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FORMULATION AND EVALUATION OF BISOPROLOL FUMARATE FAST DISSOLVING TABLET BY DIRECT COMPRESSION TECHNIQUES

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Abstract

Fast dissolving drug delivery systems offers a solution for paediatric, geriatric, mentally ill people and those patients having difficulty in swallowing tablets or capsules. In the present study, an attempt had been made to prepare fast dissolving tablets of Bisoprololfumarate, an antihypertensive agent. The fast dissolving tablets were prepared by direct compression method using sodium starch glycolate, Croscarmellose sodium and Crospovidone as super disintegrants in different concentration. Compatibility studies of excipients and drug were carried out using FT-IR spectroscopy. Formulations were evaluated for precompressional parameters such as density, angle of repose, Carr's index and hausner's ratio. The tablets were evaluated for weight variation, thickness, hardness, friability, drug content, wetting time, disintegration time and *in-vitro* dissolution study. No chemical interaction between drug and excipients was confirmed by FTIR studies. All the formulation showed satisfactory tablet properties. The formulation F9 contain (5%) crospovidone showed maximum drug release

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INTRODUCTION

The concept of Mouth dissolving drug delivery system emerged from the desire to provide patient with conventional mean of taking their medication. Geriatric and paediatric patients and travelling patients who may not have ready access to water are most in need of easy swallowing dosage forms.[1] Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, another study shows that an estimated 50% of the population suffers from this problem, because of physiological changes associated with these groups of patients.[2-4]

Other categories that experience problems using conventional oral dosage forms includes the mentally ill, uncooperative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack or coughing. Recent advances in Novel Drug Delivery System (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to improved the treatment, compliance and quality of life of patients.[5-6]

This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva.[7-9]On placing mouth-dissolving tablet in the mouth, saliva serves to rapidly dissolve the dosage form. The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach & it may produce rapid onset of action. In such a cases Bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [10-12].

MATERIALS & METHODS

Bisoprololfumarate was obtained as a gift sample from Atra Pharmaceutical, Aurangabad, India. The superdisintegrants such as sodium starch glycolate, Croscarmellose sodium, Crospovidone, microcrystalline cellulose were purchased from SD Fine chemicals, Mumbai. Other materials used in the study were of pharmaceutical grade.

Preparation of Bisoprololfumarate Fast Disintegration Tablet

Fast dissolving tablets of Bisoprololfumarate were prepared by direct compression method. The drug and excipients were passed through sieve (#60) to ensure better mixing. MCC was used as a direct compressible material. Superdisintegrants like Sodium starch glycolate, Croscarmellose sodium and Crospovidone were used in different concentration. All the ingredients were mixed in mortar and pestle then magnesium stearate and talc were added. The formulations were compressed with a ten station rotary tablet punching machine (Chamunda, Mini Press-1, India) using 8mm flat punches set.

Precompression studies of powder blend

Bulk Density

Apparent bulk density (g/ml) was determined by placing pre-sieved bulk powder blend into a graduated cylinder via a large cylinder and measuring the volume and weight "as it is".

$\rho b = M/v$

Where: ρb - bulk density, M- is the weight of powder and V- is the volume of powder.

Tapped Density

It was determined by placing a graduated cylinder, containing a known mass of powder on mechanical tapping apparatus, which was operated for fixed number of taps (around 500) until the powder bed volume reached a minimum. Using the weight of powder in a cylinder and this minimum volume, the tapped density was computed. From the results of bulk density and tapped density, Carr's index was calculated.

$\rho t = M/Vt$

Where, ρt - bulk density, M- weight of powder and Vt- volume of powder.

Angle of Repose

The angle of repose was determined using funnel method. Funnel that can be fit vertically with stand at 6.3 cm height. The opening end of funnel is closed with thumb until drug is poured. The 5 gm of powder was poured into funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was

measured and the angle of repose (θ) was calculated using the formula.

θ = Tan-1 (h / r)

Where, θ- angle of repose, h- cone height and r- radius of heap

Compressibility Index

The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by Compressibility Index. The value below 15% indicates a powder with give rice to good flow properties, whereas above 25% indicate poor flowability. Which is calculated follow.

% C.I. = ρt – ρb/ ρt × 100

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property.

