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FORMULATION AND EVALUATION OF BISOPROLOL FAST DISSOLVING TABLETS

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ABSTRACT

Bisoprolol Fumarate is a cardio selective β-blocker which is used for the treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, diuretics, and optionally cardiac glycosides. The presently preferred route of administration for Bisoprolol Fumarate is oral. Bisoprolol was chosen to be the active pharmaceutical ingredient (API) in a fast-dissolving tablets FDTs formulation, being a model of fast dissolving tablets of Bisoprolol Fumarate, an antihypertensive agent. The present study was aimed to formulate, evaluate and optimized a tablet which disintegrates and fast dissolving to show a rapid onset of action. In the present study, attempt has been made to prepare FDTs of Bisoprolol using superdisintegrants like croscarmellose sodium, and crospovidone in different ratios by direct compression. The prepared batches of tablets were evaluated for weight variation, hardness, friability, disintegration time, wetting time and in-vitro drug release which tested. Among the all formulations F2 formulation was found to be showed improved drug release characteristics. F2, which consists of (Bisoprolol, mannitol, avicel PH101, crospovidone, aspartame, aerosil, talc, magnesium stearate), showed the best result in drug disintegrated time, faster dissolution rates and higher efficiency values.

KEYWORDS: Bisoprolol, Fast dissolving tablets, Antihypertensive agent, Superdisintigrants, Formulations.

INTRODUCTION

Oral drug delivery has been known as the most widely used route of drug administration when compared to all the other routes that have been explored for delivery of different dosage forms to systemic circulation.[1-5]

The reason for such popularity of oral route may be attributed to its ease of administration. Recent advances in novel drug delivery systems (NDDS) aim at formulating a convenient dosage form for administration and to achieve better patient compliance to enhance safety and efficacy of drug molecules. One such approach is fast dissolving tablet. [6-9]

An oral fast dissolving drug delivery system is a novel tablet dosage form, which dissolves or disintegrates in the oral cavity with a good taste and flavor increasing the acceptability of bitter drugs without the need of water or chewing and hence called melt in mouth tablets or orodispersible or rapid disintegrating or quick dissolving tablets. The drugs may be absorbed from mouth, pharynx or esophagus while the saliva passes down into stomach. Advantages of the fast dissolving tablets include rapid onset of action, ease of swallowing without the aid of water, enhanced dissolution rate, increased gastric absorption, minimized first pass metabolism, improved oral bioavailability and improved patient compliance. FDTs formulation combines the advantages of both conventional tablets and liquid formulations.[10,13]

Solid dosage forms are popular because of low cost, ease of administration, accurate dosage self-medication, pain avoidance, and the most importantly the patient compliance. FDTs releases the medicament in the mouth for absorption through local oromucosal tissue and through pre-gastric (oral cavity, pharynx, and esophagus), gastric (stomach), and post-gastric (small and large intestine) segments of gastrointestinal tract. [14-18]

Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available.[11]

One important drawback of these dosage forms however is the difficulty to swallow. It is estimated that 35% of the population is affected by this problem which results in a high incidence of non-compliance and ineffective therapy.[12]

The basic approaches to develop FDTs include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation. Most fast dissolving delivery system tablets should include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients.[19-20]

In the present study, it was proposed to formulate fast dissolving tablets of Bisoprolol by using direct compression technique, with the aim of reaching high serum concentration of the drug in a short period of time using superdisintegrants like croscarmellose sodium and crospovidone.

MATERIALS AND METHODS

Bisoprolol Fumarate as a gift from (Modern Pharmaceutical Industry Company-Yemen). While Talc, Crospovidone, Croscarmellose Sodium, Aspartame, Aerosil, Magnesium Stearate, Avicel PH 101, Mannitol as a gift from (Shephaco Pharmaceutical Industry Company-Yemen).

Formulation of Fast Dissolving Tablets

Fast dissolving tablets containing selected solid dispersion were prepared by direct compression method using single punch tablet machine to produce convex faced tablets part of them weighing 100mg. 150 tablets were prepared for each batch. The formulations were developed by using superdisintegrants (croscarmellose sodium and crospovidone) in varying concentration (2-10%) to develop the tablets. The all ingredients were shown in table (1) were passed through sieve no.18 except, magnesium stearate passed through sieve no 35 and were co-grounded in a glass pestle motor.

