figure 5: Cumulative % Drug Release of Nebivolol pure drug and SDs

Evaluation of FDTs containing Nebivolol SDs

Table 3: Data of Pre-compression parameters

Formulation Code	Angle of Repose (θ) ±SD	Bulk density (g/cc) ± SD	Tapped density (g/cc) ± SD	Carr's Index (%) ± SD	Hausner's ratio ± SD
F1	24.3±0.11	0.391±0.27	0.413±0.23	14.01±0.75	1.03±0.12
F2	28.65±0.07	0.402±0.12	0.433±0.17	15.60±0.42	1.02±0.65
F3	20.6±0.05	0.382±0.35	0.406±0.04	13.51±0.33	1.04±0.27
F4	22.73±0.01	0.418±0.24	0.523±0.41	12.73±0.22	1.04±0.06
F5	27.10±0.24	0.368±0.22	0.478±0.35	15.16±0.01	1.02±0.15
F6	26.49±0.11	0.434±0.05	0.502±0.26	13.23±0.17	1.031±0.17
F7	24.12±0.46	0.397±0.26	0.452±0.02	14.35±0.08	1.076±0.43
F8	24.67±0.54	0.471±0.06	0.568±0.04	12.28±0.04	1.06±0.04

*All readings were in triplicate (n=3)

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Table 4: Observation of post-compression parameters of FDTs

PARAMETER	F1	F2	F3	F4	F5	F6	F7	F8
Weight Variation test (mg) ±SD	148.96 ±0.01	149.61 ±0.04	151.03 ±0.03	150.32 ±0.04	148.36 ±0.01	149.94 ±0.13	149.59 ±0.01	150.07 ±0.03
Thickness (mm) ±SD	3.18 ±0.12	3.88 ±0.13	4.09 ±0.11	3.92 ±0.12	3.85 ±0.12	3.91 ±0.14	4.19 ±0.25	3.93 ±0.03
Hardness (kg/cm^2) ±SD	4.54 ±0.13	5.04 ±0.12	4.16 ±0.13	4.38 ±0.14	4.70 ±0.11	4.76 ±0.14	5.74 ±0.03	4.52 ±0.04
Friability (%) ±SD	0.393 ±0.08	0.433 ±0.14	0.922 ±0.05	0.521 ±0.12	0.507 ±0.04	0.425 ±0.09	0.758 ±0.12	0.514 ±0.02
Wetting time (sec) ±SD	34 ±0.06	22 ±0.09	36 ±0.12	19 ±0.04	26 ±0.07	29 ±0.11	26 ±0.14	18 ±0.05
Water absorption ratio (%) ±SD	87.48 ±0.12	89.47 ±0.14	88.05 ±0.06	98.36 ±0.16	94.65 ±0.19	96.93 ±0.13	95.22 ±0.12	98.10 ±0.01
***In vitro* dispersion time (sec) ±SD**	25 ±0.15	23 ±0.11	26 ±0.05	21 ±0.12	24 ±0.02	23 ±0.16	22 ±0.05	20 ±0.03
Disintegration time (sec) ±SD	32 ±0.15	31 ±0.09	33 ±0.16	27 ±0.02	30 ±0.12	25 ±0.07	31 ±0.19	24 ±0.03
%Drug content (%) ±SD	96.02 ±0.11	97.33 ±0.46	96.36 ±0.32	97.72 ±0.02	96.05 ±0.12	96.16 ±0.18	96.42 ±0.02	97.81 ±0.01

*SD= Standard Deviation

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***In vitro* Drug dissolution studies**

From the data, formulation F4 released 79.21 % of drug whereas the formulation F8 released 88.48 % of drug in 150 seconds. On the basis of drug release, formulation F8 containing croscarmellose sodium as superdisintegrant released drug at a faster rate. Therefore, formulation F8 was selected as the best formulation. The graph between cumulative % drug release versus time is shown in figure 6.

