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FORMULATION AND EVALUATION OF NEBIVOLOL ORAL DISINTEGRATING TABLETS

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ABSTRACT

The Fast dissolving tablet (FDT) is one of the most widely employed commercial products. The development of Fast- or mouth dissolving tablets have been formulated for pediatric, geriatric, and bedridden patients and for active patients who are busy and traveling and may not have access to water. Nebivolol is a beta blocker with a unique function which distinguishes it from other betablockers. It increases the release of nitric oxide (NO) which produces vasodilatation and thereby improves arterial compliance and reduces peripheral vascular resistance. It also reduces heart rate without improving maximal exercise tolerance. These effects are beneficial in hypertension and angina pectoris. Fast dissolving disintegrating tablets prepared by direct compression method using superdisintegrants like crospovidone, croscarmellose sodium, sodium starch glycolate, Ac-Di-Sol in different concentrations and evaluated for the pre-compression parameters such as bulk density, compressibility, haunser' ratio and angle of repose. The prepared batches of tablets were evaluated for hardness, weight variation, thickness, friability, drug content, disintegration time, wetting time, and *in-vitro* dissolution profile and found satisfactory. Among all, the formulation F_6 containing Crosprovidone (6.5%) was considered to be the best formulation, which releases up to 99% of the drug in 10 min and disintegration time is 24 sec. All the formulations were compared with the commercial product. The disintegration time and release profile of the optimized formulation F_6 showed better results than the commercial product. It was thus finally concluded that Fast dissolving tablets of Nebivolol can successfully be formulated by adding the super-disintegrants and with improved patient compliance.

INTRODUCTION

The tablet is the most widely used dosage form existing today because of its convenience in terms of self-administration, compactness and ease in manufacturing. However geriatric, pediatric and mentally ill patients experiences difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome these problems, scientists have developed innovative drug delivery system known as fast dissolving/disintegrating tablets (FDTs).

These are novel types of tablets that dissolve/ disintegrate/ disperse in saliva within few seconds without water. According to European pharmacopoeia, these FDTs should dissolve/disintegrate in less than three minutes. The formulation is more useful for the bed-ridden and patients who have the swallowing problem. The benefits of FDTs is to improve patients compliance, rapid onset of action, increased bioavailability and good stability which make these tablets popular as a dosage form of choice in the current market. Fast dissolving tablets are also called as Orodispersible tablets, mouth disintegrating tablets, orally disintegrating tablets, quick disintegrating tablets, mouth dissolving tablets, rapid dissolving tablets, porous tablets, quick melt tablets and rapid melt tablets. However, of all the above terms United States Pharmacopoeia (USP) approved these dosage forms as ODTs. United States Food and Drug Administration (FDA) defined ODTs as "A solid dosage form containing medicinal substances or active ingredients which disintegrates rapidly within a few seconds when placed up on tongue".

Fast disintegrating tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry.

Recent developments in the technology have prompted scientists to develop FDTs with improved patient compliance and convenience. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation resulted in development of several FDT technologies. FDTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water.

Oral Dispersible Tablets

FDTs or orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules.

MATERIALS AND METHODS

List of Materials Used:

Nebivolol Hydrochloride, Magnesium Stearate, Avicel PH 102, Supertab 11SD, Ac-Di-Sol, Crospovidone, Croscarmellose sodium, Sodium starch glycolate, Aspartame, Purified Water, Peppermint.

Selection of Drugs:

The ideal characteristics of a drug for FDT include:

- Dose lower than 20mg.
- Nebivolol has bitter taste but taste masking can be achieved.
- Small molecular weight 405.435 g/mol.
- Nebivolol has Good stability in water and saliva.
- Nebivolol has Ability to permeate oral mucosal tissue.

Analytical method development for Nebivolol:

λmax determination:

Nebivolol λmax was determined by using 0.1N HCl medium. First dissolve 100mg of pure drug in 100ml 0.1 N HCl this is primary stock solution. From this 10µg/ml solution was prepared by using 0.1 N HCl.10µg/ml solution absorbance was measured at 200-400 nm range by spectrophotometrically (Shimazdu-1601, UV Visible spectrophotometer, Shimadzu Corp, Kyoto, Japan) using 0.1 N HCl as reference solution.

Preparation of standard curve

Standard calibration curve of Nebivolol in 0.1 N HCl were prepared. First dissolve 100mg of pure drug in 100ml 0.1 N HCl buffer which becomes primary stock solution. From the above primary stock solution pipette out 10ml of solution and again make up to 100ml which becomes secondary stock solution. From this secondary stock solution different concentrations of Nebivolol (2, 6, 10, 14, 18, 22, 26, 30µg/mL) in 0.1 N HCl buffer were prepared.

