FABRICATION AND CHARACTERIZATION OF BISOPROLOLFUMRATE ORAL MOUTH DISSOLVING FILM BY SOLVENT CASTING METHOD

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Abstract

Medical professionals and pharmaceutical companies have continuously emphasized patient acceptance of the oral route of administration over the parenteral, topical, rectal, and vaginal routes. Patients have shown interest in this technique because of how simple it is to use and how little it costs. The oral cavity has the potential to be a site for medicine delivery due to its unique environment. Oral solid dose forms like mouth-dissolving films disintegrate and dissolve in the mouth without the use of water. Choking-averse youngsters, elderly people, and those with dysphasia are increasingly embracing the usage of mouth-dissolving films. Weight uniformity of the film was performed and find in an average of 30.9 mg and the thickness was 0.85 mm. The formulation pH was optimum in range. The folding durability was good. The disintegration time of the film was in the range 30-54 second. In-vitro drug release was performed and get in the range of 89.34-97.17 %.

Keywords- Bisoprolol Fumarate, Fast Dissolving Film, Pectin, Solvent Casting Technique.

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INTRODUCTION

Mouth Dissolving Films, a type of oral solid dosage form, break down and dissolve in the mouth without the need of water. The use of mouth-dissolving films is growing in acceptance and appeal among choking-phobic children, seniors, and dysphagia sufferers. The use of mouth-dissolving films is growing in acceptance and appeal among choking-phobic children, seniors, and dysphagia sufferers. Making mouth-dissolving films requires judicious choice of ingredients convey both aesthetic and functional qualities such tasting concealment, quick look, mouth-feel, or dissolving. A mouth-dispersing film's excipients must all be dosage authorized for usage in dosage forms for medicines designed for chewing and GRAS-listed. The technique that involves dissolving a water-soluble polymer in water to produce a clear viscous solution is the most popular and advised one for making oral films. After adding the polymer solution, dissolving the API and other excipients in water, and stirring the mixture until it is homogeneous. The viscous solution is then vacuum-degassed, poured into a petri plate, and cast into film before being dried at 45–50°C in an oven. After being cut to the correct form and size, the film is then placed in desiccators for storage.[1]

MATERIALS:

Bisoprolol Fumrate drug obtained from gift sample JIPS Pharmaceutical Pvt.Chandigarh. Poly vinyl Achohol, Pectin, Citric Acid and Mannitol, were purchased from Devson Impex private Ltd, Mumbai. Potassium Hydrogen Orthophosphate were purchased from S.D.Fine Chem.Ltd.,Mumbai (Mumbai, India). All other chemicals and reagents used were of analytical grade and were used without further purification.

Identification of drug-

a) Melting Point- Melting point of the drug was determined using capillary method by the melting point apparatus. Drug was filled in the capillary after sealing the capillary from one end and then the sample was placed in the apparatus along with the thermometer and when the drug melted its temperature was recorded. [2]

b) Solubility- Solubility of the drug was determined by dissolving 10mg of the drug in 10ml different solvents. Drug sample was found to be freely soluble in the solvent Chloroform and alcohol, distilled water and Phosphate buffer pH 6.8, slightly soluble in acetone and in ethyl acetate. [3]

c) U.V Spectrophotometric Study- The stock solution of Bisoprolol Fumarate was prepared in phosphate buffer pH 6.8; UV spectrum of 1µg/ml solution of Bisoprolol Fumarate was taken to determine its absorption maxima (λ_{max}).

Preparation of calibration curve: From stock solution IInd take 0.2, 0.4, 0.6, 0.8, 1 ml of solution in 10 ml of volumetric flask. The volume was made up to mark with Phosphate Buffer pH 6.8 to produce concentration as 2, 4, 6, 8, 10 µg/ml of Bisoprolol Fumarate respectively. The absorbance of prepared sample of Bisoprolol Fumarate was measured at 224 nm in Systronic UV spectrophotometer against Phosphate Buffer pH 6.8 as blank. By using same procedure Calibration curve of Bisoprolol Fumarate in Phosphate Buffer pH 6.8 was plotted. The absorbance: λ_{max} 224 nm.

d) Drug –Excipients compatibility study: FT-IR study-The FTIR spectrophotometer was used to record the FTIR absorption spectra of the pure medication.PVA, Pectin, and their combination in the 4000-400 cm^{-1} range using this technique (Perkin-Elmer, USA).

e) DSC study: Differential Scanning Calorimetry of Bisoprolol fumarate and optimized formulations was recorded between 30.0°C to 300.0°C at the rate of 20.0°C per minute under the atmosphere of nitrogen.

Dosage calculation:- Bisoprolol Fumarate comes in a 2mg dose. As a result, 2mg of bisoprolol fumarate is contained in a 2 x 2 cm^2 film. The 9 cm-diameter petri-dish has a surface area of 63.64 cm^2, which means 32 mg of medication must be put into that area.

