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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF NEBIVOLOL HYDROCHLORIDE

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ABSTRACT

In the present work fast dissolving tablets of Nebivolol hydrochloride were prepared using a combined effect of various super disintergrants consisting of sodium starch glycolate, cros carmellose sodium and crospovidone in different ratios (1:1, 1:2 & 1:3) in vice versa. Nebivolol hydrochloride is a drug choice in the treatment of hypertension. Drug compatibility with excipients was checked by FT-IR studies. The powder blends were subjected to pre-compression parameter. All the formulation was subjected to post compression parameter indicated that tablets had a good mechanical strength and resistance. Drug content was found to be in the range 93.51% - 98.99%. Among all the formulation, formulation F9 was found to be promising and was displayed an *in-vitro* disintegration time of 110 sec. When compared to marketed product, the formulation F9 containing combined form of super disintegrants (1:3 mixture of cross carmellose sodium and crospovidone) emerged as the overall best formulation based on drug release characteristics with 0.1 N hydrochloric acid as dissolution medium . Short term stability studies on promising formulation F9 indicated that were no significant changes. From this study, it can be concluded that dissolution profile, drug release rate was increased significantly with increase in ratio of superdisintegrants i.e. higher the concentration of super disintegrants greater the drug release.

Key words: Nebivolol hydrochloride, sodium starch glycolate, cross carmellose sodium and crospovidone.

INTRODUCTION

The oral route is the most favourable route for administration of drugs because of low cost of therapy, accurate dosage, non-invasive method, self-medication and ease of administration leading to a high level of patient compliance [1].

United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as “A solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue. Fast dissolving tablets are also known as mouth dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapid melts, porous tablets, quick dissolving tablet. Fast dissolving tablets dissolve or disintegrate in the oral cavity without the need of water [2].

Advantages of Fast Dissolving Tablets

1. Quick onset of action and improved bioavailability.
2. Useful for patients who cannot swallow the dosage forms and for pediatric, geriatric and mentally retard patient.
3. Frequently administered when water is not available [3].

Disadvantages of Fast Dissolving Tablets

1. The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
2. The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
3. Drugs with relatively larger doses are difficult to formulate into FDT e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500mg of the drug [4].

Hypertension

Hypertension is a common disease that is simply defined as persistently elevated arterial blood pressure (BP). Although elevated BP was perceived to be "essential" for adequate perfusion of essential organs during the early and middle 1900s, it is now identified as one of the most significant risk factors for cardiovascular disease [5].

These are drugs used to lower BP in hypertension. Antihypertensive drug therapy has been remarkably improved in the last 50 years. Different classes of drugs have received prominence with passage of time in this period [6].

Nebivolol hydrochloride

Nebivolol hydrochloride is chemically known as α, α-[iminobis (methylene)] bis [6-flouro-3,4-dihydro-2H-1-benzopyran-2-methanol]hydrochloride.

It is a highly selective β1-blocker with nitric oxide mediated vasodilatory actions and beneficial effects on vascular endothelial function. Nebivolol is used in the management of hypertension. It is given by mouth as the hydrochloride although doses are expressed in terms of base. The usual dose is 5 mg daily. An initial dose of 2.5 mg daily is employed in the elderly and in patients with renal impairment [7].

MATERIALS AND METHODS

Nebivolol hydrochloride (yarrowchem limited), Cross carmellos sodium (Balaji drugs), Crospovidone (Indian fine chem limited), Sodium starch glycolate, Micro crystalline cellulose, Saccharin sodium, Magnesium sterate, Lactose and Talc (S.D fine chem limited).

Preparation of Fast Dissolving Tablets by Direct Compression Method

Nebivolol hydrochloride fast dissolving tablets were prepared by direct compression method by using various super disintegrants like crospovidone, sodium Starch Glycolate and cross carmellose sodium. Microcrystalline Cellulose and Lactose as a diluent, Sodium saccharin as a sweetening agent, Magnesium Stearate, Talc are used as a lubricant and glidant. All the ingredients (except granular directly compressible excipients) were passed through # 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order after sufficient mixing of drug as well as other components and compressed into tablets of 150mg using 8mm round flat punches on 12 station rotary tablet machine.