Absorbance of these solutions are measured at 281 nm by spectrophotometrically (Shimazdu-1601, UV/Visible spectrophotometer, Shimadzu Corp, Kyoto, Japan) using 0.1 N HCl as reference solution.

Preparation of Standard solutions

Preparation of 0.1N HCl

0.1NHCl was prepared by diluting 8.5 ml of concentrated Hydrochloric acid to 1000 ml distilled water.

Preparation of pH 6.8 buffer

27.22g of monobasic potassium phosphate was weighed and diluted up to 1000 ml to get stock solution of monobasic potassium phosphate. 8g Sodium hydroxide was weighed and diluted up to 1000ml to get 0.2M sodium hydroxide solution. 50 ml of the monobasic potassium phosphate solution was taken from the stock solution in a 200-ml volumetric flask and 22.4 ml of sodium hydroxide solution from stock solution of 0.2M sodium hydroxide solution was added and then water was used to make up the volume.

Drug-Excipient compatibility studies

Fourier transformer infrared spectroscopy (FTIR)

FTIR spectroscopy was found to be the most reliable technique for predicting the possible interaction between the drug and the polymer and excipients used for formulation. The IR spectra of physical mixtures were studied using KBr disc method.

The IR absorption spectra of the pure drug and with different excipients were taken in the range of 4000-400 cm-1 using KBr disc method. Triturate 1-2 mg of the substance to be examined with 300-400 mg, specified quantity; of finely powered and dried potassium bromide.

These quantities are usually sufficient to give a disc of 10-15mm diameter and spectrum of suitable intensity by a hydraulic press. The Infrared spectrum of Nebivolol was recorded by using FTIR spectroscopy and observed for characteristic peaks of drug.

Formulation of Nebivolol orally disintegrating tablets

By varying the proportion of alginic acid and xanthan gum of formulation different ratios design into 6 batches which is summarized in table

Results and Discussion

Calibration curve of Nebivolol in 0.1N HCl (pH 1.2):

The calibration curve and the data obtained by the procedure described in methodology section are given in tab.6 and Fig.7 below. The absorbance of standard solutions of Nebivolol in 0.1N HCl (pH 1.2) at 281nm.Fig.7 shows the standard calibration curve for pure drug. The curve was found to be linear in the range of 5-30µg/ml. The data had correlation coefficient of 0.999 and the equation of regressed line depicted as below.

Standard plot of Nebivolol

Table 1: Analytical profile for Nebivolol

Concentration (mcg/ml)	Absorbance at 281nm
2	0.073
4	0.177
6	0.288
8	0.395
10	0.504

Fig.1Standard plot of Nebivolol in 0.1N HCL

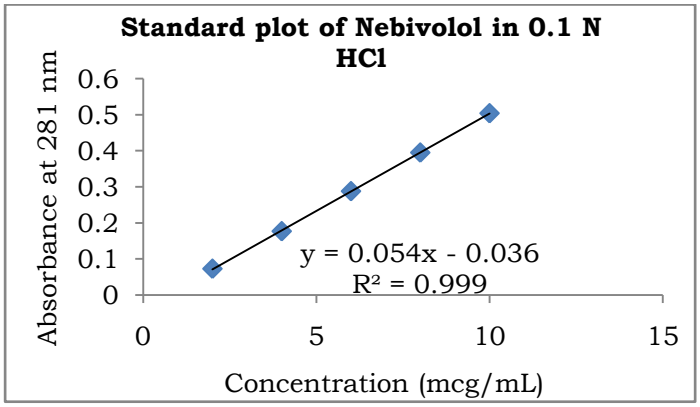


Table 2: Formulation of Nebivolol tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Nebivolol	5	5	5	5	5	**5**
Supertab11SD	97	97	97	97	97	**97**
Avicel PH 102	19.6	18.3	17	19.6	18.3	**17**
Ac-Di-Sol	3.9	5.2	6.5	-	-	**-**
Crosprovidone	-	-	-	3.9	5.2	**6.5**
Sodium starch glycolate	-	-	-	-	-	**-**
Croscarmellose sodium	-	-	-	-	-	**-**
Aspartame	2	2	2	2	2	**2**
Peppermint	1	1	1	1	1	**1**
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	**1.5**
Total weight (mg)	130	130	130	130	130	**130**

PREPARATION OF NEBIVOLOL TABLETS

Step1 Each tablet (weight 130 mg) consisted of Nebivolol, cross povidone or cross carmellose or sodium sodium starch glycolate (SSG) or Ac-Di-Sol, mannitol, Avicel, Supertab 11SD, Magnesium stearate, Aspertame, Peppermint.