Mouth-dissolving film formulation:-The process of Mouth-dissolving film via solvent casting method. A magnetic stirrer was used to weigh and combine the components in a glass beaker. The mixture was then transferred to a glass plate and allowed to dry for 24 hours at ambient temperature. After drying, the film was cut into the necessary sizes and shapes.

Formulation Table:

S.No.	Ingredient	F1	F2	F3	F4	F5	F6
1.	Bisoprolol Fumarate (mg)	2	2	2	2	2	2
2.	Pectin(mg)	200	200	200	250	250	250
3.	Glycerol(ml)	0.25	0.50	0.75	0.5	0.50	0.75
4.	Citric Acid (mg)	5	10	15	5	10	15
5.	PVA(mg)	250	250	250	200	200	200
6.	Ethanol(ml)	5	5	5	5	5	5
7.	Amaranth(mg)	0.01	0.01	0.01	0.01	0.01	0.01

Evaluation Parameters Of Formulation -

a) Scanning Electron Microscope: A scanning electron microscope (Model S-4700, Hitachi, Japan) operated at 15 kV was used to study the surface morphology of mouth dissolving film. Prior to observation, the samples were coated with gold in an argon environment while being vacuum-coated, and then double-sided sticky tape was used to secure them to a glass stub. Micrographs of Bisoprolol fumarate blank, and Bisoprolol fumarate -loaded mouth dissolving film were taken in order to examine their morphology and surface properties.

b) Weight Variation: Their (2x2 cm^2) films were randomly chosen from each film formulation. Individual films were weighed on an electronic scale, and the mean weight of each batch was calculated.

c) Thickness of Films: Film thickness was measured with the manual Vernier Caliper at five distinct points (the center and all four corners), and the mean thickness was calculated at each site.

d) Folding endurance: Folding endurance was evaluated by folding the film several times at the same location until it broke, then calculating the number of times the film could be folded without breaking. The folding endurance is directly proportional with the film flexibility.

e) Drug content: Bisoprolol fumarate was determined by dissolving the prepared mouth dissolving film of Bisoprolol fumarate in 100 ml of phosphate buffer (pH 6.8). From this 1ml was taken and diluted to 10ml with distilled water. Then solution was filtered with Whatman filter paper and the solution was analyzed on UV spectrophotometer at desired wavelength 224 nm to calculate the amount of drug present in the film.

f) Surface pH: The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 1 hour. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and kept for 1 minute to allow equilibrium condition. The procedure was performed in triplicate and average with standard deviation was determined.

g) *In-vitro* disintegration test: Test was performed using disintegration test apparatus. One square inch film was placed in the basket. The beakers containing the 900ml phosphate buffer solution at 37 ±2˚C raised and lowered it in such a manner that the complete up and down movement at a rate equivalent to thirty times a minute. Time required by the film, when no traces of film remain above the gauze was noted. Test was performed in triplicate.

f) *In- vitro* dissolution - The *in-vitro* dissolution study of mouth dissolving film was performed USP dissolution testing apparatus type II with a paddle stirrer. The speed of rotation of paddle was set at 50 rpm. Dissolution study was performed using 900 ml of phosphate buffer pH 6.8 maintained at a temperature of 37 ± 0.5 °C. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium or phosphate buffer pH 6.8 at maintained temperature of 37 ± 0.5 °C. The samples withdrawn were analyzed, for drug release and release kinetics, spectrophotometrically using UV spectrophotometer (after suitable dilutions)

g) Kinetics of drug release *in vitro* : It is important to fit into an appropriate mathematical model in order to anticipate and compare the behavior of the in vitro release of Bisoprolol fumarate from prepared oral rapid dissolving films. Using significant mathematical models, the data from the in vitro release of drugs was analyzed kinetically.

h) Stability study-Stability study was conducted by storing the film at 40±2º/75±5% Relative humidity for three months. The content, hardness, weight variation and release behavior from mouth dissolving film were tested after three month (ICH guidelines).

RESULT AND DISCUSSION

a) Melting Point Determination (Capillary Method): Melting point of the drug sample was found to be 101^0C (Ideal m.p.100 – 103^0C).

b) Solubility study :Solubility of the drug was determined by dissolving 10mg of the drug in 10ml different solvents. Drug sample was found to

be freely soluble in the solvent Chloroform and alcohol, distilled water and Phosphate buffer pH 6.8, slightly soluble in acetone and in ethyl acetate.

c) U.V Spectrophotometric Study-In UV spectroscopy study, the maximum wavelength (λ_{max}) of Bisoprolol fumarate in phosphate buffer pH 6.8 was found to be 224nm.

