WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 5, 1026-1039. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF NEBIVOLOL HYDROCHLORIDE FAST DISSOLVING TABLETS BY USING HYDROPHILIC POLYMERS

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Article Received on
20 Feb. 2020,
Revised on 12 March 2020,
Accepted on 02 April 2020
DOI: 10.20959/wjpr20205-17235

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ABSTRACT

The purpose of this research was to develop Nebivolol fast dissolving tablets. Nebivolol hydrochloride is the racemate (dl-nebivolol hydrochloride) of the enantiomers l-nebivolol hydrochloride and d-Nebivolol hydrochloride. It is a competitive and highly selective β1 receptor antagonist with mild vasodilation properties, possibly due to an interaction with the L-arginine/nitric oxide pathway. Six formulations of Nebivolol 250 mg were formulated by direct compression technique using different hydrophilic polymer grades such as PEG-400, HPMC K4 were used as polymers in different concentrations and other ingredients are, Micro crystalline cellulose (MCC), sodium starch glycolate (SSG), mannitol, Talc and Magnesium stearate before the formulation the granules are evaluated by pre-compression studies like density, floe properties, FT-IR and DSC. The obtained tablets were evaluated with different post-compression parameters like hardness, friability, thickness, weight variation, *In-vitro* disintegration studies and *In-vitro* dissolution studies. The formulation F1 was selected as an optimized formulation because it gives best results in terms of *In - vitro* drug release in a fast release manner and best fitted to first order model with r value of 0.999.

KEYWORDS: Nebivolol Hydrochloride, PEG-400, HPMC K4M, Micro Crystalline Cellulose (MCC), Sodium Starch Glycolate (SSG), Mannitol, Fast Dissolving Tablets.

INTRODUCTION

Recent day's blood pressure can lead to major health issue like heart disease, stroke and death. In this case quick onset of action needs to control the blood pressure. So there is a need to develop fast dissolving tablets. The fast dissolving tablets are rapid onset of action, patient convince and more bio availability. Nebivolol hydrochloride is the racemate (dl-nebivolol hydrochloride) of the enantiomers l-nebivolol hydrochloride and d-Nebivolol hydrochloride. It is a competitive and highly selective β1 receptor antagonist with mild vasodilating properties, possibly due to an interaction with the L-arginine/nitric oxide pathway and it is also used for hypertension. Treatment with nebivolol leads to a greater decrease in systolic and diastolic blood pressure than atenolol, propranolol, or pindolol. Nebivolol and other beta blockers are generally not first line therapies as many patients are first treated with thiazide diuretics. Nebivolol is a beta blocker used to treat high blood pressure and heart failure. The basic goal of this investigation is to achieve steady state blood level of that Nebivolol hydrochloride is therapeutically effective. Frist dissolving tablets, with an aim of improved. Better therapeutic efficacy. Reduced dosage regimen, for treatment of many diseases. Keeping this in view the present investigation has aimed at designing a suitable fast dissolving tablets by using Hydrophilic polymers. Nebivolol hydrochloride was chosen as the model candidate for this study since it possesses near ideal characteristics that a drug must have in formulating a fast dissolving drug delivery system following benefits.to improve maximum bioavailability, Avoidance of first pass metabolism., Maximum therapeutic effect, Dose reducing., Onsite action is high. In the present study the polymers selected as PEG-400, HPMC K4, acting as fast release action and to evaluate the different parameters to optimized and best formula.

MATERIALS AND METHODS

Nebivolol (Hetero Drugs Limited, Hyderabad), PEG-400 (Finar Chemicals Gujarat), HPMC K4M (Chemiloids, Vijayawada), Micro crystalline cellulose (Chemiloids, Vijayawada) Sodium Starch Glycolate (S.D. Fine-Chem limited, Mumbai), Talc (Reidel Chemicals, Hapur) and Magnesium stearate (S.D. Fine-Chem limited, Mumbai.)

