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Research Article

Formulation and Evaluation of Oral Fast Dissolving Film of Bisoprolol Fumarate

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Abstract

The present work aimed to prepare fast dissolving film of bisoprolol fumarate with the reason of developing a dosage from, for a very fast onset of action, the film were prepared by solvent casting method with polymers. The compatibility study between drug and physical mixture was performed by FT-IR. The film were characterized for various physicochemical properties such as, physical appearance-Transparent, surface texture, weight uniformity, thickness, folding endurance, disintegration time, tensile strength, % elongation, drug content, *in-vitro* drug release study, SEM Study shows smooth surface and Stability study indicate the good observation. All parameter shows better results. A marked increase in the disintegration time was exhibited by fast dissolving time formulation. The fast dissolving film of bisoprolol fumarate can be considered suitable for clinical use. The prepared film proved to be potential candidate for safe and effective fast dissolving drug delivery.

Keywords: Bisoprolol fumarate, Fast dissolving film, Physical characterization, disintegration study, *In-vitro* drug release study, Solvent casting method.

INTRODUCTION

Bisoprolol fumarate (BPF) is a beta adrenergic blocking agent used to treat cardiac disease. The marketed tablets are available in 5mg, 10mg, and 20mg. the half of drug is 10 Hrs and shows bioavailability of more than 80 %. The drug has relative high bio-availability and half life, the controlled release formulation has its own significance for the improving the onset of action, release characteristics and reducing the side effects[1]. Nanotechnology has at last provided a way for us to rearrange and restructure matter on an atomic scale, allowing us to reach down to the very roots of any problem[2].

A new oral fast dissolving dosage form such as the fast dissolving film has been developed which multiple advantaged of ease of dosing and convenience of dosing in the absence of water. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach and it may produce rapid onset of action. In such cases bioavailability of drug is significantly greater than those observed from conventional tablets dosage form[3]. Silver nanoparticles have citadel importance in the present era and are extensively used in pharmaceutical sciences, catalysis[4].

An ideal fast dissolving delivery system should have the following properties like High stability, transportability, ease of handling and administration, no special packaging material or processing requirements, no water necessary for the application and pleasant taste. So they are very suitable for pediatric and geriatric patients, bedridden patients or patients suffering from dysphasia, Parkinson's disease[5]. The gel stimulates cell growth and enhances the restoration of damaged skin[6].

The novel technologies of oral fast dispensing dosage forms are also known as fast dissolve, rapid

dissolve, rapid melt and quick disintegrating systems. The function and concept of all these dosage forms are similar. These fast dissolving systems are used in the conditions called Dysphasia[7]. The chemical agent that could supplant patient dependent mechanical plaque control and it reduce and prevent oral disease[8].

The medicine to such patients like pediatric, geriatrics and children etc. fast dissolving drug delivery system is a new drug delivery technique to provide films have acquired great importance in the pharmaceutical industry due to their unique properties and advantages[9]. The accuracy and selectivity of convectional UV absorption method is also increased by conversion of normal zero order[10].

The advantage of oral films are large surface area, enhanced safety compared to liquid forms, high level of patient compliance, high precision during dose administered and quick relif[11]. In the last few decades, the application of nanomaterials in the area of biology and medicine has revolutionized the field of drug delivery[12, 13]. Initial investigations were focused on the development of placebo fast dissolving films with good peelability, appearance and a quick disintegration time[14].

The dissolving film has minimum disintegration time and it was quickly dissolve in mouth. The film prepared by the using pullulan as polymer by solvent casting method.

MATERIALS AND METHOD

Chemicals and Reagents

The list of chemicals and instruments are given in Table 1 and Table 2 Respectively.

EXPERIMENTAL

Drug excipient compatibility

The analysis of pure drug as well as all excipients and physical admixtures of the drug with excipients were carried out using DSC, temperature range, room temperature to 200°C. The various blank film trials also perform of different concentration[15].

Formulation of Film[16]

The fast dissolving films of Bisoprolol Fumarate were prepared by solvent casting method using pullulan as polymers in selected concentration. The pullulan were dissolved in 8ml water by using magnetic stirrer and similarly aspartame was dissolved in remaining 2ml of hot water and to this mixed sucralose.

The drug dissolved in polymer solution, plasticizer and citric acid were added to polymer solution. Sweetener solution also added to polymer solution. The solution was allowed to stand for 30min to allow deaeration to take place. The solution was casted on a petridish and dried at room temperature for 24 Hr. the film was removed and cut into the required size of 3x2 cm^2. The formulation plan of fast dissolving film was given in Table 3.

EVALUATION OF FILM[17, 18]

The formulations were subjected to evaluation parameters as mentioned below-

Physical appearance

This parameter was checked simply with visual inspection of films and evaluation of texture by feel or touch.

Weight uniformity of films

Three films of the size 3x2 cm2 were weighed individually using digital balance and the average weights were calculated.

Thickness

The film thickness was measured by using a micrometer screw gauge apparatus. A strip of 2 X 2cm was placed between the thickness was measured in five different positions.