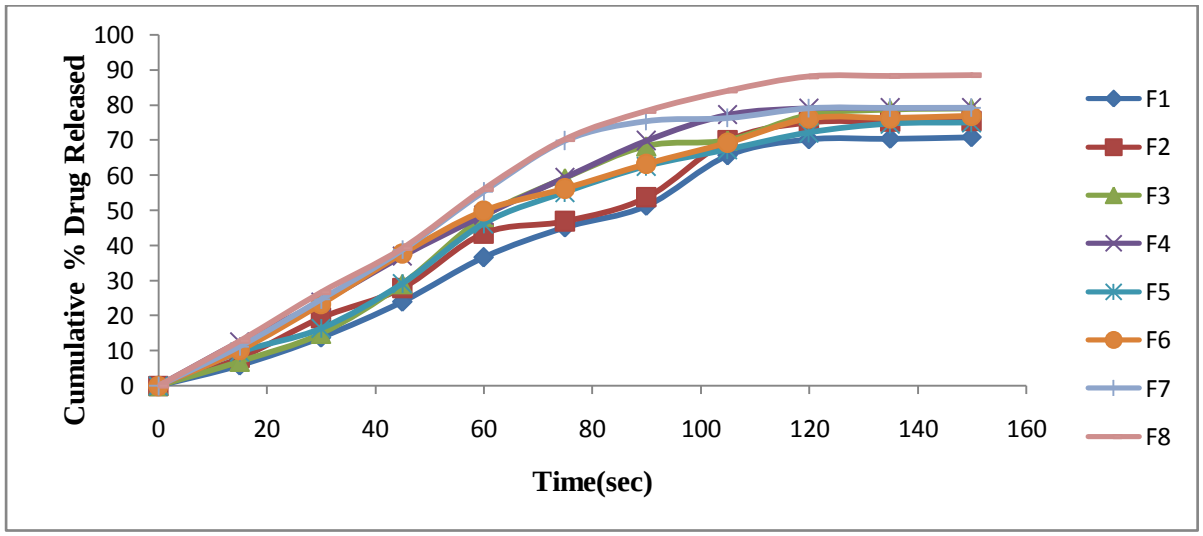

Figure 6: Graph showing Cumulative % Drug Release from FDTs

Comparative Study of Formulation 'F8' with Nebivolol marketed formulation (Nebicard)

Formulation F8 was compared with conventional Nebivolol tablet. Nebivolol conventional tablet released 81.02% of drug in 45 minutes, whereas Nebivolol fast dissolving tablet released 88.48% of drug in 150 seconds. After comparing the drug profile of both the formulations it is clear that fast dissolving tablet of Nebivolol released drug rapidly in a short span of time as compared to conventional Nebivolol tablet. Data of percentage drug release for conventional Nebivolol and graph is shown in figure 7.

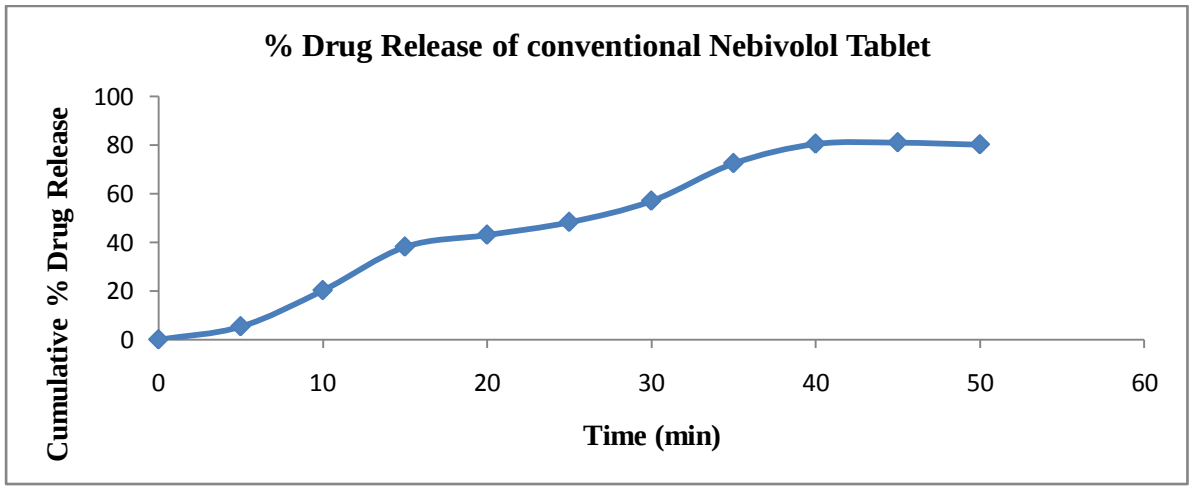

Figure 7: Cumulative % Drug Release profile of marketed formulation

Stability Study

There was no significant change in physical appearance, Drug content at the end of two months and the results of drug content is shown in table 5.

Table 5: Drug Content data during Stability Study

Time (days)	Accelerated Conditions (40± 2°C / 75 ± 5% RH)	
	Physical Appearance	Drug Content
0	+	97.81±0.06
15	+	96.43±0.11
30	+	96.24±0.07
45	+	95.52±0.03
60	+	95.03±0.16

(+) indicates no change in physical appearance

CONCLUSION:

In the present research work, an attempt was made to formulate fast dissolving tablets of Nebivolol. As Nebivolol is a BCS Class II drug with low solubility and high permeability. Therefore, the solid dispersions were prepared to improve the solubility of the drug. They were prepared by solvent evaporation method using two different polymers i.e. Guar Gum and PEG 6000. On the basis of dissolution studies SD4 and SD8 solid dispersions were selected for tableting. Eight formulations of fast dissolving tablets were prepared. All the formulations F1 to F8 were subjected to *in vitro* release studies and formulation F8 showed maximum release 88.48% of drug in 150 sec. The release rate was compared with the conventional marketed tablet (Nebicard). It can be concluded that the FDTs containing Nebivolol with Guar gum (F8) is better than conventional marketed tablet for getting better therapy. Hence, side effects associated with the low solubility and the dose of Nebivolol can be minimized to a greater extent.

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