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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF NEBIVOLOL HYDRO CHLORIDE

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ABSTRACT

Nebivolol is a β-1 receptor blocker with nitric oxide-potentiating vasodilatory effect used in treatment of hypertension and also for left ventricular failure Nebivolol has half-life about 10 hrs. In hypertension the initial dose of nebivolol is 5mg once daily and maximum dose is 40mg once daily. Nebivolol is poorly soluble in water hence the basic objective of this study was to produce immediate release nebivolol tablets containing super disintegrant and solubilizer via wet granulation, to improve disintegration, dissolution and to get faster onset of action. super disintigrants used in this formulation microcrystalline cellulose, cross povidone and cross carmellose. pregelatinized starch as binder solution. tablets were subjected to physicochemical characterization such as thickness, weight uniformity, drug content, pH study, in vitro drug release, and stability studies. Tablets were found to be satisfactory when evaluated for thickness, weight uniformity, invitro drug release, drug content and disintegration time.

The in vitro drug release in optimized formulation F6 was found to be 98 % in 60 min. The optimized formulation F6 also showed satisfactory pH, drug content (98.12%), disintegration time of 20 seconds and satisfactory stability.

INTRODUCTION

The oral route of drug administration is the most popular and successfully used for conventional delivery of drugs. It offers the advantages of convenience, ease of administration, greater flexibility in dosage form design, ease of production, and low cost. The parenteral route of administration is important in case of emergencies, while the topical route of drug administration recently employed to deliver drug to the specific part of the body for systemic effect. It is probable that almost 90% of all the drugs are administered by oral route. Tablets are solid preparations each containing a single dose of one or more active substances and 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 particles consist of one or more active substances with or without excipients such as diluents, binders, disintegrating agents, glidants, lubricants, substances capable of modifying the behavior of the preparation in the digestive tract coloring matter authorized by the competent authority and flavoring substances. The dosage form available for oral administrations are solutions, suspensions, powders, tablets and capsules. The physical state of most of the drugs being solid, they are administered in solid dosage form. The drugs administered by oral route are versatile, flexible in dosage strength, relatively stable, present lesser problem in formulation and packaging and are convenient to manufacturer, store, handle and use. Solid dosage forms provide best protection to drugs against temperature, light, oxygen and stress during transportation.

ADVANTAGES OF TABLETS

- They are unit dosage form, and they offer the capabilities of all oral dosage forms for the dose precision and the least content variability during dosing
- Accuracy and uniformity of drug content
- Optimal drug dissolution and hence, availability from the dosage form for absorption consistent with intended use (i.e., immediate or extended release).

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- Usually taken orally, but can be administered sublingually, rectally or intravaginally.
- Their cost is lowest of all oral dosage forms
- They are the most compact of all oral dosage forms
- They are in general the easier and cheaper to package and ship as compare to other oral dosage forms
- Product identification is simple and cheap, requiring no additional processing steps when employing an embossed or monogrammed punch face
- They are ease to administer, does not require a specialist
- They are better suited to large-scale production than other unit oral forms
- They have the better properties of chemical, mechanical and microbiological stability

DISADVANTAGES 2

- Some drugs resist compression, due to their amorphous nature or low-density
- Drugs having bitter taste, objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating of tablet
- Bioavailability problems.
- Chance of GI irritation caused by locally high concentrations medicament.
- Difficulty in swallowing tablets in a small proportion of people and so size and shape become important considerations.
- Slow onset of action as compared to parenterals and solutions.

The objective of the present study is to formulate and evaluate immediate release tablet according to Biophannaceutical Classification System (BCS) and compare the effect of lubricant on dissolution profile. Select the antihypertensive drugs according to the Biopharmaceutical Classification System (BCS). To prepare the immediate release tablets by using the different concentrations of the Lubricants. Compare the dissolution profile of all the trial batches formulated and select the best lubricant for the final formulation.