Folding endurance

The folding endurance was measured by manually or practically for the prepared films. Take a 2x2 cm films and folded repeatedly at the same place till it broke. The no times the film could be folded at the same place without breaking gave the extract valve of folding endurance.

pH

The pH was determined by dissolving a film in 1-2ml of distilled water and then the pH of the obtained solution was measured by the pH meter.

Dissolution studies

In-vitro dissolution of fast dissolving film was studied in USP paddle dissolution test apparatus us-

ing 0.1N HCL as the dissolution medium. The temperature was maintained at 37±0.5°C throughout the experiment. 5ml sample was withdrawn at 2min intervals and the same quantity was replaced with 0.1N HCL. The cumulative percentage of drug released was determined using UV visible spectrometry.

Disintegration time

The disintegration test was performed in the USP disintegration time testing apparatus. One film from formulation was introduced into the each tube of disintegration apparatus IP. A disc was added into the tube. The assembly was suspended in 0.1N HCL and operated until the film disintegrated.

Table 1: List of chemicals used with grade and suppliers

Sr. No.	Materials	Grade	Suppliers
1	Bisoprolol Fumarate	Pharma	Mylan Pharma, Aurangabad.
2	Pullulan	Pharma	Hayashibara Co. Ltd, Okayama, Japan.
3	HPMC E5	Pharma	C. Jivanlal & Co. Thane.
4	HPMC E15	Pharma	C. Jivanlal & Co. Thane.
5	Aspartame	Pharma	Latika Pharma, Pune.
6	Sucralose	Pharma	Latika Pharma, Pune.
7	Citric acid	Pharma	Latika Pharma, Pune.
8	Polyvinyl alcohol	AR	Loba chemicals, Mumbai.
9	Glycerine	LR	S.D. Fine Chemicals, Mumbai.
10	Propylene glycol	LR	S.D. Fine Chemicals, Mumbai.
11	Polyethylene glycol 400	LR	S.D. Fine Chemicals, Mumbai.
12	Mercury	LR	Loba chemicals, Mumbai.

The pure drug obtain as Gift sample and other are purchase as listed table

Instruments

Table 2: List of instruments used and manufacturer

Sr. No.	Instruments	Manufacturer
1	Electronic Balance, Model No. AW-220 and BX-6205	Pioneered (OHAUS), USA.
2	Double beam UV visible Spectrometer Mode No. UV 1700 PC.	Shimadzu Corporation, Japan.
3	Bath Sonicator	Remi International, Mumbai.
4	Dissolution apparatus	Electrolab Ltd.
5	Hot air oven	Shital scientific industries, Mumbai.
6	FT-IR Model-84005	Shimadzu Asia Pacific Pvt Ltd, Singapore.
7	Scanning electron microscopy Model No. E7210.	JEOL-5400, Japan.
8	Differntial Scanning Calorimetry, Model No. DC 8541.	SIIO-6300, Japan.
9	Magnetic Stirrer	Remi Equipments, Mumbai.
10	Programmable environmental test chamber	Remi Equipments, Mumbai.
11	pH Meter Model No. EQ-612	Equip Tronics.
12	Screw gauge	Mitutoyo, Japan.

Table 3: Formulation of Film

Formulation Batches	Drugs (mg)	Pullulan (mg)	Glycerine (mg)	Aspartame (mg)	Sucralose (mg)	Citric acid (mg)	Water (ml)
B1	15	400	100	40	20	20	10
B2	15	400	120	40	20	20	10
B3	15	400	140	40	20	20	10
B4	15	500	125	50	25	25	10
B5	15	500	150	50	25	25	10
B6	15	500	175	50	25	25	10
B7	15	600	150	60	30	30	10
B8	15	600	180	60	30	30	10
B9	15	600	210	60	30	30	10

Note- Four Films of each batch were prepared.

Stability studies

The purpose of the stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factor factors such as temperature, humidity and light, enabling recommended storage condition, retest periods and shelf life. Stability study carried out as per ICH International Conference of Harmonization guidelines at 40^0C / 75% RH for 3 months and evaluated for their physical appearance, drug content and *in-vitro* dispersion time at specific interval of time.

RESULT AND DISCUSSION

Several methods were described in the methodology for the development and evaluation of film containing bisoprolol fumarate as a drug. These formulations were intended to produce immediate release of drugs in the buccal region. The results are show below.

Preformulation Studies

Confirmation of Pure drug

Description

Melting point determination

The melting point of bisoprolol fumarate drug sample was found to be 100^0C and range 98-100^0C. It complies with purity of the drug sample.

FTIR determination

The FT-IR spectrum of the bisoprolol fumarate pure drug was found to be similar to the standard spectrum of bisoprolol fumarate peaks of sample were matched with standard.

Spectrometric method for the estimation of bisoprolol fumarate

λ max determination of bisoprolol fumarate in phosphate buffer pH 6.8

After scanning 10 µg/ml solutions, only one peak at 249.60 nm was observed and considered as λmax. The UV spectrum was as shown in Figure 1.