Hausner's ratio = ρb/ ρt

Drug- Excipients compatibility Study

There is always a possibility of drug-excipient interaction in any formulation due to their intimate contact. The technique employed in this study is IR spectroscopy. IR spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. The Bisoprololfumarate and its blend with excipientswere scanned and recorded in the range of 4000-400 cm^{-1} by using Infrared spectrophotometer, (Shimazdu FT-IR 8400S, Japan). The drug and excipients were triturated with dried potassium bromide (KBr) using mortar and pestle. The mixture after grinding into fine powder was kept uniformly in suitable die and compressed into a pellet form by using hydraulic press. The resultant pellet was mounted in a suitable holder in the IR spectrophotometer.

Evaluation of fast dissolving tablets:

Weight Variation Test

From each batch twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight, the variation in the weight was expressed in terms of % deviation.

Hardness

Five tablets from each formulations were selected for the hardness and it was determined by using Pfizer hardness tester.

Thickness

Five tablets form each formulationswere taken for thickness and it was measured using Vernier caliper.

Friability Test

The friability of the tablet was determined by Roche Friabilator. Initially weighed 20 tablets (Wo) after dusting and placing them in a friability tester, which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of tablets (Wt) was recorded and the percent friability was calculated by

$$friability = \frac{\mathrm{Wo} - \mathrm{Wt}}{\mathrm{Wo}} * 100$$

Content uniformity

Five tablets were weighed individually and powdered. The powder equivalent to 20 mg of Bisoprololfumarate was weighed and extracted in water (100 ml) and the concentration of drug was determined by measuring absorbance at 222 nm by spectrophotometer.

Disintegration Time

The test was carried out on 6 tablets using the Disintegration Test Apparatus. Distilled water at 37^{o}C was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured.

Wetting Time

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and time required for complete wetting was measured.

***In Vitro* Drug Release**

Dissolution rate of fast dissolving tablet of Bisoprololfumarate was studied by using USP Type-II apparatus at 75 rpm using 900 ml of water as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5ºC, an aliquot of dissolution medium was withdrawn at every specific time interval and filtered. The absorbance of filtered solution was checked by UV spectrophotometer (Shimadzu, Japan) at 222 nm and concentration of the drug was determined from standard calibration curve.

RESULTS AND DISCUSSION

The fast disintegration tablet of Bisoprololfumarate was prepared by direct compression method and the composition of formulation were shown in Table No.1. The synthetic superdisintegrants such as SSG, Croscarmellose sodium and Crospovidone was used in different concentration in the formulations. The compatibility of drug and excipients were characterized by FTIR spectroscopy. The FTIR spectra of Bisoprololfumarate and formulation containing different superdisintegrants have same characteristic peak it indicates no chemical interaction between drug and excipients. The powder blend were evaluated for precompressional properties and shown in Table No.2. The angle of repose of formulations were in the range of 28.65^0 to 33.60^0,this value indicate that all the formulation exhibited good flow property.

The bulk and tapped density of all the formulations were in the range of (0.38 to 0.43) and (0.43 to 0.50) respectively. These values showed that blend have good packability properties. Thus the blended powder parameter was satisfactory and showed good flowability and compressibility.

All the formulation has sufficient mechanical strength and hardness found in the range of 3.2 to 3.5. $Kg/cm.^2$ The friability and thickness of all formulations was found to be in the acceptable limit. The drugs content of all the formulations were in the range of 99.10 % to 102.5%. Disintegration time is very important parameter for fast disintegrating tablets which desired to be less than 60 seconds. This rapid disintegration assists swallowing and also plays role in drug absorption in buccal cavity, thus promoting bioavailability. All the formulation showed disintegration time less than 78 seconds. Among the three superdisintegrants used crospovidone showed less disintegrating time than Croscarmellose sodium and sodium starch glycolate. Formulation (F9) showed disintegration time 25 second. The disintegration time is depending upon concentration and type of superdisintegrants used. Wetting time is used as an indicator for the ease the tablet disintegration in the buccal cavity. It was observed that wetting time of tablets was in

the range of 22 to 75 seconds. It was observed that type of disintegrating agent affected the wetting time of tablet. The in vitro dissolution studies of the Bisoprololfumarate fast dissolving tablets was performed in the water using USP dissolution apparatus type 2. The dissolution rate was found to increase linearly with increasing concentration of superdisintegrants. This was marked by decreased disintegration time values for tablet formulation containing higher proportions of Superdisintegrants. Formulation F1, F2, F3 containing increasing concentration of sodium starch glycolate showed 82.5%, 85.4% and 89.5% drug release, where as formulation F4, F5, F6 containing Croscarmellose sodium showed 85.5%, 90.4% and 96.5% drug release. The formulations F7, F8, F9 containing crospovidone showed better in vitro drug release 91.7%, 93.4%, 98.5%. Among the all formulations (F9) contained 5% of crospovidone showed maximum drug release.