METHODS

Pre- formulation studies

Bulk Density (Db)

It is the ratio of the mass of powder to the bulk volume of powder. It was measured by

pouring the weight powder into a measuring cylinder and the volume was noted. It is expressed in gm /ml and is given by

$$Db = M/Vb$$

Where, M= mass of powder. Vb = bulk volume of the powder.

Tapped Density (Dt)

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by

$Dt = M/Vt$

Where, M=mass of powder. V_t = tapped volume of the powder.

Carr's Index (I)

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$I= Dt-Db/Dt*100$$

Where, D_t =tapped density of the powder. D_b = bulk density of the powder.

Angle of Repose (θ)

The friction force sin loose powder can be measured by the angle of repose θ. It is defined as maximum angle possible between the surface of a pile of powder and the horizontal plane.

$$\text{Tan } \theta= h/r$$

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

Where θ= is the angle of repose

h = is the height

r= is the radius.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

FT-IR Spectral studies

The IR spectra for the formulation excipients and pure drugs were recorded on Jasco FT-Infrared spectrophotometer using KBr palette technique (1:100) at their solution rate of 4cm-1. Spectrum was integrated in transmittance mode at the wave number range 400 - 4000 cm-

1utions were.

Differential scanning calorimetry

Conventional DSC and MTDSC experiments were performed using DSC Q200 (TA Instruments, NJ, USA) with a refrigerated cooling assembly (RCS) and a modulated capability. The DSC cell was purged with 50 ml/min dry nitrogen, and the RCS was purged with 150 ml/min nitrogen. The DSC cell was calibrated for baseline using empty pans of matched weight and for temperature using three temperature standards (cyclohexane, $T_m = 279.54^o$ K; indium, $T_m = 429.61^o$ K; tin $T_m = 504.93^o$ K). About 3-5 mg of samples was exposed to the desired heating rates from the desired starting temperature to above the melting point of nebivolol under dry nitrogen purging (50 ml/min) in hermetically sealed aluminum pans. The data was analyzed using Universal Analysis Software from TA Instruments.

Analytical method for estimation of Nebivolol

U. V Spectrophotometer

Calibration curve of the pure drug Nebivolol was prepared in the concentration range from 2-1µg/ml at the wavelength of 282 nm by using 0.1N HCL buffer solutions. A graph of absorbance vs concentration was plotted which indicated in compliance to Beer's law in the concentration range. The calibration curve showed good linearity and regression coefficient (r2) value is 0.999, and intercept 0.006.

Preparation of standard Stock solution of Nebivolol

100 mg of Nebivolol was dissolved in 100 ml of 0.1N HCL buffer in a100 ml volumetric flask and made up to the volume with 0.1N HCL buffer. From this 1 ml of solution was taken and made to 100 ml with 0.1N HCL buffer.

Method

For the estimation of Nebivolol in 0.1N HCL buffer the stock solution has to be diluted subsequently with 0.1N HCL buffer to get a series of dilutions containing 2, 4, 6, 8, 10 µg/ml of solution. The absorbance of the solution was measured at 282 nm against blank. The calibration curve was constructed.

Formulation of Nebivolol Fast Dissolving tablets

Nebivolol Fast Dissolving tablets were prepared by direct compression method. Six formulations of tablets each containing 250 mg dose of Nebivolol. Were prepared with different concentrations of various excipients which were shown in given below. Nebivolol and polymers such as PEG-400, HPMC k4 M and SSG were accurately weighed, mixed uniformly and passed through # 40 mesh. Microcrystalline Cellulose and mannitol is used as diluents were weighed accurately and passed through #40 meshes. Both were mixed properly and the mixture of Talc and magnesium stearate was added and mix for few minutes. Then the above mixture was compressed in to tablets by using station rotary compressed machine with punch size of 8 mm.