Mixing and Compression Processes

Mixing was done by using geometric mixing, in which all excipients were accurately weighed then all of them except silicon dioxide, magnesium stearate, were blended with specified quantity of Bisoprolol for 15minutes, whereas the other excipients were blended for 5 minutes and added to the former excipients. Then all formulae were passed through sieve # 18 for particle size uniformity. This method of ordering mixing of excipients with Bisoprolol in first sex formulae. Then each mixture has compressed directly into tablets using rotary tablet compression machine of punch size 6.25mm (7mm) to prepare tablets each weighing 100 mg.

Table 1: Composition of Bisoprolol Fumarate Formulations FDTs.

Ingredients	Quantity per Tablet (mg)					
	Formulation Code					
	F1	F2	F3	F4	F5	F6
Bisoprolol Fumarate	5	5	5	5	5	5
Avicel PH 101	30	33	31	34.5	32.5	30
Mannitol	59	54	54	54	54	54
Crospovidone	2	4	6	---	---	---
Croscarmellose Sodium	---	---	---	2	4	6
Aspartame	2	2	2	2	2	2
Aerosil	1	1	1	1	1	1
Mg Stearate	1	0.5	---	1	0.5	1
Talc	---	0.5	1	0.5	1	1
Total	**100**	**100**	**100**	**100**	**100**	**100**

Evaluation of Bisoprolol Fumarate Formulations FDTs

The compressed tablets were evaluated for the following parameters.

Diameter Test

One of tests which used for determination of the tablets size, it is done by taking ten tablets randomly. Diameter may have obtained by using suitable micrometer.

Thickness Test

The thickness was determined for ten pre-weighed tablets of each batch using a Vernier, and the average thickness were reported. The thickness was denoted in millimeter.

Hardness Test

This test was done to determine whether the tablets will be able to withstand the rigors of handling and transportation experienced in manufacturing plant, in the drug distribution systems and in the field at the hands of end users(patients/consumers). Five tablets were randomly selected from each batch and hardness is determined by using digital hardness tester. The mean value of hardness was recorded.[21]

Friability Test

This test was performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap, or break. It determines the tablets ability to withstand mechanical stress, chipping, surface abrasion. The weight of 10 tablets was noted and placed in Roche friabilator. The device subjects the tablets to the combined effect of shock and abrasion by utilizing a plastic chamber which revolves at 25 rpm, rolling the tablets a distance of 6 inches

with the revolution. The tablets were removed after 100 revolutions. Tablets that loose less than 0.5 to 1 percent in weight are generally acceptable.

Weight Variation

With a tablet designed to contain a specific amount of drug in a specific amount of tablet formula, the weight of tablet being made is routinely measured to ensure that a tablet contains the proper amount of drug. As per IP/BP the weight variation test was run by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage deviation.[21]

Wetting Time

The wetting time of dosage form is related to contact angle. The wetting time of sublingual tablets is another parameter which needs to be assessed to give an insight into the disintegration properties of tablets. A lower wetting time implies quicker disintegration of tablet. The wetting time of the tablets was measured using a simple procedure. Circular tissue paper of 10 cm diameter was placed in a petri dish of 10 cm diameter. Ten milliliters of water containing a yellow water- soluble dye (sunset dye), was added to the petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time.[21]

Disintegration Test

The disintegration test was carried out at 37°C±0.5°C in 900 ml of distilled water. The disintegration time of tablets from each formulation were determined using disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus containing distilled water. One disk was added to each tube. The time taken in seconds for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured.[21]

***In-vitro* Dissolution Studies**

Dissolution Parameters

The apparatus of dissolution tester (RC-80C), medium: 900 ml distilled water, RPM :75, temperature: 37°C±0.5°C, sampling interval: 5, 15 minutes, wavelength: 227 nm UV spectroscopy. The procedure in vitro dissolution studies of Bisoprolol fast dissolving tablets were performed using dissolution tester (RC-80C). The volume of dissolution medium

distilled water used was 900 ml and the temperature was maintained at 37°C±0.5°C. The speed of the basket was set at 75rpm. One tablet was placed in each vessel of dissolution apparatus. 5 ml of sample from each vessel was withdrawn at 5 minutes and 15 minutes and same volume of distilled water was replaced to each dissolution vessel, so that volume of dissolution medium was maintained to 900 ml. Then the sample was filtered and diluted with distilled water and the amount of Bisoprolol released from FDTs was determined spectrophotometrically at 227 nm using distilled water, as blank. [21]

RESULTS AND DISCUSSION

Post Compression Parameters

Table 2: Evaluation of Post Compression Parameters of Bisoprolol Fumarate Formulations FDTs.