From the standard curve, it was observed that the drug obeys Beer's law in concentration range of 5-50 µg/ml in phosphate buffer pH 6.8. drug showed good linearity with regression coefficient (r^2= 0.990) and equation for this line obtained was found to be (Y= 0.045x-0.089) which is used for the calculation of amount of drug and dissolution study.

Drug Excipient Interaction studies

FTIR spectroscopy study

The spectrum of bisoprolol fumarate shows the following functional groups at their frequencies mention in Table 4. The FTIR spectrum of Bisoprolol fumarate shows in Figure 3, spectrum of drug and pullulan has shows in Figure 4, spectrum of pullulan shows in Figure 5. The peaks obtained in FTIR of pure drug are tabulated in Table 4.

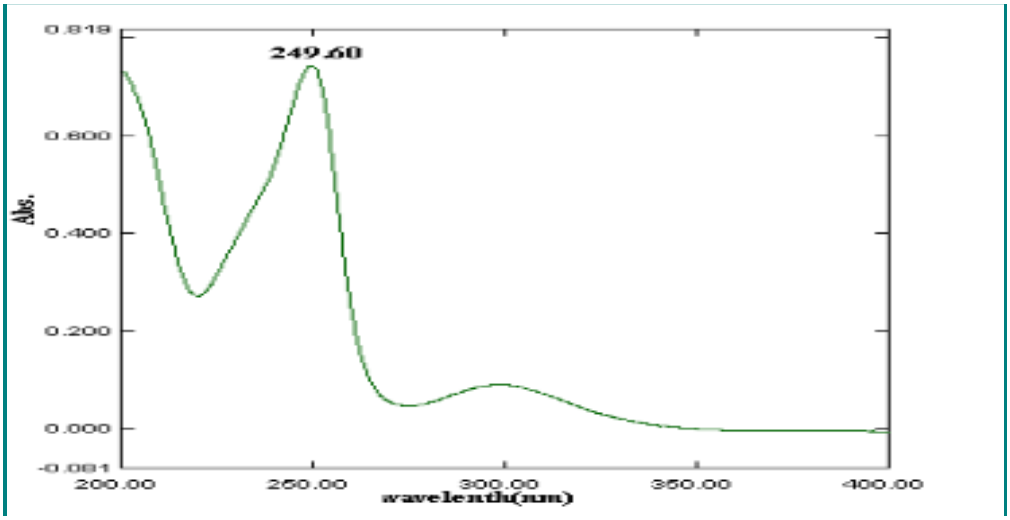

Figure 1: UV Spectrum of bisoprolol fumarate in phosphate buffer pH 6.8

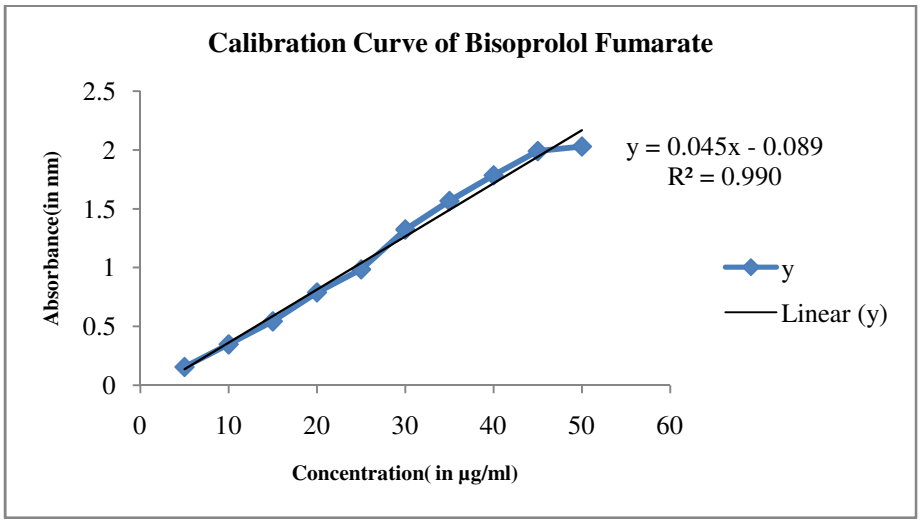

Figure 2: standard calibration curve of bisoprolol fumarate at 249.60nm in phosphate buffer pH 6.8

Table 4: Functional groups and their frequencies

Groups	Principal peaks (cm^{-1})	Mode of vibration
C-H Aromatic	3137-3140	Stretching
C-H Aliphatic	2973,2914	Stretching
-C=O	1611,1573	Stretching
C=C Aromatic	1514	Stretching
CH_3 Asymmetric	1478,1433	Bending vibration
CH_3, CH_2 Symmetric	1385,1368,1347	Bending vibration
C-H Aromatic	913,655	-