CONCLUSION

The Bisoprolol fumarate fast dissolving tablet were prepared by direct compression method. Formulation (F9) containing 5% of concentration of crospovidone showed less disintegration time and fast drug release than formulation containing sodium starch glycolate and croscarmellose sodium.

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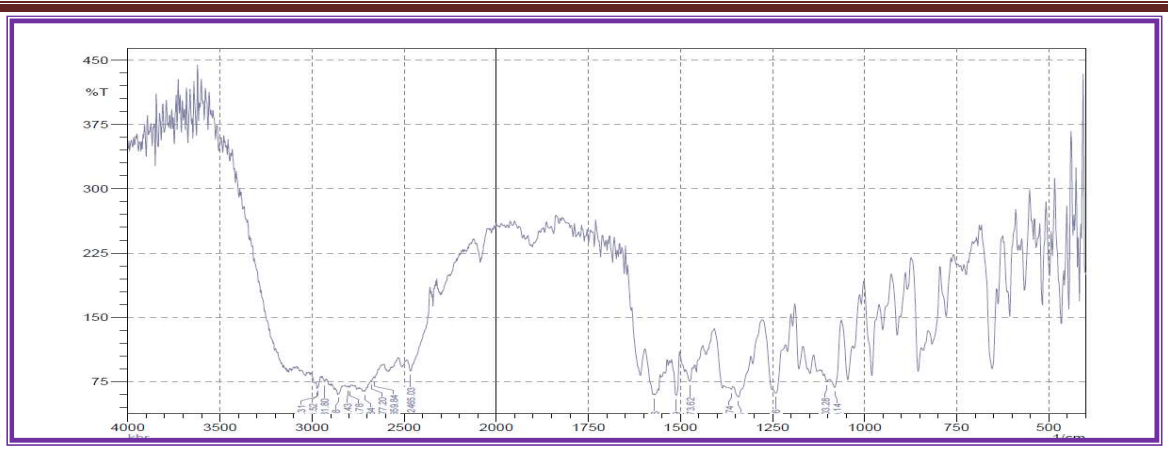
a)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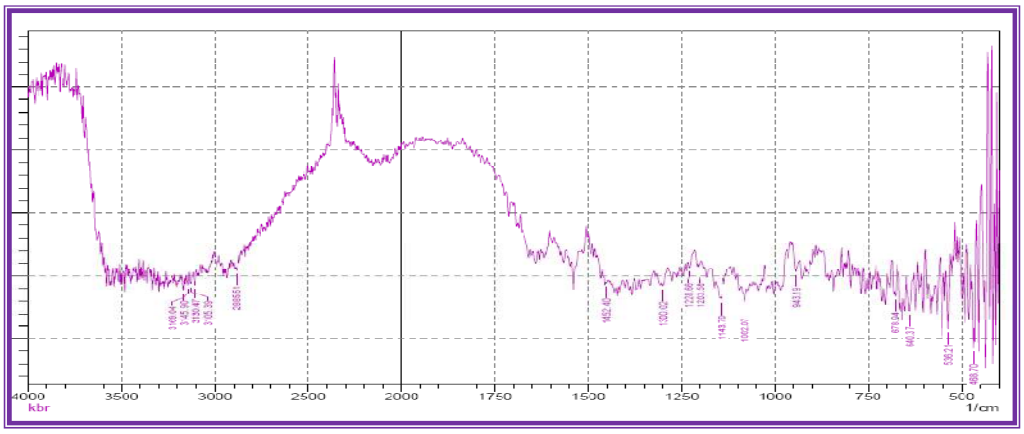
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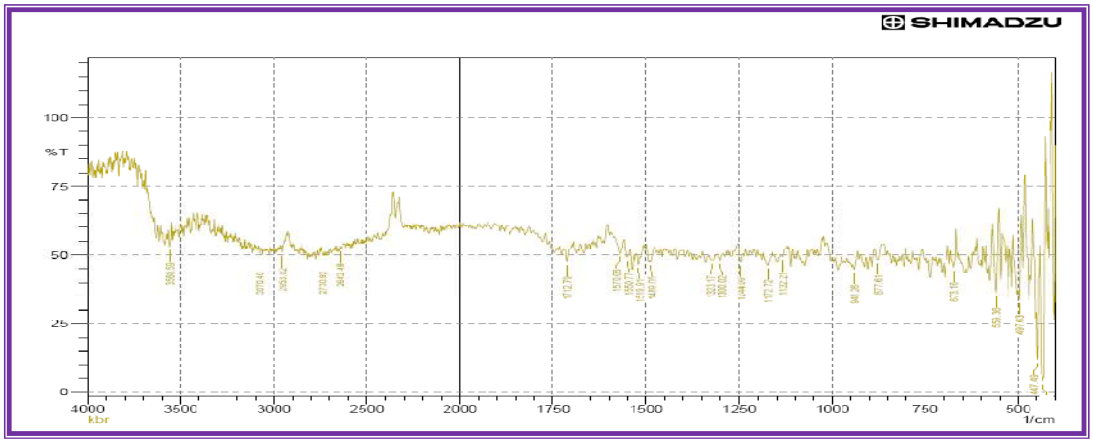
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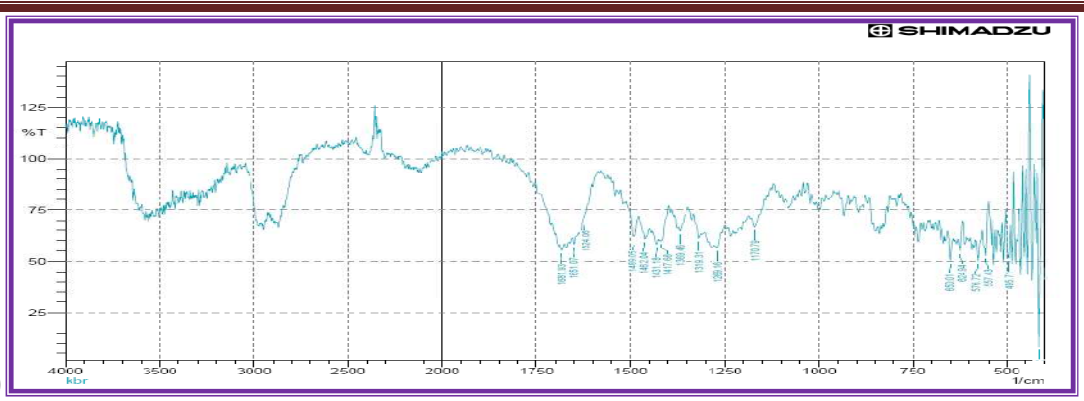