Table 1: **Formulation of Nebivolol Fast Dissolving tablets.**

Ingredients mg/tab	**Formulation**					
	F1	F2	F3	F4	F5	F6
API (Nebivolol)	10	10	10	10	10	10
PEG-400	10	20	30	-	-	-
HPMC K4	-	-	-	10	20	30
SSG	10	15	20	10	15	20
MCC	166	151	136	166	151	136
Mannitol	50	50	50	50	50	50
Magnesium Stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Total weight (mg)	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg

Post- compression of Nebivolol Fast Dissolving tablets

Weight variation test

The weight variation test is performed by taking 20 tablets from each formulation and weighing the individual tablets by using electronic balance. Their average weight was calculated as

$$\% \text{ Weight variation} = (WA - WI) \times 100 / WI$$

Where,

WI = Individual weight of the tablets

WA = Average weight of the tablet

Thickness

Thickness of the tablets was determined using vernier calipers. Five tablets from each batch were used, and an average value was calculated.

Hardness (kg/cm^2)

Hardness of the tablets was tested using a Monsanto hardness tester. Five tablets from each batch were tested for hardness.

% Friability

Friability of the tablets was determined in a roche friabilator. Ten tablets were weighed initially (w_1) and placed in the friabilator that revolves at a speed of 25 RPM, dropping those tablets at a distance of six inches height with each revolution and rotated in the friabilator for 100 revolutions. After completion of rotations, the tablets were dedusted and weighed (w_2).

The percent loss in weight or friability (f) is calculated by using the formula.

% Friability= (Initial weight- Final weight)/ Initial weight × 100

***In-vitro* disintegration studies**

In -vitro disintegration time was performed by apparatus specified in USP. The water was used as disintegration medium, and the temperature was maintained at 37±2°C and the time in seconds taken for the complete disintegration of the tablet, with no palpable mass remaining in the apparatus, was measured in seconds.

***In-vitro* dissolution studies**

In-vitro dissolution study was performed by using USP type II dissolution test apparatus (paddle type) [Lab, India (DS-8000, Mumbai)] at 75 RPM. 900ml of 0.1N HCL buffer was used as the dissolution medium which was maintained at 37±0.5^{o}C. Aliquots of dissolution medium (5mL) were withdrawn at specific time intervals (10min, 20min, 30min, 40min, 50min and 60min) and were filtered. The amount of drug dissolved was determined by UV spectrophotometer by measuring the absorbance of the sample at 282nm.

RESULTS AND DISCUSSION

Formulation of fast dissolving tablets of nebivolol hydrochloride utilizing the natural polymers like PEG-400, HPMCK4 and then super disintegrants impact on *In- Vitro* dissolution study were carried out by addition of these polymers.

Pre-formulation studies: Active pharmaceutical and excipients were blended and evaluated for different parameters as clarified before. Bulk density was found in the limit of 0.419 - 0.510 g/cm3 and the tapped density between 0.622 - 0.640 g/cm3. By using both density data, Carr's compressibility was determined. The compressibility record was found between 18.20-

23.75%, and the Hausner's ratio was found to be 1.22-1.32. The result shows good flow properties of blend. The good flow properties of powder were also evident from angle of repose that range from 23.01-25.17°. In the present examination all powder mixes indicated excellent flow property. The outcomes are appeared in Table no 2.

Table 2: Micromeritic properties of the granules of Nebivolol formulation.

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Angle of repose(ɵ)	Compressibility Index (%)
F1	0.510	0.634	1.31	23.01	18.20
F2	0.491	0.626	1.32	24.18	18.30
F3	0.500	0.622	1.29	25.11	20.57
F4	0.510	0.632	1.28	23.23	21.42
F5	0.508	0.640	1.27	25.17	22.80
F6	0.509	0.636	1.22	23.15	23.75

FT-IR Spectral studies

FT-IR studies

From the FT-IR spectra, it was concluded that similar characteristic peaks with minor difference for the drug and the FT-IR formulation. Hence, it appears that there was no chemical interaction between the drugs and excipients used**.** The IR Spectra of nebivolol with PEG-400, HPMCK4, SSG, and MCC were shown. The following peaks were observed in as well as nebivolol with excipients.