Standard Calibration Curve of Nebivolol Hydrochloride in Methanol

Nebivolol hydrochloride (100 mg) was accurately weighed and dissolved in small amount of methanol and volume was made up to 100 ml, (=1000µg/ml) to get stock-I solution. From the stock –I, take 1 ml of the above solution isdiluted to 100ml in water, (=100 µg/ml) in another volumetric flask which is get to Stock-IIsolution. From this stock-II solution serial dilutions were made by pipetting out 1 ml, 2 ml, 3 ml, 4 ml, and 5 ml to obtain solutions of the drug inthe concentration ranging from 1, 2, 3, 4, 5, µg/ml respectively. Theabsorbance of the solutions was measured at 281nm using UV-visible spectrophotometer.A graph of concentration Vs. absorbance was plotted.

Evaluation of Fast Dissolving Tablets

The pre-compression parameter and post-compression parameter like bulk density, tapped density, angle of repose, carr's index, hausners ratio, friability, hardness, weight variation, hardness were evaluated as per the literature [8,9].

Compatibility studies:
A successful formulation of a stable and effective solid dosage form depends on careful selection of the excipients that are added to facilitate administration that promote the consistent release and bioavailability of the drug and protect it from degradation. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies are of paramount importance. Compatibility of the drug with the excipients is determined by subjecting the physical mixture of the drug and the polymers of the main formulation to infrared absorption spectral analysis (FT-IR).Any changes in chemical composition of the drug after combining it with the polymers were investigated with FT-IR spectral analysis.

Procedure: Weighed amount of drug (3mg) was mixed with 100mg of potassium bromide (dried at 40-50oC). The mixture was taken and compressed under 10-tonpressure in a hydraulic press to form a transparent pellet. The pellet was scanned by IR spectrophotometer.Similar procedure is followed for all relevant excipients used.

***In-vitro* dissolution studies [10]:**
Dissolution testing of Nebivolol hydrochloride fast dissolving tablets was carried out with paddle type in USP dissolution apparatus at rpm 50 and temperature 37±0.5°C in 0.1N Hydrochloric acid. At each specified intervals of time 5 ml sample was withdrawn and replaced by fresh media. The samples were analytically tested to determine the concentration by UV spectroscopy method at wavelength of 281 nm.

Mathematical modeling of drug release profile [11]:
The cumulative amount of Nebivolol hydrochloride release from the formulated tablets at different time intervals were fitted to zero order kinetics, first order kinetics, higuchi model and korsmeyer-peppas model to characterize mechanism of drug release.

Stability Studies [12]:
Stability can be defined as the capacity of drug product to remain within specifications established to ensure its identity, strength, quality, and purity.
Storage conditions:

Table no 1: Drug substances intended for normal storage

Study	Storage conditions	Minimum period of time
Long term	25ºC ±2 ºC/60%RH±5%RH 30 ºC±2 ºC/65%RH±5%RH	12 Months
Intermediate	30 ºC±2 ºC/65%RH±5%RH	6 Months
Accelerated	40 ºC±2 ºC/65%RH±5%RH	4 Months