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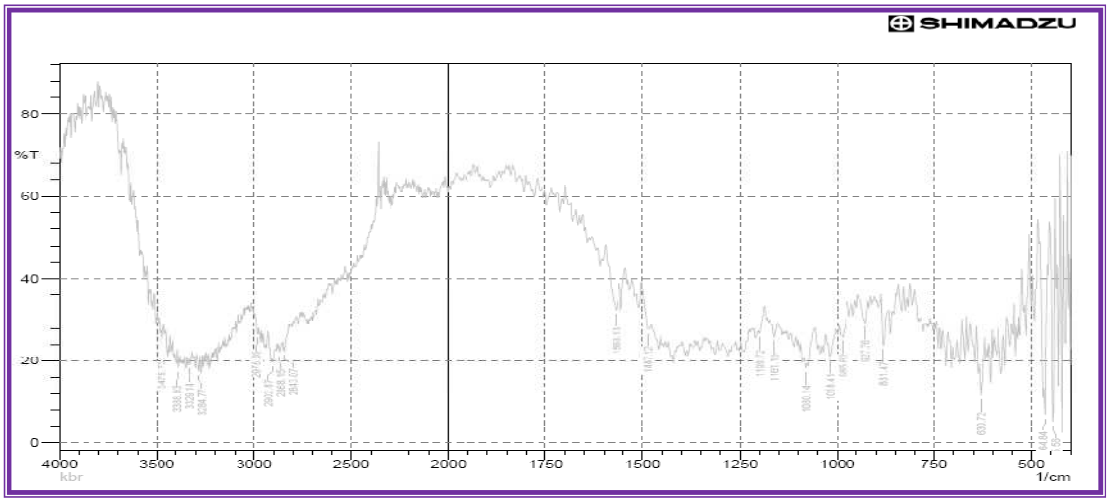
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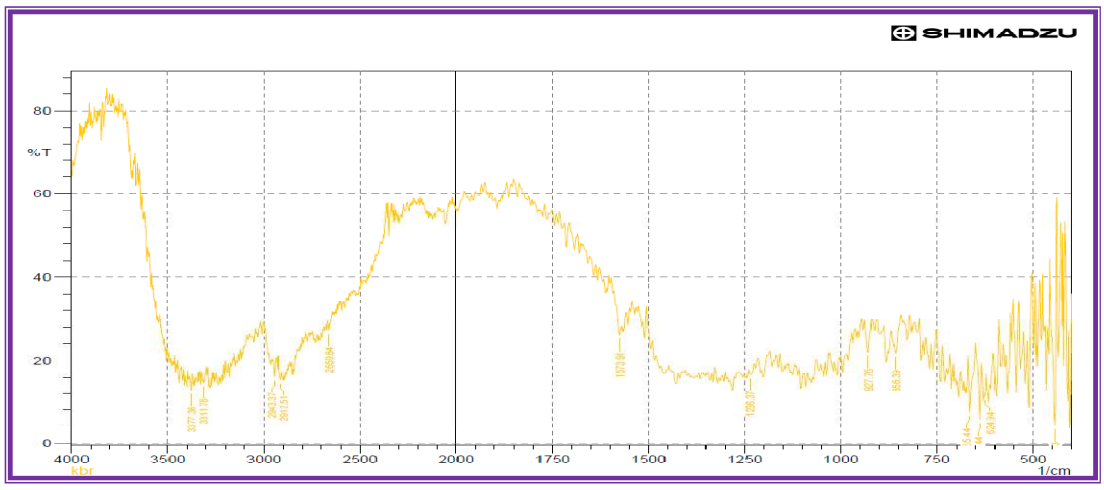
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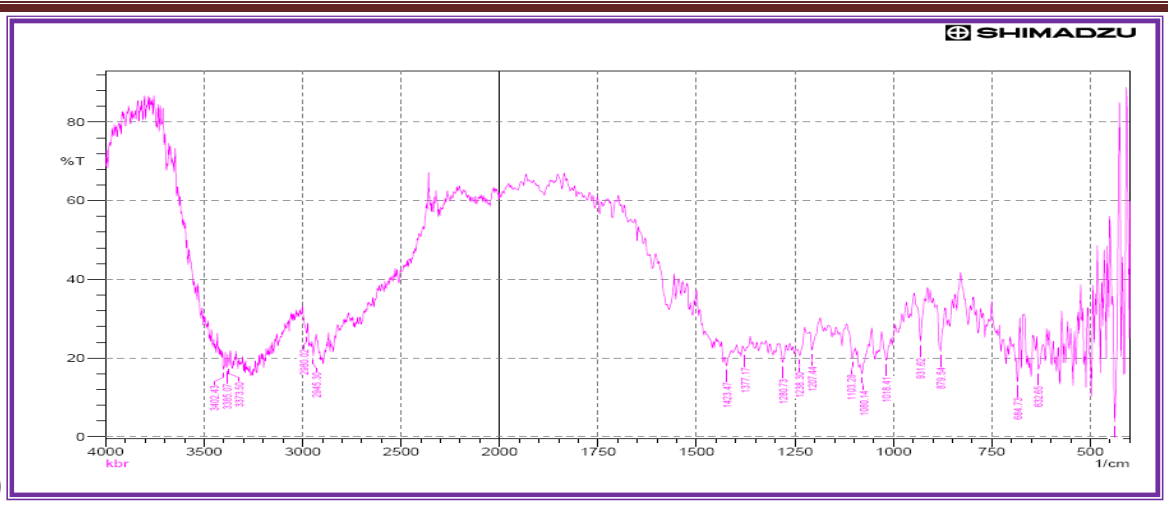