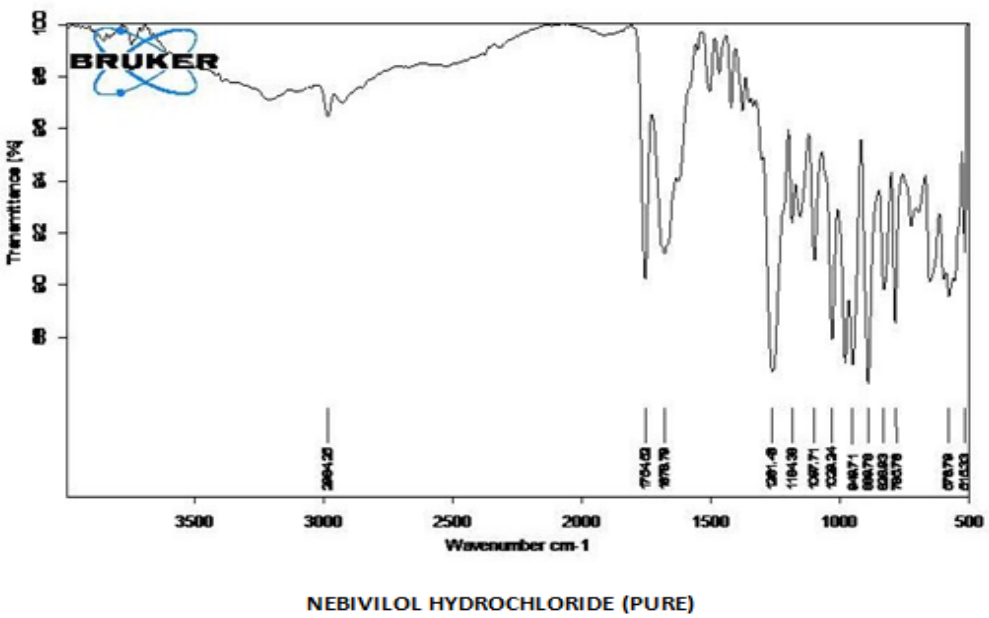

Fig 1: FT-IR Reports of Nebivolol hydrochloride.

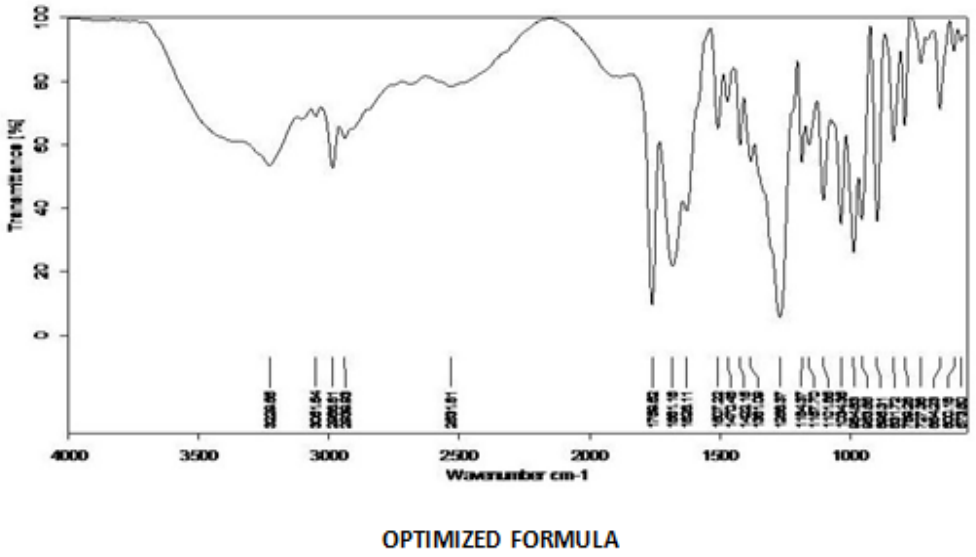

Fig 2: FT-IR Reports for optimized formula.