MATERIAL AND METHODS

In Vitro Dissolution Study 23

In vitro dissolution studies were done with tablets in a following way:

Nebivolol hydrochloride tablets 23

1) Dissolution parameter 4

Medium-Dilute Hydrochloric acid (0.01N HCL)

Apparatus- USP-2 (paddle)

RPM-50 rpm

Time- 5, 10, 15, 20, 25, 30 min.

Temperature- 37°C±0.5ºC

INGREDIENTS (mg)	**FORMULATION CODE**										
Intragranular											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Nebivolol	21.76	21.76	21.76	21.76	21.76	21.76	21.76	21.76	21.76	21.76	21.76
MCC PH 101	135.24	134.04	133.14	135.24	134.04	133.14	145.14	137.94	133.14	131.88	133.8
Mannitol	30	30	30	30	30	30	30	30	30	30	30
SLS	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6		0.6
CCS	-	-	-	2.4	3.6	4.8	4.8	4.8	4.8	5.76	3.84
CP	2.4	3.6	4.8	-	-	-	-	-	-	-	-
Binder solution											
Pre gelatinized	24	24	24	24	24	24	12	19.2	24	24	24

starch											
Water	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
Extragranular											
MCC PH 102	20	20	20	20	20	20	20	20	20	20	20
CCS	-	-	-	2.4	3.6	4.8	4.8	4.8	4.8	3.84	5.76
CP	2.4	3.6	4.8	-	-	-	-	-	-	-	-
Mg.stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Aerosol	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Totalweight(mg)	240	240	240	240	240	240	240	240	240	240	240

Table-1: Formula for preparation of Nebivolol hydrochloride tablets

PREPARATION OF TABLETS

All the tablets, each containing 6mg of Nebivolol HCl were prepared by wet granulation method. The manufacturing process involves following steps they were
Method:

Accurately weigh the drug with diluents (MCC and Lactose monohydrate) and CCS, pass through 40 no. Sieve and mix it properly for 3-5 minutes in a mortar. Prepare the binder solution by dispersing pre gelatinized starch in water. Granulation of the above mixture is done by prepared binder solution until end point is obtained (dough mass). Pass the mass via sieve and keep in a tray dryer for the dried granules to be obtained. Remove the dried granules from oven and pass via sieve 12 to get optimum sized granules. Lubrication is done by using aerosil previously passed through 40 sieves of the granules for 3-4 min. Cross carmellose sodium as disintegrate. Compression is done by using rotary CADMACH punching machine.

1. The intragranular ingredients were sifted through # 40 meshes and mixed.
2. The granulating agent was dissolved in granulating fluid until it to forms a homogeneous medium.
3. The dry mix of step 1 was granulated using granulating solution of step 2 in Rapid Mixer Granulator
4. The wet mass was dried at 55 +/-5^{o}C in rapid dryer until to get the desired LOD.
5. The dried granules were sifted through # 30 mesh and mill the retentions through 0.5 mm screen using Oscillating granulator.
6. The sifted and milled granules were mixed.
7. Extra granular ingredients were sifted through # 40 mesh except Mg. stearate and mixed with the sifted granules of step 5. Mg. stearate was sifted through #60 mesh and was lubricated with the contents of step 6.
8. The lubricated blend of step 7 was compressed into tablets

8.4 Evaluation of granules:

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

a) Bulk density (B.D):
It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve#20) in to a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/cc and is given by

$$B.D=m/V_o$$

where,
m=mass of the powder
$\mathbf{V_o}$**=** bulk volume of the powder

b) Tapped density (T.D):