RESULTS AND DISSUSION

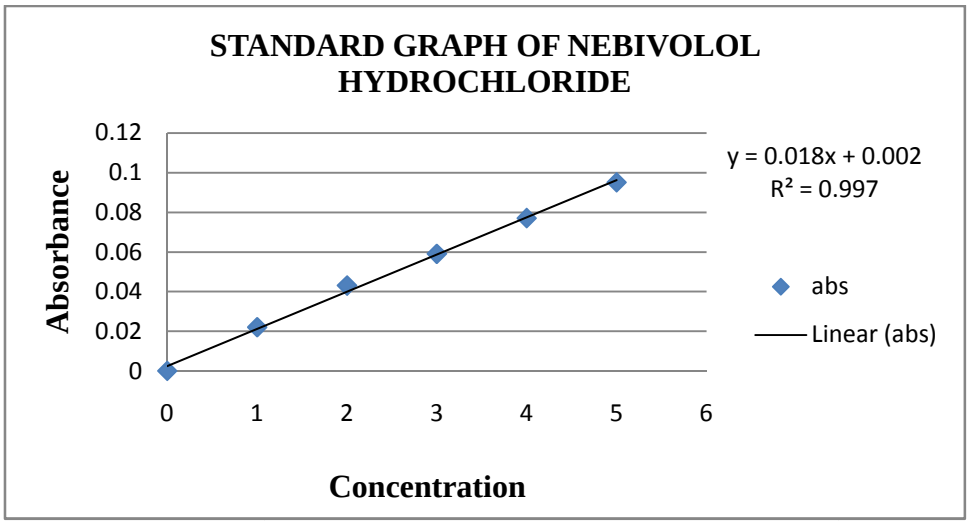

Figure 1: Standard graph of Nebivolol hydrochloride

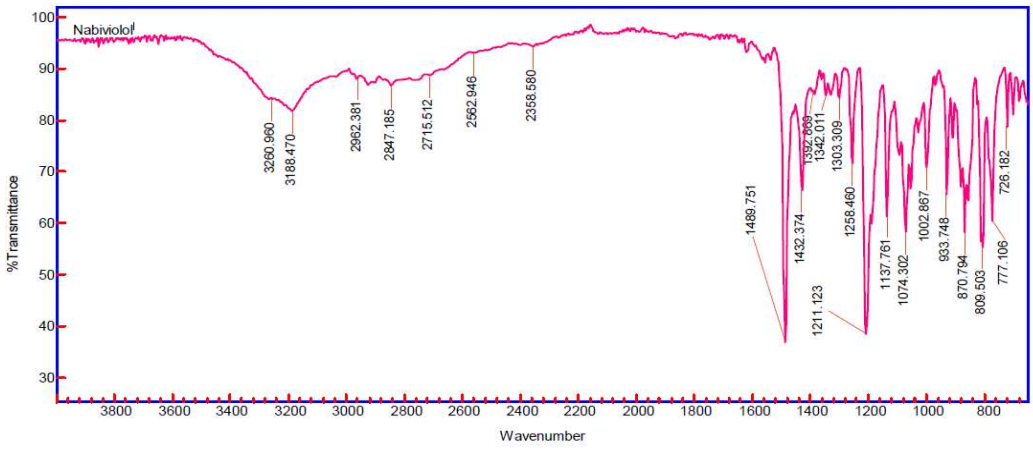

Figure 2: IR spectrum of Nebivolol hydrochloride

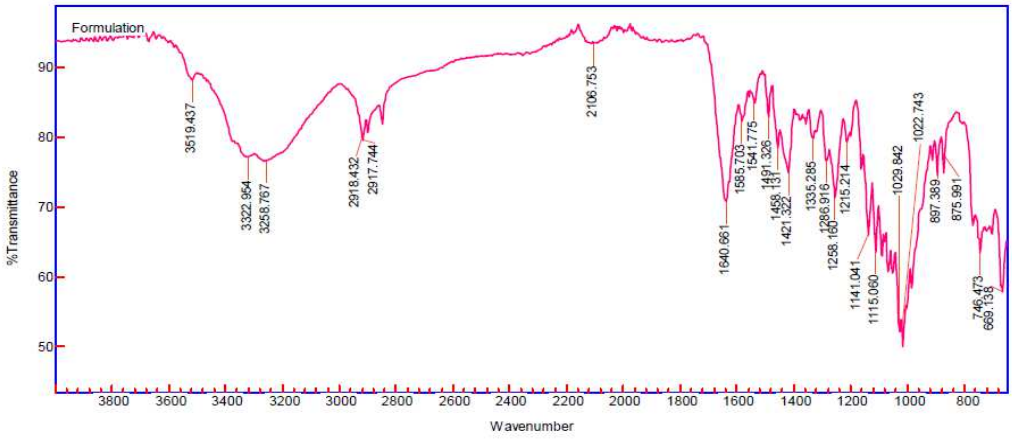

Figure 3: IR spectrum of formulation

From the results, it was concluded that there was no interference of the functionalgroup as the principle peaks of the Nebivolol hydrochloride were found to be unaltered in the drug-polymer physical mixtures, indicating they were compatible chemically.

Table 2: Pre-Compression Parameter results

Code	Bulk density g/cm^3	Tapped density g/cm^3	Carr's index%	Hausner's ratio	Angle of repose(°)
F1	0.321±0.094	0.401±0.120	19.95±0.03	1.24	18.98±0.04
F2	0.339±0.101	0.412±0.034	17.71±0.094	1.21	21.80±0.067
F3	0.301±0.074	0.370±0.069	18.64±0.065	1.22	28.98±0.051
F4	0.308±0.089	0.38±0.091	18.94±0.074	1.23	26.56±0.079
F5	0.324±0.093	0.393±0.113	17.55±0.093	1.21	18.26±0.084
F6	0.330±0.112	0.401±0.108	17.70±0.034	1.21	25.54±0.099
F7	0.329±0.107	0.411±0.07	19.95±0.107	1.24	25.73±0.021
F8	0.326±0.099	0.408±0.074	20.09±0.099	1.25	24.74±0.044
F9	0.308±0.094	0.374±0.043	17.64±0.102	1.21	21.00±0.042