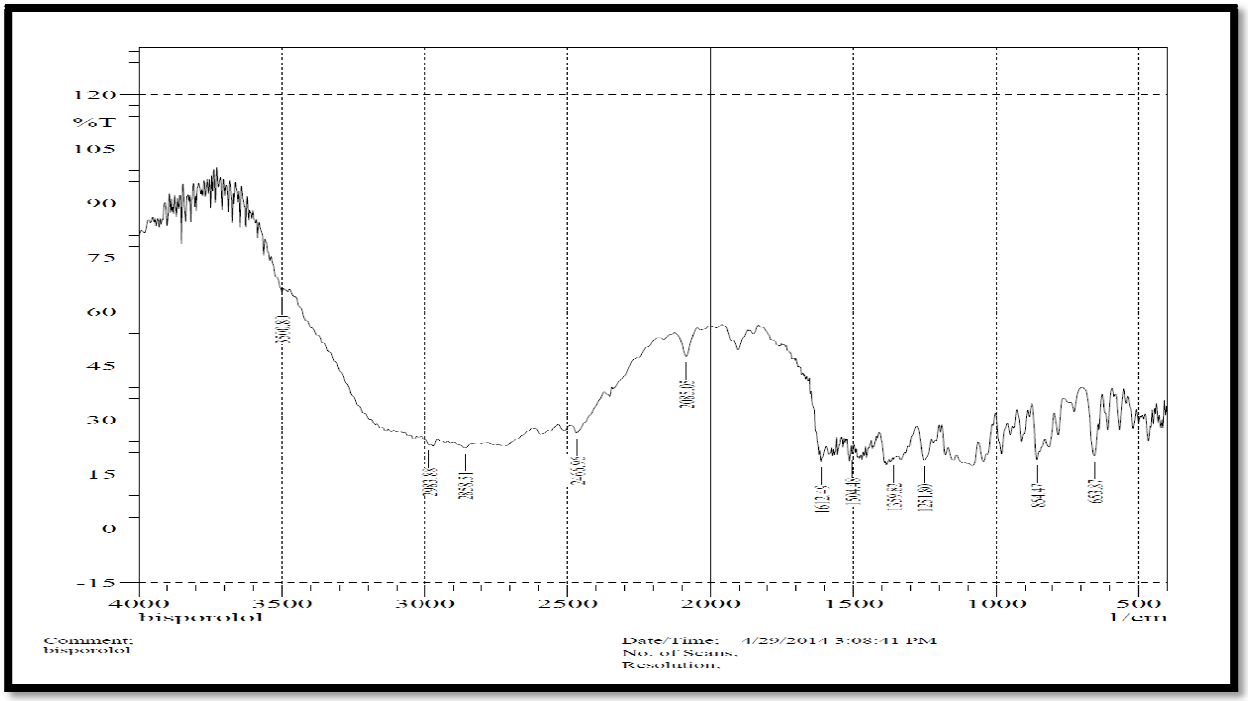

Figure 3: FTIR Spectrum of Bisoprolol fumarate

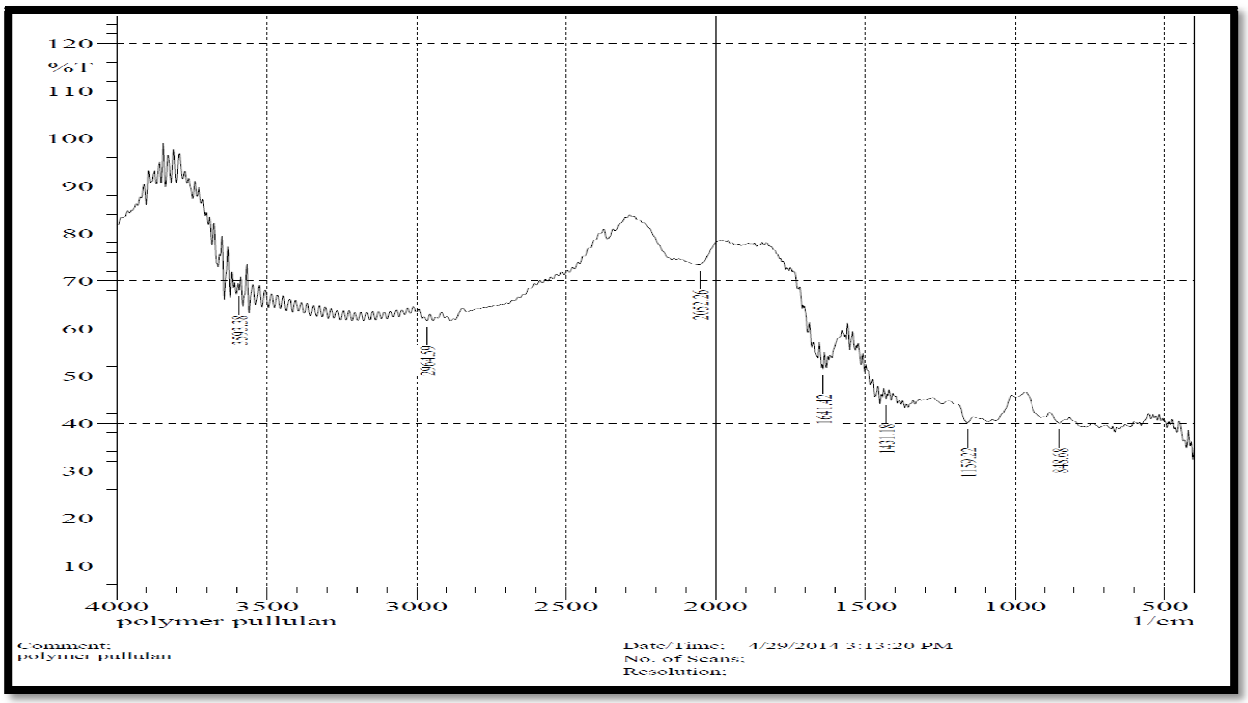

Figure 4: FTIR spectrum of Pullulan

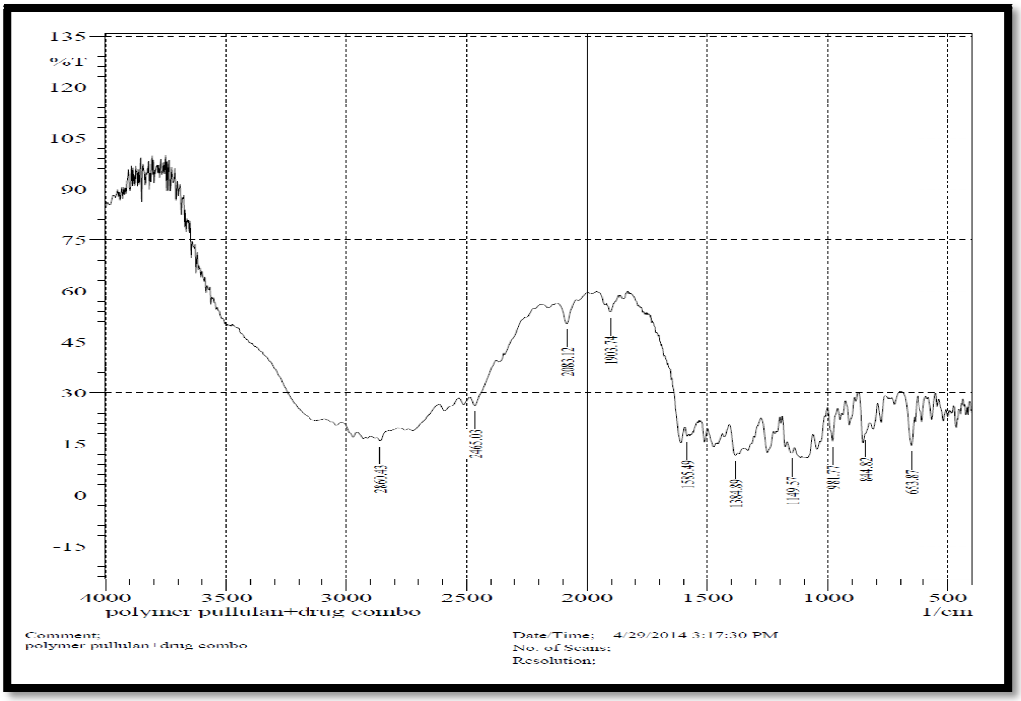

Figure 5: FTIR Spectrum of Drug and Pullulan

Table 5: Evaluation of prepared Films

Batch No.	Appearance	Folding endurance	Thickness (mm)	DT (Sec)	Tensile strength (gm/mm²)	% Elongation
B1	Transparent	82±0.57	0.063±0.018	09±0.57	5.09	13.33
B2	Transparent	136±1.52	0.066±0.008	10±0.58	4.80	16.66
B3	Transparent	125±1.02	0.068±0.0008	11±0.57	4.49	20.00
B4	Transparent	185±1.15	0.077±0.0008	11±0.68	5.65	20.00
B5	Transparent	257±2.51	0.079±0.001	04±0.69	5.52	26.66
B6	Transparent	201±1.59	0.082±0.001	13±0.57	4.89	30.00
B7	Transparent	166±1.20	0.086±0.0013	15±0.57	6.98	26.33
B8	Transparent	223±1.61	0.089±0.002	16±0.57	6.29	30.00
B9	Transparent	210±1.53	0.092±0.0012	18±0.68	6.03	36.66

Table 6: Evaluation of Formulation

Formulations batches	Drug content	Surface pH	Taste Acceptability
B1	98.12	6.6	+++
B2	98.50	6.5	+++
B3	98.36	6.6	+++
B4	97.02	6.8	+++
B5	99.86	6.8	+++
B6	97.76	6.5	+++
B7	98.66	6.9	+++
B8	96.34	6.6	+++
B9	97.55	6.7	+++

+ = very bitter, +++ = moderate to bitter, +++slightly bitter after taste

Physical appearance

The observation suggests that the films were having smooth surface and transparent.