Physico-mechanical characterization

Bulk Density: It refers to packing of particles. Bulk density is used to determine the amount of drug that occupies the volume in g/ml. **Procedure:** Weighed quantity (10gm) of Drug X was transferred into 100 ml measuring cylinder without tapping during transfer. The volume occupied by drug was measured. Bulk density was measured by using formula

$$\rho i = m / Vi$$

where, m = mass of the blend
Vi = untapped volume

Tapped density: Weighed quantity (10gm) of drug was taken into a graduated cylinder. Volume occupied by the drug was noted down. Then the cylinder was subjected to 500, 750 &1250 taps in tap density apparatus (Electro Lab USP II). According to USP, The blend was subjected for 500 taps. % Volume variation was calculated and subjected for additional 750 taps. % Variation is calculated.

$$\rho t = m/Vt$$

where, Vt is tapped volume

Carr's Index (Compressibility):

The compressibility index and Hausner ratio are measures of the property of powder to be compressed. The packing ability of drug was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping. It was indicated as Carr's compressibility index was calculated as follows.

Carr's index = [Tapped density - Bulk density/Tapped density] X 100

Hausner Ratio: It is measurement of frictional resistance of the drug .The ideal range should be 1.2-1.5. It was determined by the ratio of tapped density and bulk density

Hausner Ratio = Tapped density / Bulk density

Angle of Repose:
It is defined as the maximum angle that can be obtained between the free standing of powder heap and horizontal plane, which is given by the equation:

$$\Theta = \textbf{tan-1 h/r}$$

where, Θ *= Angle of repose.*
h = Height of powder heap.
r = Radius of the powder cone.

d) Compressibility Index (C.I):
The flow ability of powder can be evaluated by comparing the Bulk density (BD) and Tapped bulk density (TD) of powder and the rate at which it packed down. Compressibility index was calculated using the following formula;

C.I = 100 X (1 – 1/H.R.)

Evaluation of matrix tablets:
The prepared tablets were evaluated for General appearance, thickness, hardness, weight variation, friability and uniformity of weight.

1) Hardness test:
Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The hardness was tested using Monsanto hardness tester. The average of the five determinations was determined and reported.

2) Friability test(F):
Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This In-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm.

Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (i.e. in 4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%.

The percent friability was determined using the following formula:

$$(W_1 - W_2)/W_1 \times 100$$

where,
W_1 = weight of the tablets before test
W_2 = weight of the tablets after test

3) Thickness:
Thickness of the tablets was calculated by the use of vernier calipers.

4) Content Uniformity Test:

Drug content:

For determination of drug content three tablets from each formulation were weighed individually and powdered. The quantity of powder was equivalent to 10 mg. The equivalent weight NebivololHCl was transferred into 100 ml volumetric flask diluted to 100ml with sufficient amount of buffer (0.01N HCL). Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 269nm against blank.

In-vitro dissolution studies:

Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP - II paddle method and 900ml of 0.01N HCL as the dissolution medium. The medium was allowed to equilibrate to temp of 37°c ±0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for1 hr in 0.01N HCL at 50 rpm. At definite time intervals of 5 ml of the aliquot of sample was withdrawn and filtered (0.45µm) .The volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 269 nm using UV-spectrophotometer.

Kinetic data analysis:

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero, first-order, diffusion and exponential equations .The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics.

- **Kinetic Studies**

A) Zero Order Release Equation

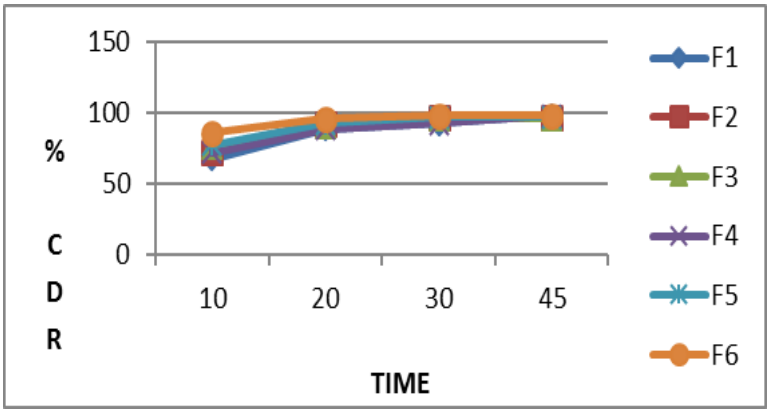
B) First Order Release Equation

Stability Studies:

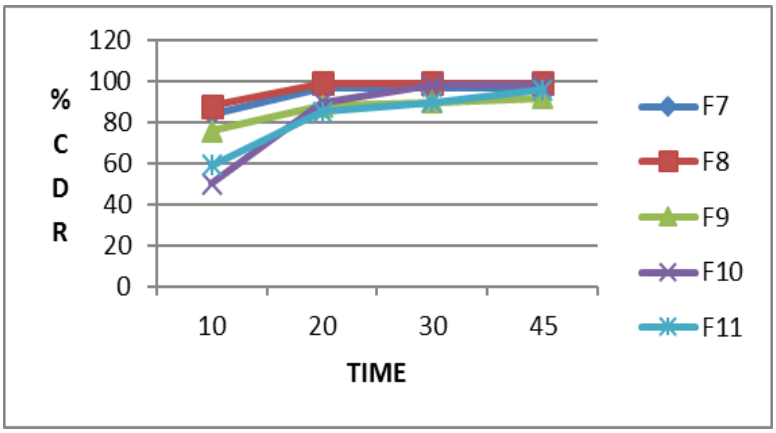
The optimized matrix tablets were subjected to stability studies(as per ICH guide lines) at 25°C ± 2°C / 60% ± 5% RH and 40°C ± 2°C / 75% ± 5% RH The products were evaluated for their physical characteristics, drug content, and In-vitro drug release profiles over a period of 3 months.

T Time In min	F1	F2	F3	F4	F5	**F6**	F7	F8	F9	F10	F11
5	36	40	48	39	46	**54**	55	53	45	38	42
10	68	73	76	72	78	**86**	84	88	76	50	59
15	79	81	85	80	87	**91**	92	90	80	79	76
20	85	92	90	89	93	**98**	97	99	88	90	85
30	93	97	96	93	97	**98**	97	99	90	98	90
45	98	97	96	98	97	**98**	97	99	92	98	96
60	98	97	96	98	97	**98**	97	99	96	98	96