Figure 1 FT-IR spectra of: a) Bisoprololfumarate, b) SSG, c) CCS, d) CP, e) formulation Containing SSG, f) formulation containing CCS and g) formulation containing CP.

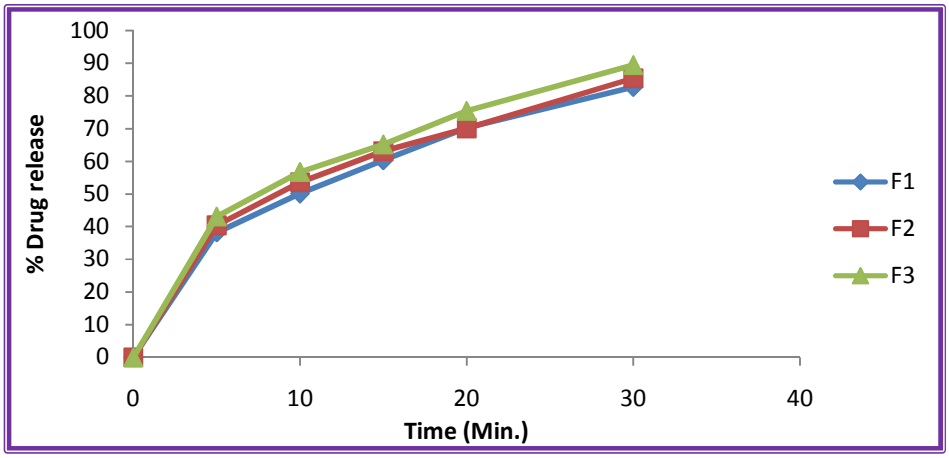

Figure 2 Dissolution profile of formulation F1, F2 and F3 containing SSG

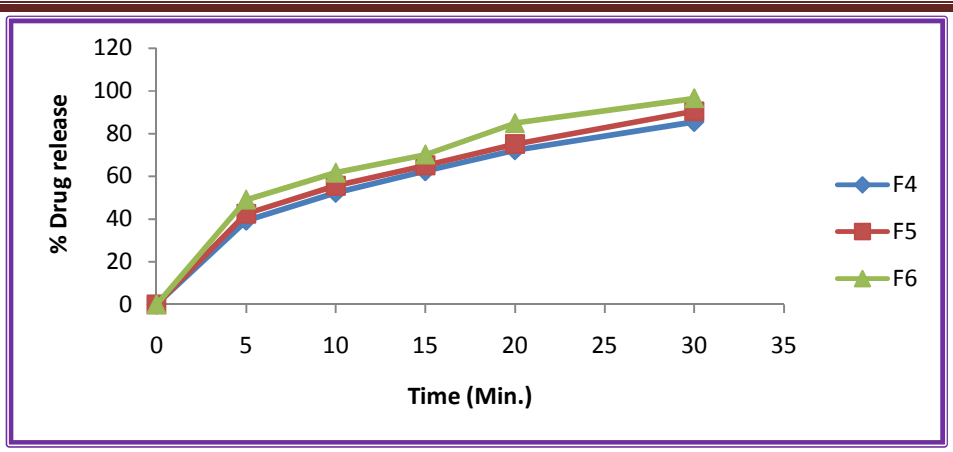

Figure 3 Dissolution profile of formulation F4, F5 and F6 containing Croscarmellose