Weight uniformity of films

Weights of all films formulation are about 51.4±0.12, 51.9±0.15, 52.5±0.22, 53.9±0.10, 54.3±0.24, 54.8±0.18, 55.6±0.15, 60±0.10, 60.6±0.28 mg respectively. Films were found to be uniform in weight with same concentration of polymer.

Thickness of films

The thickness of the films was measured using micro meter screw gauge and the average thickness of all films was given in Table 5.

From the data of thickness of films in Table 5 it was observe that increase in polymer concentration increase thickness of the film. Similarly increase in plasticizer concentration slightly increases film thickness.

Folding endurance of films

The average folding endurance of all films was given in Table 5.

From the data of folding endurance in Table 5 it was shows higher folding endurance.

In-vitro disintegration time of films

The average disintegration time of different formulation was shown in Table 5.

From the data of disintegration time in Table 5 it was observe that as the concentration of polymer increase disintegration time increased.

Mechanical properties

Mechanical properties such as Tensile strength and % Elongation of different formulation was shown in Table 5.

From the data of mechanical properties in Table 5 it was concluded that Tensile strength decreased with increase in plasticizer concentration and % Elongation increase in plasticizer concentration.

Surface pH of Films

Surface Ph was measured to determined formulation having range of salivary pH. Acidic or alkaline pH may produce irritation to oral mucosa. Surface pH for all formulations found in the range of 6.5-6.9. The surface pH of all the films was within the range of salivary pH. No significant difference was found in surface pH of different films.

Drug content uniformity study of films

Drug content uniformity for all formulation was as shown in Table 6.

The observation shows uniformity of drug content in all formulation.

Taste Evaluation

Taste acceptability for all formulations was shown in Table 6.

Taste acceptability was measured by a taste panel consisting of human volunteers and from observation all formulation shows slightly bitter after taste.

***In-vitro* drug release study**

In vitro drug release study of fast dissolving film from each batch was carried out in phosphate buffer pH 6.8 solutions for 30 min and the values are shown in Table 7 and Figure 6.

From the data in Table 7 it was observed that as the concentration of polymer increases drug release from film decreases. About 90 to 98% drug released within 5 min.

Scanning Electron Microscopy

The determination of surface morphology was done by scanning electron microscope JEOL-5400, Japan. The scanning electron photomicrograph of the film carried out at 200 X and 500 X Magnification. It was smooth surface of the film.

SEM study was carried out to determine surface characteristic of film. It was carried out at 200 X and 500 X Magnification. Results show film has smooth surface.

Table 7: *In-vitro* drug release study (Drug release ± SD)

Time (min)	B1	B2	B3	B4	B5	B6	B7	B8	B9
0	0	0	0	0	0	0	0	0	0
2	967.5±1.04	900±1	930±1	867±1	768±1.52	750±1	768±1	789±1	733.5±1.05
5	1311±1	1117.5±1.5	1170±2	918±1	1117.5±1.63	1071±1	1111.5±2.41	969±2.08	984±1
10	1417.5±1.2	1524±1	1672.5±1	1534±51.521	1218±1.52	1447.5±0.95	1633.5±1.36	1498.5±1.47	1434±1.52
15	1518±2.08	1849.5±1.0	1968±1	1863±1	1834.5±1.52	1984.5±2.17	1834.5±1.36	2034±1	1834.5±1.5
20	2434.5±1.05	2184±1	2281.5±0.52	2467.5±1	2634±1	2319±1	2467.5±0.95	2319±1	2181±1.52
25	3525±1.52	3316.5±1.01	3319.5±1.05	3184.5±1.258	3028.5±1.04	3279±1.52	2982±1.16	2947.5±0.57	2784±1
30	3616.5±0.3	3849±1	3487.5±1.10	3798±1	3754.3±1.01	3534±1	3288±1	3064.5±1.04	3367.5±1.20