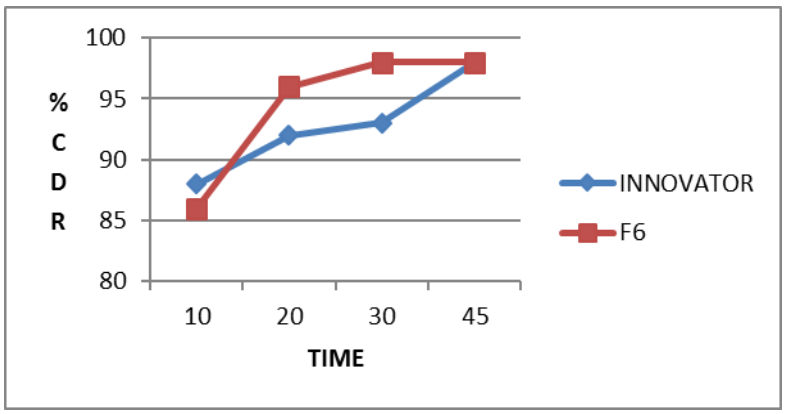
Dissolution Values



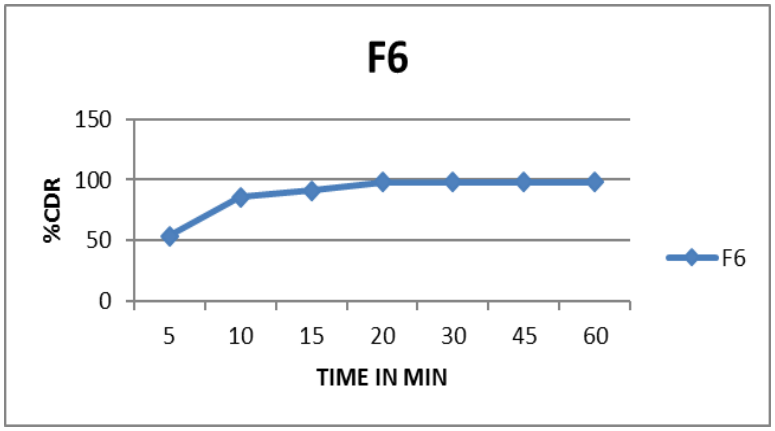
Cumulative % drug released for formulations F1-F6



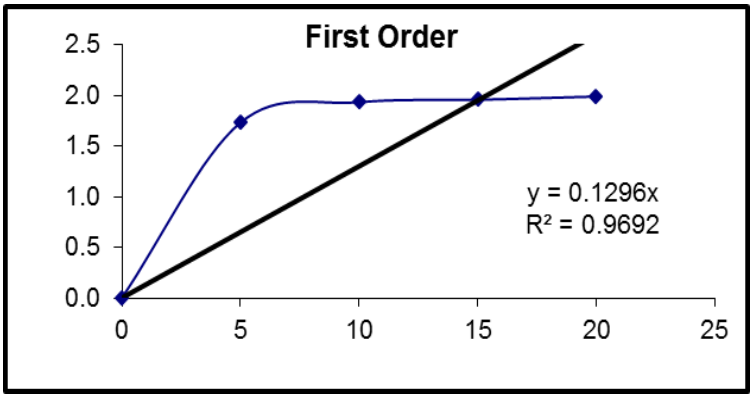
Cumulative % drug released for formulations F7-F11

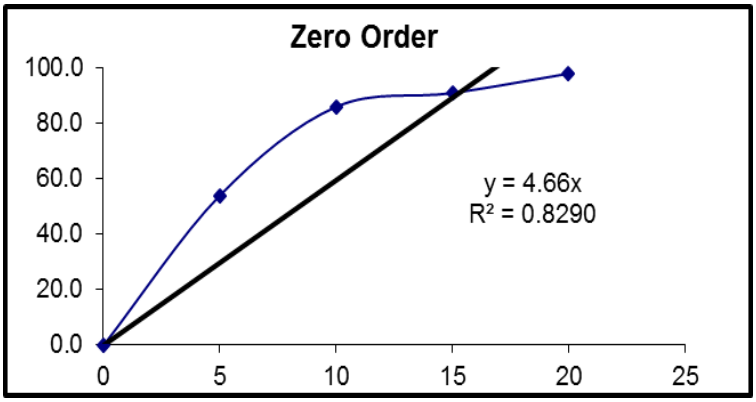


Comparative graph of innovator and optimized formulation



Cumulative % drug released formulations F6





Physical characterization of IR Tablets of Nebivolol hydrochloride:

Tablet thickness, hardness, weight variation, friability and drug content of formulated.

Tablets of batches from F1 to F11 are presented in Table.

Uniformity of weight:

All the prepared tablets of Nebivolol hydrochloride were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits of ±7.5%.

Hardness and friability:

The hardness of the tablet formulations was found to be in the range of 5.0 to 6.5 kg/cm^2. The friability values were found to be in the range of 0.65 to 1.8 %.

Uniformity of drug content:

The low values of standard deviation indicates uniform drug content within the tablets The percent drug content of all the tablets was found to be in the range of 98.68 to 101.1 percent (which was within the acceptable limits of ±5%.).

In vitro dissolution study:

In vitro dissolution studies were performed in pH 1.2 buffers on the above promising formulation, namely, formulation 6. The results are shown in Table.

In the dissolution studies, the maximum drug release was found to be with formulation F6 of maximum drug release (98%).

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