Differential scanning calorimetry

DSC indicated better drug stability presence of hydrophilic polymers. A stronger drug amorphization and entrapment in hydrophilic polymers was observed.

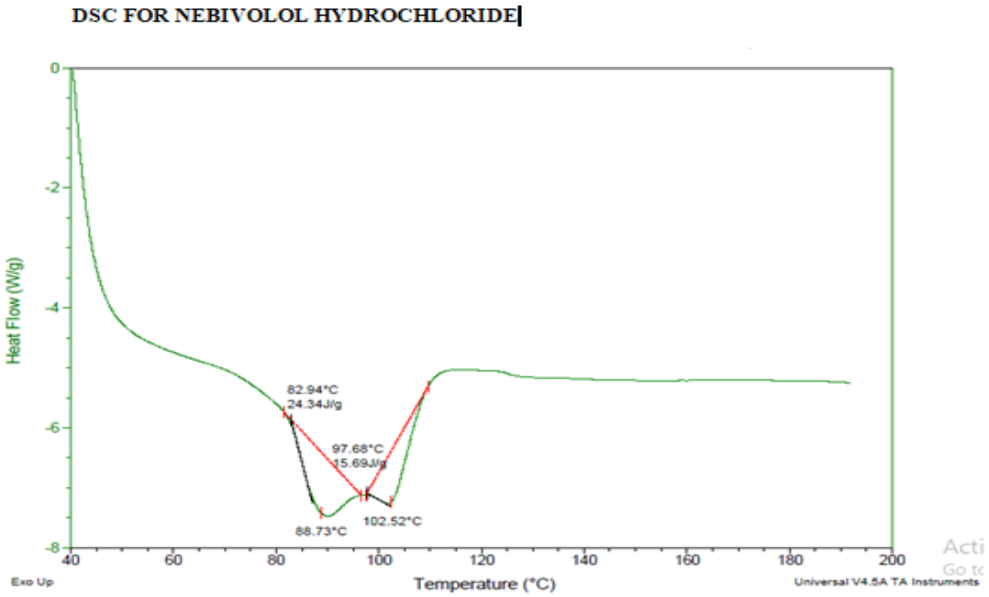

Fig 3: DSC Reports for Nebivolol hydrochloride.

Analytical method development

Nebivolol was estimation using UV/VIS spectrophotometer method .it was found that under UV/VIS spectrophotometer standard absorbance of the peak of nebivolol was 0.719 µg/ml,

Table 3: Standard Calibration Data of Nebivolol in 0.1N HCl.

Concentration (µg/ml)	Absorbance (nm)
0	0
2 (µg/ml)	0.259
4 (µg/ml)	0.501
6 (µg/ml)	0.719
8 (µg/ml)	0.971
10 (µg/ml)	1.226

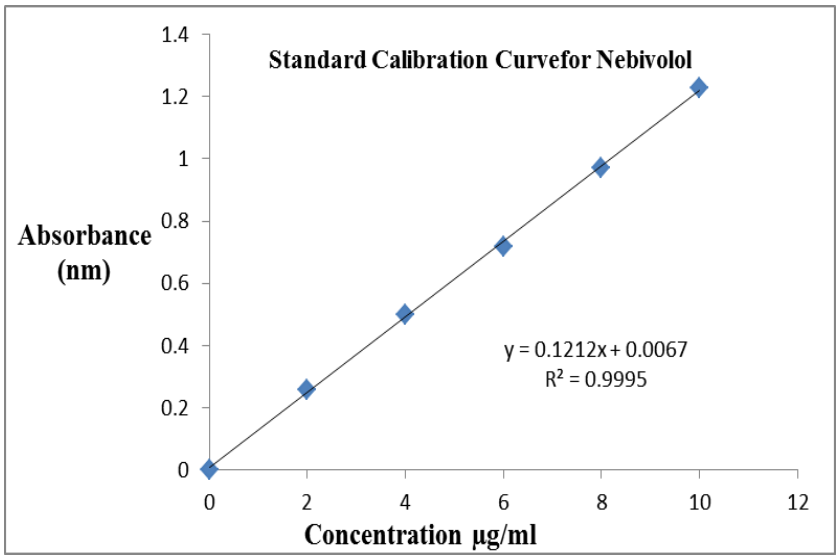

Fig 4: Calibration curve of Nebivolol 0.1N HCl.