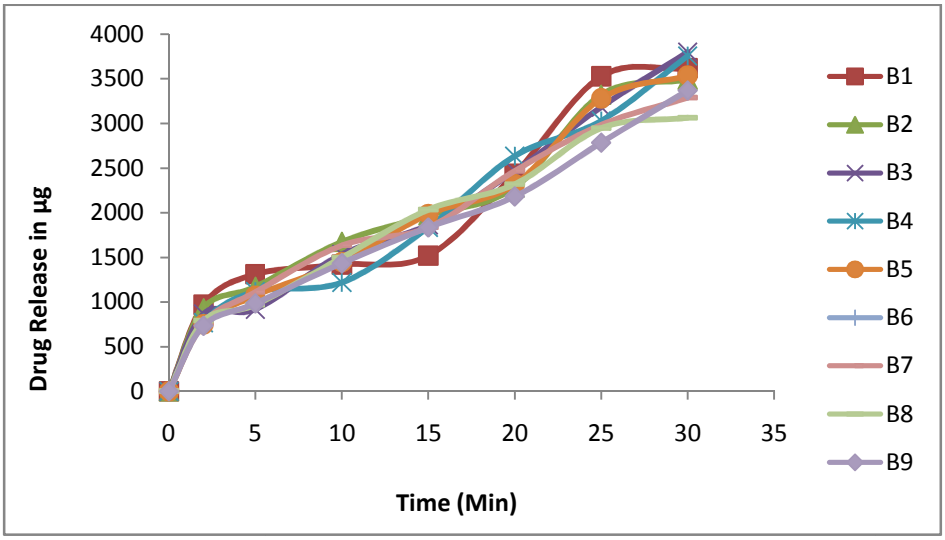

Figure 6: In-vitro Drug release

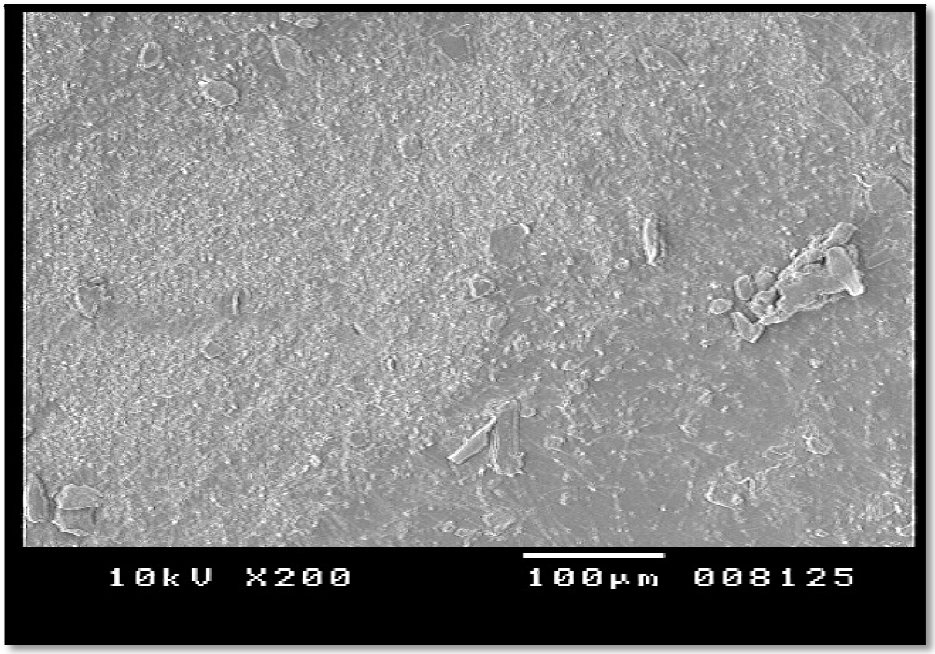

Figure 7: Morphology of Film 200 X Magnification

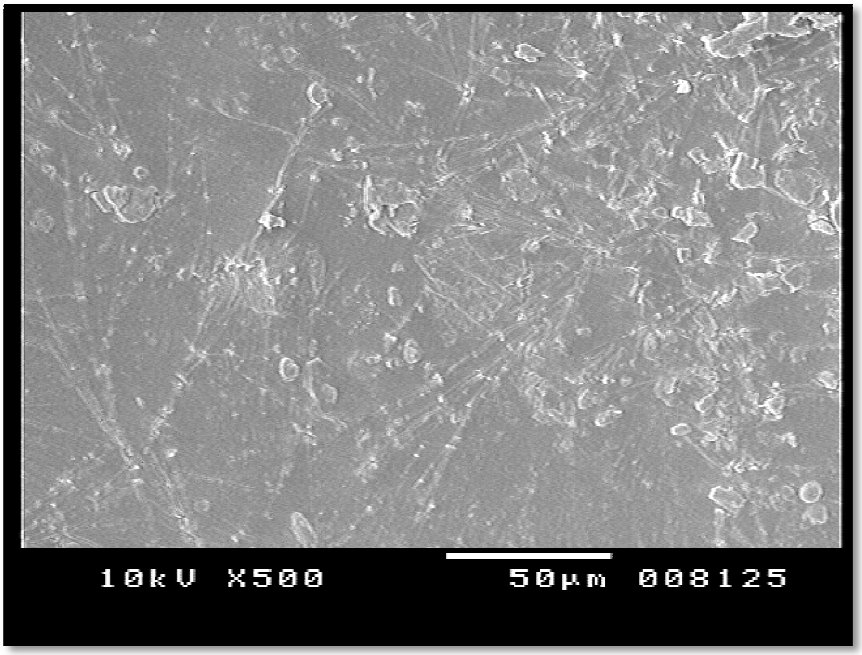

Figure 8: Morphology of Film 500 X Magnification

Table 8: Stability Study

Stability (Days)	Appearance (At room Temp & 45±2⁰, 75±5% RH)	Drug content (room temp)	Drug content (45±2⁰, 75±5% RH)	Disintegration time (room temp)	DT (45±2⁰, 75±5% RH)
0	Transparent	97.81	97.82	12	12
7	Transparent	97.7	97.67	12	12
14	Transparent	97. 65	97.48	12	12
21	Transparent	97.44	97.28	11	11
28	Transparent	97.12	97.12	11	10

Stability Study

The stability of optimum formation revealed that there is no significant reduction in drug content, disintegration time, and appearance was observed over period of 28 days. The Result is show in Table 8.