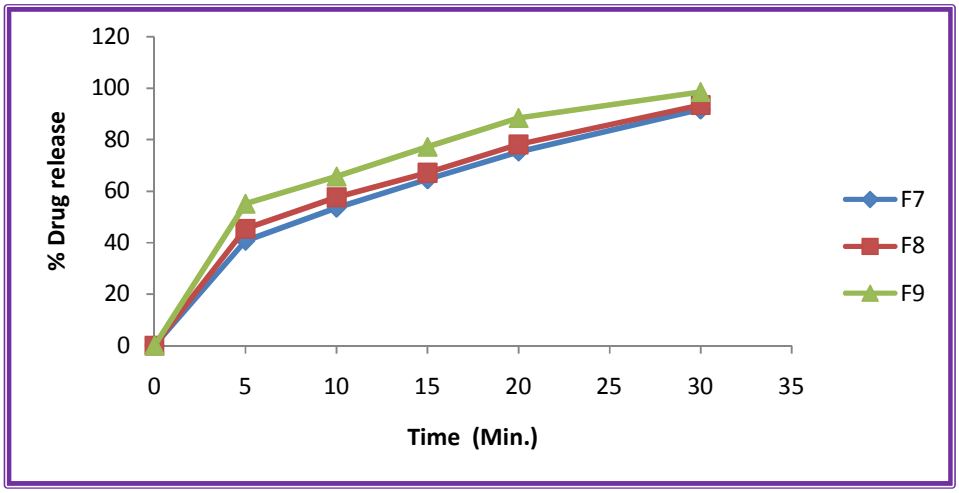

Figure 4 Dissolution profile of formulation F7, F8 and F9 containing Crospovidone

Table 1

Composition of different formulation of Bisoprolol mouth dissolving tablet.

Excipients	Formulation								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	20	20	20	20	20	20	20	20	**20**
MCC	60	60	60	60	60	60	60	60	**60**
Mannitol	102	100	98	102	100	98	102	100	**98**
SSG	6	8	10	-	-	-	-	-	**-**
CC	-	-	-	6	8	10	-	-	**-**
CP	-	-	-	-	-	-	6	8	**10**
Sucrose	10	10	10	10	10	10	10	10	**10**
Magnesium Stearate	02	02	02	02	02	02	02	02	**02**
Total weight	200	200	200	200	200	200	200	200	**200**

Table 2

Pre-compression properties of formulations

Formulation	Angle of repose (^{0})	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's Ratio
F1	32.15 ± 0.12	0.40 ± 0.16	0.45 ± 0.24	11.11 ± 0.12	1.12 ± 0.03
F2	30.44 ± 0.22	0.40 ± 0.35	0.44 ± 0.28	09.09 ± 0.18	1.10 ± 0.05
F3	28.85 ± 0.17	0.43 ± 0.18	0.50 ± 0.13	14.00 ± 0.20	1.16 ± 0.02
F4	32.35 ± 0.31	0.43 ± 0.24	0.49 ± 0.19	12.24 ± 0.32	1.13 ± 0.05
F5	29.45 ± 0.24	0.41 ± 0.27	0.47 ± 0.24	12.76 ± 0.30	1.14 ± 0.05
F6	29.30 ± 0.15	0.38 ± 0.34	0.43 ± 0.32	11.62 ± 0.28	1.13 ± 0.07
F7	33.60 ± 0.19	0.40 ± 0.25	0.45 ± 0.27	11.11 ± 0.14	1.12 ± 0.03

F8	32.22 ± 0.21	0.41 ± 0.26	0.46 ± 0.34	10.86 ± 0.22	1.12 ± 0.05
F9	28.65 ± 0.23	0.41 ± 0.41	0.47 ± 0.26	12.76 ± 0.28	1.14 ± 0.07

Table 3

Different evaluation tests of Bisoprolol mouth dissolving tablets

Formulation code	Weight Variation	Hardness (Kg/cm^2)	%Friability	Thickness	Disintegration Time (sec)	Drug content (%)	Wetting Time (sec)
F1	Pass	3.6±0.01	0.24±0.01	3.3	78±0.10	100.5±0.2	75±0.1
F2	Pass	3.5±0.26	0.21±0.05	3.4	66±0.24	99.23±0.7	63±0.2
F3	Pass	3.6±0.12	0.24±0.02	3.3	56±0.28	101.3±1.1	52±0.4
F4	Pass	3.2±0.28	0.35±0.09	3.5	71±0.36	102.5±0.2	67±0.3
F5	Pass	3.8±0.32	0.27±0.03	3.2	53±0.43	99.10±0.7	50±0.2
F6	Pass	3.8±0.15	0.27±0.12	3.5	46±0.38	100.6±0.4	42±0.3
F7	Pass	3.9±0.23	0.25±0.15	3.3	67±0.12	100.9±1.4	64±0.3
F8	Pass	3.6±0.12	0.24±0.02	3.2	46±0.28	101.3±1.1	43±0.5
F9	Pass	3.6±0.22	0.35±0.09	3.3	25±0.36	102.5±0.2	22±0.3

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