Post – compression parameters

The preliminary studies were carried out by preparing various formulations with different process variable and subjecting the formulation to all post-compression parameters has fulfilled according to IP standards.

Weight variation: Average weight of 20 tablets of Nebivolol was calculated for each formulation which varied from mg 242.3 ± 1 to 234.4 ±3 mg. the complied the official requirements as per IP.

Tablet thickness: The thickness of the Nebivolol formulation varied from 2.00±0.06 mm to 2.35 ±0.06 mm.

Tablet hardness (kg/cm^2): The hardness of the tablet developed formulation shows 4.1 ±1.0 kg/cm^2 to 4.5±1.0 kg/cm^2.

%Friability: The friability of the developed formulation varied from 0.352±0.1% to 0.101±0.01% loss which was less than 1% as per official requirement of IP.

***In-Vitro* Disintegration studies:** *In-vitro* disintegration study was performed by using USP disintegration test apparatus [Lab, India] 900ml of water was used as the disintegration medium which was maintained at 37±0.5^{o}C. The tablet was disintegrated in the medium was found to be 105.47 to 120.1 sec.

Table 4: Post compression parameters of Nebivolol fast dissolving tablets.

Formula	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	% Friability (% loss)	Disintegration time (sec)
F1	234.4	2.00	4.5	0.1	105.4
F2	241.5	2.10	4.1	0.1	120.1
F3	238.2	2.35	4.3	0.1	107.3
F4	239.4	2.21	4.2	0.1	117.4
F5	237.7	2.13	4.1	0.1	109.6
F6	242.3	2.28	4.2	0.1	112.2

***In-Vitro* Dissolution studies of Nebivolol Fast Dissolving tablets**

In-vitro dissolution study was performed by using USP type II dissolution test apparatus (paddle type) [Lab, India (DS-8000, Mumbai)] at 75 RPM. 900ml of 0.1 N HCL was used as the dissolution medium which was maintained at 37±0.5^{o}C. Aliquots of dissolution medium (5mL) were withdrawn at specific time intervals (10min, 20, 30, 40, 50 and 60 min) and were filtered by micron filters. The amount of drug dissolved was determined by UV-spectrophotometer by measuring the absorbance of the sample at 282 nm. The all six formulation are prepared by using different concentrations of polymers like PEG-400 and HPMC-K4. f1,f2 and f3 contains the PEG-400 was prepared in Nebivolol Fast Dissolving tablets the drug released in formulation f1 is 98.23% in 40 min, f2 is 60.25% in 50min and f3 formulation drug released is 72.21% in 60 min, f4 formulation the drug released was 85.38% in 60 min, f5 formulation the drug released was 79.53% in 60 min and f6 formulation the drug released was 82.58% in 60 min. The optimized formulation f1 the prepared with PEG-400 the dissolution medium was 0.1 N HCL the drug released in formulation f1 is 98.21% in 40 min.

Table 5: Dissolution studies for Nebivolol fast dissolving tablets.