Stability study at room temp and 45±2⁰, 75±5% RH was carried out for 0-28 days. At room temperature drug content was found to be 97.82 to 97.12 and disintegration time was about 12 to 10.

No significant change was observed on the drug content and disintegration time at room temperature and 45±2⁰, 75±5% RH. Hence formulation was found to be stable for 28 day.

CONCLUSION

The present study has been a satisfactory attempt to formulate fast dissolving film of Bisoprolol fumarate with improving its oral disintegration and giving a rapid release of the drug. Prior the formulation, pre-formulation studies were carried out in order to establish compatibility between drug and polymers by FTIR Spectroscopy. There is no physical or chemical interaction between drug and polymer. The SEM study for surface morphology it was concluded that prepared film has smooth surface. Hence, finally it was concluded that the prepared film may prove to be potential candidate for safe and effective fast dissolving drug delivery. There are various future scopes for the novel and fast action therapy.

REFERENCES

1. Chandran C S, Shijith KV, Vipin, Augusthy A R. Chitosan Based Mucoadhesive Buccal Patches Containing Bisoprolol Fumarate. Int J Adv Pharm Bio Chem. 2013;2(3): 465-469.
2. Telrandhe R. Nanotechnology for cancer therapy: Recent development. Eur J Pharm Med Res. 2016;3(11): 284-294.
3. Gurdale M S, Lade M S, Payghan S A, Disouza J L. Fast dissolving HPMC E5 based oral film for rapid absorption of metoprolol tartrate. 2014;1(1): 75-91.
4. Telrandhe R, Mahapatra D K, Kamble M A. Bombax ceiba thorn extract mediated synthesis of silver nanoparticles: Evaluation of anti-staphylococcus aures activity. Int J Pharm Drug Anal. 2017;5(9): 376-379.
5. Gorle A, Patil G. Design, Development and evaluation of fast dissolving film of amplodipine besylate. Int J ChemTech Res. 2017;10(4): 334-344.
6. Shende V, Telrandhe R. Formulation and evaluation of Tooth Gel from Aloe vera leaves extract. Int J Pharm Drug Anal. 2017;5(10):394-398.
7. Pallavi K, Pallavi T. Formulation and evaluation of fast dissolving films of eletriptan hydrobromide. Int J Cur Pharm Res. 2017;9(2): 59-63.
8. Deshmukh P, Telrandhe R, Gunde M. Formulation and Evalua-tion of Herbal Toothpaste: Compared With Marketed Preparation. Int J Pharm Drug Anal. 2017;5(10): 406-410.
9. Thonte S S, Pentewar R S, Bhusnure O G, Gholve S B, Giram P S, Khadkutkar V K. Formulation and evaluation of oral fast dissolving film of levosalbutamol sulphate. World J Pharm Res. 2017;6(7): 1298-1318.
10. Trivedi L, Telrandhe R, Dhabarde D. Differential spectrophotometric method for estimation and validatuion of Verapamil in Tablet dosage form. Int J Pharm Drug Anal. 2017;5(11): 419-422.
11. Jahangir M A, Saleem M A, Patel H R, Kazmi I, Muheem A, Ahmad K. formulation and evaluation of oral fast dissolving films of levocetirizine. World J Pharm Pharm Sci. 2014;3(9): 1310-1323.
12. Rothekar H, Telrandhe R, Jumade P. Development and validation of RP-HPLC method for simultaneous determination of rosuvastatin and clopidogrel in tablet dosage form. Int J Pharm Drug Anal. 2017;5(12): 475-482.
13. Telrandhe R. Novel UV-Spectropphotometry and RP-HPLC Method for the Simultaneous Estimation of Rosuvastatin and Clopidogrel in Tablet Dosage Form: Method Development and Validation. Inventi Rapid: Pharm Analysis & Quality Assurance, 2018(1):1-9, 2017.
14. Londhe V, Umalkar K B. Formulation development and evaluation of fast dissolving film of telmisartan. Indian J Pharm Sci. 2012;74(2): 91-188.
15. Buddhadev S, Buddhadev S. Formulation and evalution of fast dissolving film of etophylline. Int J App Pharm Bio Res. 2017;2(2): 48-55.
16. Kadam V S, Bharkad V B, Shete G A, Jameel A, Shendarkar G R, Jadhav S V. Formulation and evaluation of fast dissolving oral film of metoclopramide HCL. World J Pharm Pharm Sci. 2017;6(8): 2052-2066.
17. RaghavendraRao N G, Kistayya C, Kumar G V. Design and development of fast dissolving thin films of losartan potassium. Int J Pharm Sci Drug Res. 2016;8(1): 01-06.
18. Thonte S S, Pentewar R S, Bhusnure O G, Gholve S B, Gaikwad V M, Pujdekar A A. Folmulation and evaluation of oral fast dissolving film of glipizide. World J Pharm Res. 2017;6(7): 1279-1297.