Formulation code	Diameter (mm) Mean ± SD	Thickness(mm) Mean ± SD	Friability (%)	Hardness (kg/cm^2)
F1	6.45±0.35	3.47±0.17	0.37	3.6
F2	6.47± 0.28	3.46±0.17	0.29	3.9
F3	6.17± 0.32	3.27±0.16	0.47	3.41
F4	6.16± 0.31	2.94 ±0.15	0.36	3.38
F5	7.44± 0.29	3.09 ±0.15	0.30	4.35
F6	7.44± 0.30	3.05±0.15	1.17	3.5

As shown in table (2), the diameter of the tablets was measured and were found in the range between 6.16± 0.31 mm to7.44± 0.30 mm. All the formulations possessed uniform diameter. The hardness of the tablets was measured and the values were found in the range between 3.38 to 4.35 kg. The prepared tablets possessed good mechanical strength with sufficient hardness. The Thickness of the tablets was measured and were found in the range between 2.94± 0.15 mm to 3.47±0.17 mm. All the formulations possessed uniform thickness and in the accepted rang, except F4, F5, F6 were out of the rang. Similarly, percentage friability values of the prepared Bisoprolol fast dissolving tablets showed less than 1% weight loss which are within the acceptable limit except, F6 it showed more than 1% weight loss (present capping).

Table 3: Evaluation of Post Compression Parameters of Bisoprolol Fumarate Formulations FDTs.

Formulation code	Average Weight (mg) Mean ± SD	Wetting time (Sec)	Disintegration Test (Sec)
F1	99.24±7.44	35	16
F2	99.448±7.45	17	9
F3	98.18±7.36	21	11
F4	99.10±7.43	20	12
F5	98.69±7.40	22	23
F6	97.33±7.27	32	19

As shown in table (3), all formulations of Bisoprolol fast dissolving tablets passed the weight variation test since the values are within the acceptable limit.

The wetting time of Bisoprolol orally disintegrating tablets were found to be in the range between 17 and 35 seconds. Formulation F2 prepared by using crospovidone as superdisintegrant showed least wetting time (17 sec). The disintegration time of Bisoprolol orally disintegrating tablets ranges between 9 to 23 seconds. Formulation F2 showed least disintegration time (9 sec) compared with all other formulations.

From the above results, it was concluded that the formulation F2 showed better tableting properties compared to the other formulations and was selected as the best formulation.

***In-vitro* Dissolution Studies**

The *in-vitro* drug release of Bisoprolol formulation FDTs were given in table (4).

Table 4: Percentage of Drug Release of Bisoprolol Fumarate Formulations FDTs.

Time (min)	Percentage Drug Release (%)					
	Formulation Code					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
5	101.5%	102.29%	95.90%	94.54%	80.20%	86.70%
15	104.04%	106.08%	102.89%	96.38%	89.68%	96.41%

As shown in table (4), drug release of Bisoprolol formulations were studied in distilled water pH (7) for up to 15 minutes. The drug release of formulation F1, F2 and F3 were found to be 104.04%, 106.08% and 102.89% at 15 minutes respectively.

The drug release of formulation F4, F5 and F6 were found to be 96.38%,89.68% and 96.41% at 15 minutes respectively. The acceptable in vitro dissolution limit is not less than 80% of drug release at 15 minutes. Formulation F1, F2 and F3 passed the in vitro dissolution studies.

The higher dissolution rates were observed in formulation F2 prepared using crospovidone as superdisintegrant which may be due to rapid disintegration and fine dispersion of particles formed.

CONCLUSION

In the present study were carried out on optimization of fast dissolving tablets FDTs employing novel super disintegrate by direct compression method over the conventional dosage forms because the drug gets disintegrated rapidly and dissolves in the saliva without the use of water. Bisoprolol used to treat hypertension and symptomatic congestive heart failure. The importance of drug uses in the life to treat many dangerous diseases made us to increase drug release of Bisoprolol was formulated as fast dissolving tablets. A total of 6 formulations of tablets of Bisoprolol were prepared by using different (superdisintegrants like, croscarmellose sodium and crospovidone). Among the all formulations F2 formulation was found to be showed improved drug release characteristics. F2, which consists of (Bisoprolol, mannitol, Avicel PH 101, crospovidone, aspartame, aerosil, talc, magnesium stearate), showed the best result in drug disintegrated time, faster dissolution rates and higher efficiency values.

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