Pre-compression parameter

Bulk density was found in the range of 0.301-0.339 g/cm^3 and the tapped density between 0.370-0.412 g/cm^3.The compressibility index was found between 17.55-20.09% and the compressibility and flow ability data indicated good flow properties of all powder blends.The angle of reposewas range of 18.26^0-26.56^0. Angle of repose below 30^o indicates good flow property.

Table 3: Post- compression parameter results

Code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)	Disintegration Time (sec)
F1	147.80±0.22	3.20±0.10	3.15±0.01	0.96±0.15	93.51±0.57	180
F2	149.20±0.22	3.50±0.09	3.19±0.03	0.72±0.11	95.00±0.42	160
F3	147.60±0.49	3.38±0.04	3.14±0.03	0.81±0.09	96.85±0.32	110
F4	151.27±0.41	3.28±0.07	3.18±0.02	0.72±0.62	95.79±0.27	120
F5	148.58±0.32	3.60±0.05	3.12±0.01	0.63±0.44	97.01±0.89	150
F6	151.10±0.91	3.10±0.03	3.32±0.04	0.86±0.53	96.15±0.42	120
F7	147.78±0.99	3.70±0.10	3.19±0.01	0.58±0.20	97.97±0.84	110
F8	152.30±0.60	3.45±0.14	3.18±0.02	0.82±0.32	97.35±0.42	130
F9	149.50±0.59	3.59±0.05	3.12±0.01	0.57±0.06	98.99±0.42	110

A. **Thickness of tablet:**
The average thickness for all the formulations was found to be within 3.32±0.04 to 3.12±0.01 the allowed limit of deviation i.e. 5% of the standard value
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B. Hardness:
Hardness test was performed by "Monsanto hardness tester". All the formulations have an average hardness in between 3.10 to 3.70 kg/cm^2.This ensures good handling characteristics of all formulation batches.

C. Friability
The average percentage friability for all the formulations was found in between 0.57% to 0.96%, which is found within the pharmacopoeial limit (i.e. less than 1%). So the maximum friability was 0.96% observed for F_1 and the minimum friability 0.57% observed for F_9.

D. Weight Variation
The maximum weight was 152.30±0.60 for F8 and the minimum observed was 147.60±0.49 for F3. Thus all the formulations were found to be complying with the standards given in IP.

E .Drug Content
The percentage drug content of all formulations was found in the range of 93.51±0.57%w/w to 98.99±0.42%w/w, which was all within the acceptable limits of official standards.

F. *In-vitro* disintegration time

The average *in-vitro* disintegration time for all the formulations were in the range of was 180 to 110 seconds.

Table 4: *In-vitro* drug release studies of Nebivolol hydrochloride FDTs

Sl. no	Time in mins	% CUMULATIVE DRUG RELEASE									
		FORMULATION CODE									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	MP
1	5	8.45	11.70	14.45	7.29	12.20	17.01	10.73	15.26	19.23	14.81
2	10	15.43	28.45	31.04	21.12	26.52	38.40	25.12	33.22	41.01	30.90
3	15	27.30	40.45	44.34	28.24	39.12	44.54	39.59	42.21	47.23	49.23
4	20	52.23	61.11	69.87	50.95	65.42	72.20	58.55	61.65	69.22	62.16
5	25	66.27	77.98	79.91	69.84	81.62	85.58	71.23	75.85	83.26	78.82
6	30	85.20	89.11	96.94	88.09	92.28	97.90	86.57	94.74	98.42	96.82