Dissolution with 0.1N HCL buffer, 900ml,RPM 75, λ max 282 nm							
% Cumulative Drug Release							
S.NO	Time (mints)	F1	F2	F3	F4	F5	F6
1.	0	0	0	0	0	0	0
2.	10	39.56	31.55	28.14	16.8	18.15	25.05
3.	20	59.63	39.57	36.40	36.21	40.20	36.24
4	30	89.65	48.96	42.50	58.36	53.35	51.33
5	40	98.23	56.02	51.82	69.61	65.57	63.21
6	50	89.23	60.36	62.98	78.83	71.96	78.90
7	60	78.63	52.31	72.36	85.39	79.46	82.32

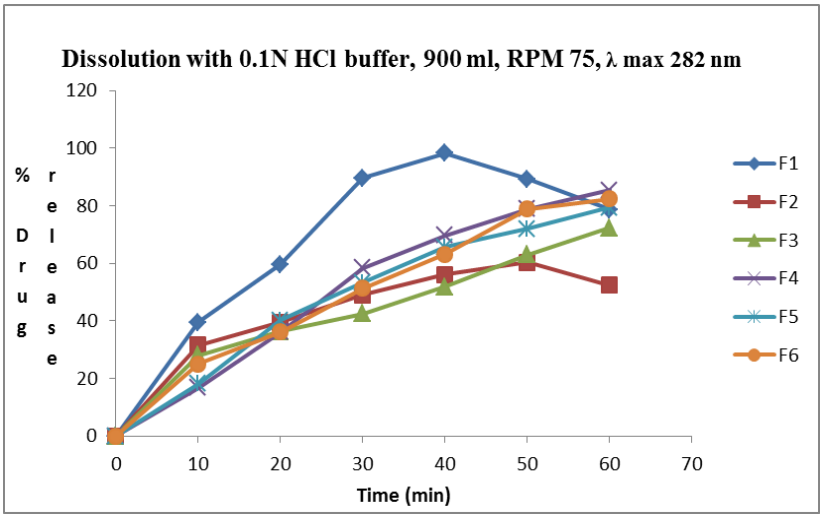

Fig. 5: % Release graph of Nebivolol fast dissolving tablets with PEG-400 (F1-F3) and HPMCK4 (F4-F6).

Table 22: Dissolution kinetics of nebivolol hydrochloride fast dissolving tablets with PEG-400 and HPMCK4.

Correlation co-efficient				
Formulation	Zero order	First order	Higuchi	Pappas
F1	0.924	0.990	0.999	0.971
F2	0.942	0.986	0.997	0.966
F3	0.959	0.975	0.996	0.938
F4	0.932	0.868	0.996	0.937
F5	0.926	0.987	0.996	0.791
F6	0.957	0.980	0.997	0.931

CONCLUSION

Nebivolol was chosen as the model candidate for this study since it possess near ideal characteristics that a drug must have in formulating a fast dissolving drug delivery system. It has low solubility and high permeability, effective in low plasma concentration and high

degree of first pass metabolism. In this present study the tablets were prepared by using direct compression technique. All the formulations were evaluated for physical characteristics, pre-compression and post-compression, *In-vitro* disintegration studies and *In-vitro* dissolution studies. The pure drug *In-vitro* dissolution studies % drug release was found to be 90% at the end of 8 hour, when compared to pure drug release the F1 formulation showed 98% drug release at the end of 40 min time. Finally we have found that from all the formulations (F1-F6) only F1 formulation has successfully attained the fast release for 40 min. The optimized formulation F1 showed highest R^2 value i.e. 0.990 for first order plots indicating that release of drug follows first order kinetics, and mechanism of release was fitted to higuchi equation with the n value of 0.999 indicating anomalous fickian diffusion mechanisms and may indicate that the drug release is higher by more than one process. Thus, in the present investigation, finally concluded that fast dissolving tablets of nebivolol were successfully designed by direct compression method and evaluated. It can be concluded that PEG-400 can be used as an effective release to fast dissolving tablets of nebivolol for the period of 40 min.

ACKNOWLEDGEMENT

I express my sincere thanks to Dunna janardhana Rao garu (Chairman), P.Kanaka Raju garu (Secretary), Ch.Kaliki Murthy garu (Vice President), P.Nagamani garu, and Dr. B. Bhavani (principal) Koringa College of pharmacy, Jawaharlal Nehru Technological University for providing me necessary research facility and also thankful to my parents.

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