Step2 Tablet was prepared by using direct compression method. The drug, diluent and super disintegrants were passed through the sieve no. 40. All the ingredients are mixed well for 15 min in the motor.

Step3 Above blend is mixed with lubricant for 3 min in a motor. The mixer was compressed by using 10mm concave punches on sixteen station rotary tablet compression machine.

Pre compression Studies

The tablet blend was tested for angle of repose, bulk density, tapped density, carr's index, hausner's ratio.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. Angle of Repose is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the measure of the flow ability of powder/granules. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform.

About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured.

Angle of repose was calculated from the average radius using the following formula.

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

Where,

θ = Angle of repose

h = Height of the pile

r = Average radius of the powder cone

Flow properties corresponding to Angle of repose

Table 3: Angle of repose range

Flow properties	Repose angle (^{0})
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very very poor	>66

Bulk and Tapped Density

An accurately weighed quantity of the granules (w) that was previously passed through # 40 was carefully poured into the graduated cylinder and the volume (vo) was measured.[68] The graduated measuring cylinder was tapped for 100 times and after that, the volume (vf) was measured and continued the operation till the two consecutive readings were equal. Bulk density and tapped density determines the floating capacity of the formulation. The bulk density and tapped density were calculated using the formulas below

$$\text{Bulk density} = w/v_o$$

$$\text{Tapped density} = w/v_f$$

Where w - Weight of powder

v_o - Initial volume.

v_f - Final volume.

Percentage compressibility

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density. A useful empirical guide is given by the Carr's compressibility or compressibility index.

Compressibility measures gives idea about flow property of the granules as per Carr's index which is as follows.

Hausner's ratio

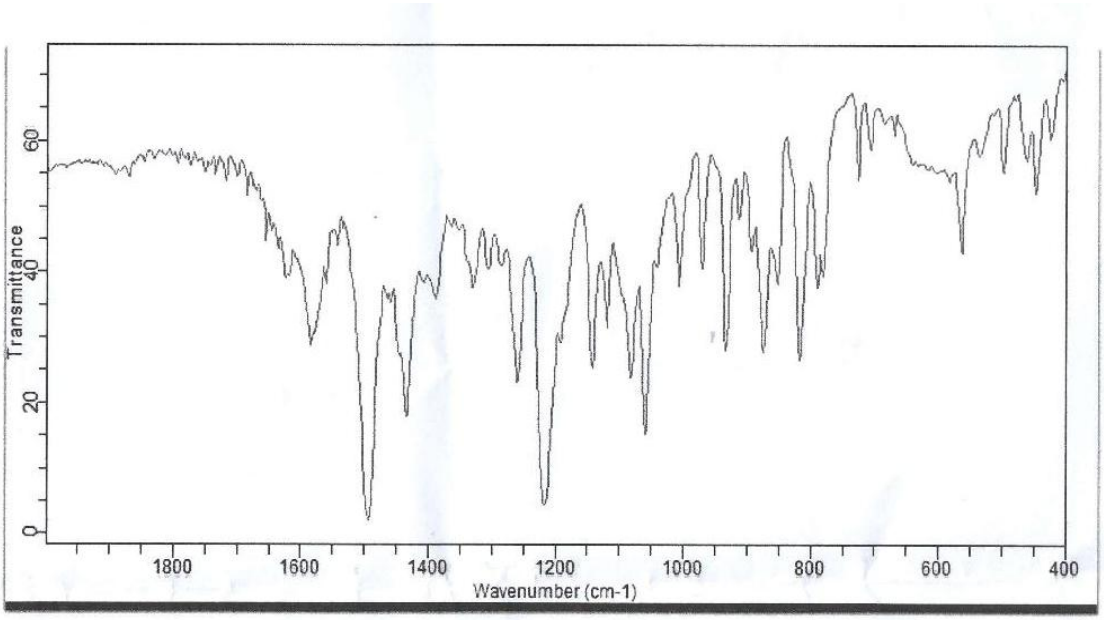
It provides an indication of the degree of densification which could result from vibration of the feed hopper.

Table 4: Hausner's ratio range

Compressibility index (per cent)	Flow character	Hausner ratio
1-10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-0.34
26-31	Poor	0.35-0.45
32-37	Very poor	0.46-0.59
>38	Very very poor	>1.60

Figure 2: Fourier Transform Infrared spectroscopy

The IR absorption spectra of the pure drug was taken in the range of 1800-400 cm-1 using KBr disc method .The major peaks were reported for evaluation of purity.