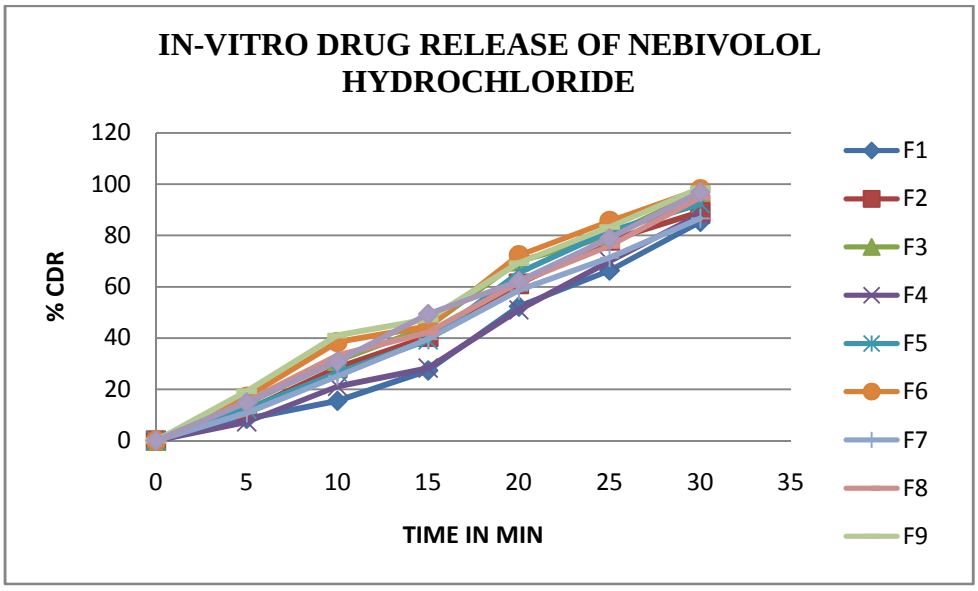

***Figure 4: In-vitro* drug release studies**

Among all formulations, formulation F9 containing 1:3 ratio of cross carmellose sodium and crospovidone showed 98.42% of drug release at the end of 30 minutes. Highest percentage of drug release from this formulation could be combined effect i.e. porosity and wicking action provided by these superdisintegrants to the tablets, which resulted in shorter disintegration and highest percentage of drug release. In formulations F1 to F6 concentration of sodium starch glycolate was kept constant while concentrations of other super disintegrants i.e. carmellose sodium and crospovidone were changed. When we see the dissolution profile, drug release rate was increased significantly with increase in ratio of super disintegrants i.e. higher the concentration of super disintegrants greater the drug release. Results of *in-vitro* dissolution studies were further subjected to various kinetic models to understood drug release mechanism by the prepared tablets.

The prepared tablets compared with marketed product (96.321% at 30 mints) hence prepared tablets F9 formulation (98.420% at 30 mints) shown good results.

Drug release kinetics:

The results obtained from in-vitro drug release were plotted adopting five different mathematical models of data treatment as follows:

1. % Cum. Drug Release Vs. Time (Zero order rate kinetics).
2. Log % Cum. Drug Retained Vs. Time (First order rate kinetics).
3. % Cum. Drug release was plotted against √T (root time). (Higuchi model)
4. Log % Cum. Drug Release Vs. Log Time (Peppas exponential equation)

The curve fitting results of the release rate profile of the designed formulation are shown in the Graph No.5,6,7 and 8 which gave an idea on the release rate and the mechanism of release. The values were compared with each other for model and drug equation as shown in Table No.25 based on the highest regression values (R^2), fitting of the release rate data to various models revealed that all the formulations (F1 to F9) follows zero order release kinetics with regression values ranging from 0.9477 to 0.9958.

Table 5: Stability studies for best formulations stored at 40ºC/75% RH

TIME	Physical appearance		Hardness kg/cm^2		Drug content		*In-vitro* drug release (%CDR)	
	F8	F9	F8	F9	F8	F9	F8	F9
15 days	White	White	3.43	3.56	97.28	98.87	94.65	98.36
30 days	White	White	3.41	3.54	97.25	98.82	94.60	98.30
45 days	White	White	3.40	3.54	97.22	98.80	95.59	98,31
60 days	White	White	3.42	3.53	97.24	98.84	95.58	98.33

Results show that after analyzing there was no change in case of physical appearance, no significant differences in the drug content and dissolution study. It was found that formulations found to be stable throughout the study period. The results of stability studies are given in the Table No.5.

CONCLUSION

It can be concluded from the present work that newer concept was applied to know combined effects of various super disintegrants. In formulations F1 to F6 concentration of sodium starch glycolate was kept constant while concentrations of other super disintegrants i.e. carmellose sodium and cros povidone were changed. When we see the dissolution profile, drug release rate was increased significantly with increase in ratio of super disintegrants i.e. higher the concentration of super disintegrants greater the drug release.

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