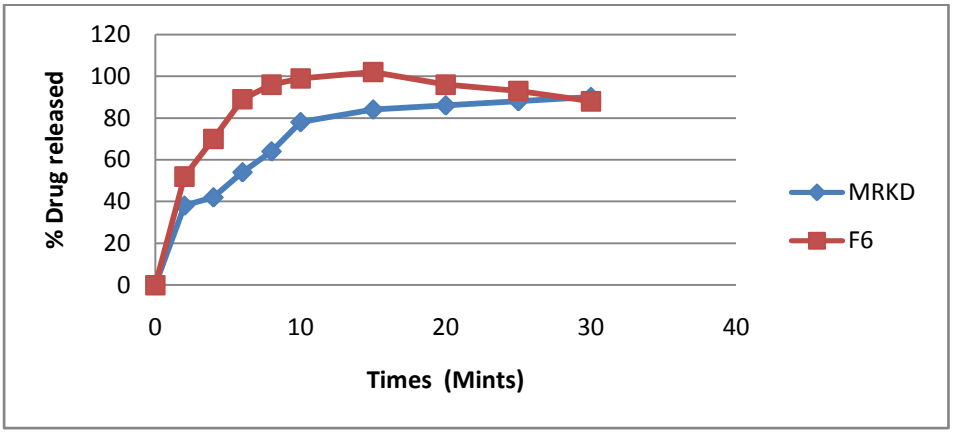


FTIR Spetra of pure drug a of Nebivolol and with Excipients

From the FTIR spectra of pure drug and combination of drug with the polymers, it was observed that all the characteristic peaks of drug are present in the combination spectra as well as indicating the compatibility of the drug with the polymers used. The spectra of pure drug, polymers and optimized formulation of IR spectrum were shown in the Figure 3

Figure 3: dissolution data of Nebivolol

All value Comparison of dissolution profile of marketed and F6 formulations s expressed as mean ±S. D n=3



In *vitro* Dissolution Study:

Table 3: Dissolution profiles of F1-F6 formulations

Time(min)	MRKT	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
2	38±0.2	34±0.4	38±0.2	34±0.2	50±0.3	46±0.6	52±0.3
4	42±0.3	38±0.3	48±0.2	39±0.4	52±0.4	52±0.5	70±0.2
6	54±03	42±0.3	51±0.2	51±0.3	55±0.5	58±0.2	89±0.2
8	64±0.2	58±0.2	62±0.4	66±0.4	66±0.2	72±0.2	96±0.4
10	78±0.4	67±0.5	71±0.6	74±0.2	78±0.2	85±0.3	99±0.2
15	84±0.5	72±0.2	75±0.2	78±0.2	82±0.4	88±0.2	102±0.48
20	86±0.3	74±0.2	78±0.3	82±0.3	85±0.2	91±0.3	96±0.3
25	88±0.2	75±0.3	82±0.2	85±0.4	90±0.3	95±0.2	93±0.2
30	90±0.3	77±0.2	85±0.3	88±0.3	93±0.3	97±0.4	88±0.4

All values were expressed as mean ± S.D;

Number of trials (n) = 3

In vitro Dissolution studies:

The Dissolution study of various batches from F1, F2 and F3 containing 3.9, 5.2 and 6.5mg of Ac-Di-Sol showed 78%, 69% and 64% of drug release at 10 min, F4, F5 and F6 containg 3.9, 5.2 and 6.5mgof Crosprovidone showed 78%, 85% and 99% of drug release at 10 min, F7, F8 and F9 containg3.9, 5.2 and 6.5mgofsodium starch glycolate showed 59%, 63% and 65% of drug release at 10 min and F10, F11 and F12 containg Croscarmellose sodium showed51%, 48% and 46% of drug release at 10 min. These super disintegrantsat lower to higher concentrations showed lower to higher drug release. As the concentration increased the drug release. The dissolution rate of NEB was enhanced significantly as increasing the superdisintegrant concentration level from 3.9 to 6.5% w/w.

The Dissolution study of various batches from F1- F12 shows that Nebivolol release from tablets containing Crosprovidone 6.5mg showed higher drug release. Further we can say that as concentration of super disintegrants increases it causes higher % of drug release.

All the formulations showed rapid disintegration and fast dissolution rate when compared with marketed formulation.

The formulation F6 containing 6.5mg of crospovidone showed 99% of drug release in 10 min. Drug release was very much less for formulations F11 and F12 which contain Croscarmellose sodium when compare to formulations containing crosprovidone.

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