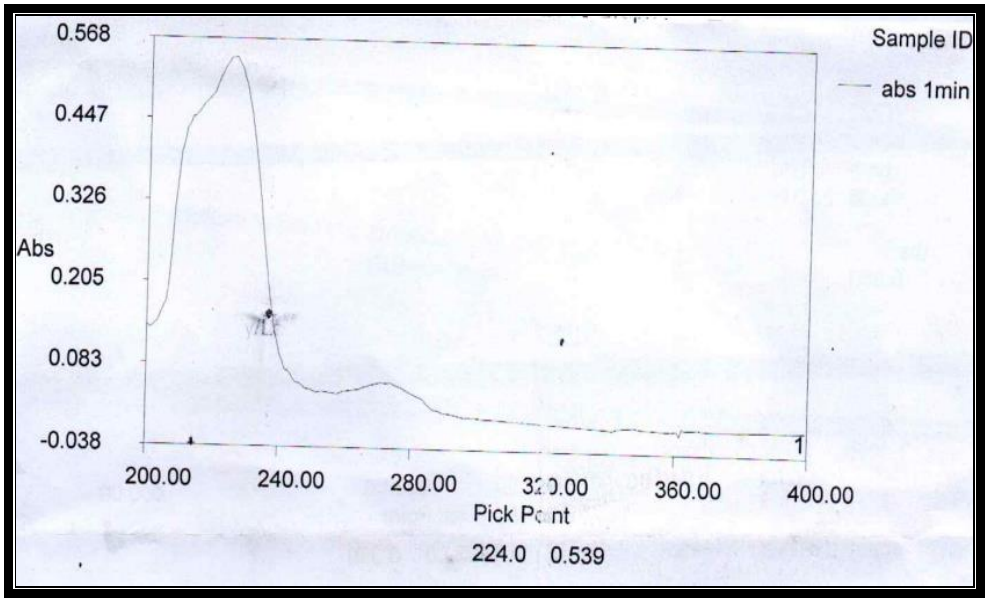


Fig. 1 Calibration Curve of Bisoprolol Fumarate

The standard calibration curve of Bisoprolol fumarate was prepared in phosphate buffer pH 6.8. Absorbance at 224 nm and result was reported in below table and graphically this calibration curve was presented in given figure.

d) FT-IR study: The Fourier transform infrared spectroscopy (FTIR) spectrum of Bisoprolol fumarate was studied. The below FTIR spectrum shown the characteristics peak from this result it was conclude that the sample of Bisoprolol fumarate, PVA, Pectin was pure. The spectra acquired from research using FT-IR spectroscopy at wavelengths 4000 cm^{-1} to 400 cm^{-1}.

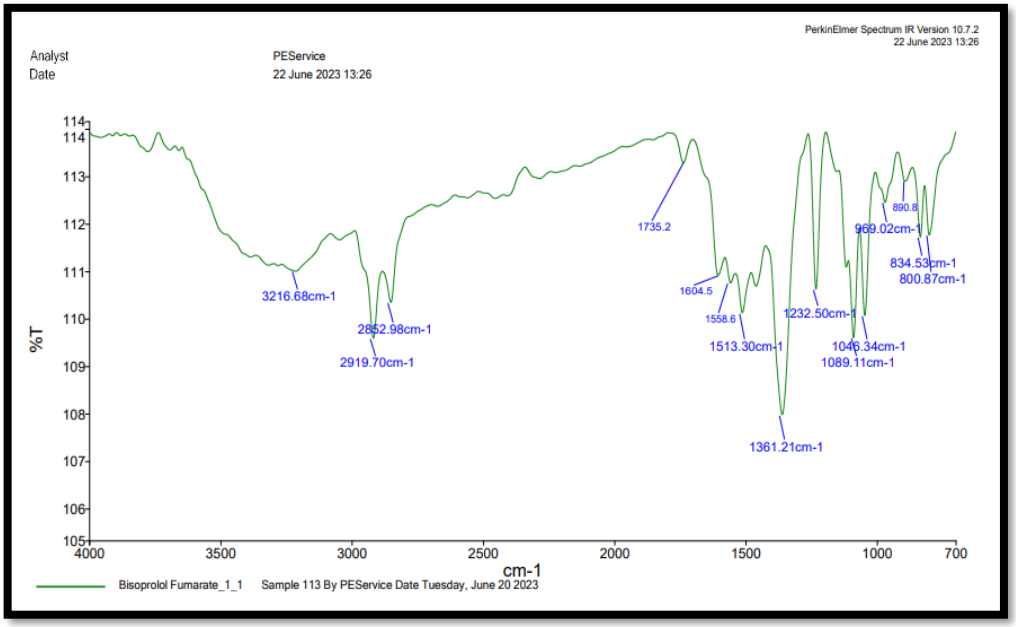


Fig. 2 FT-IR spectra of Bisoprolol Fumarate

FTIR (mixture**)**

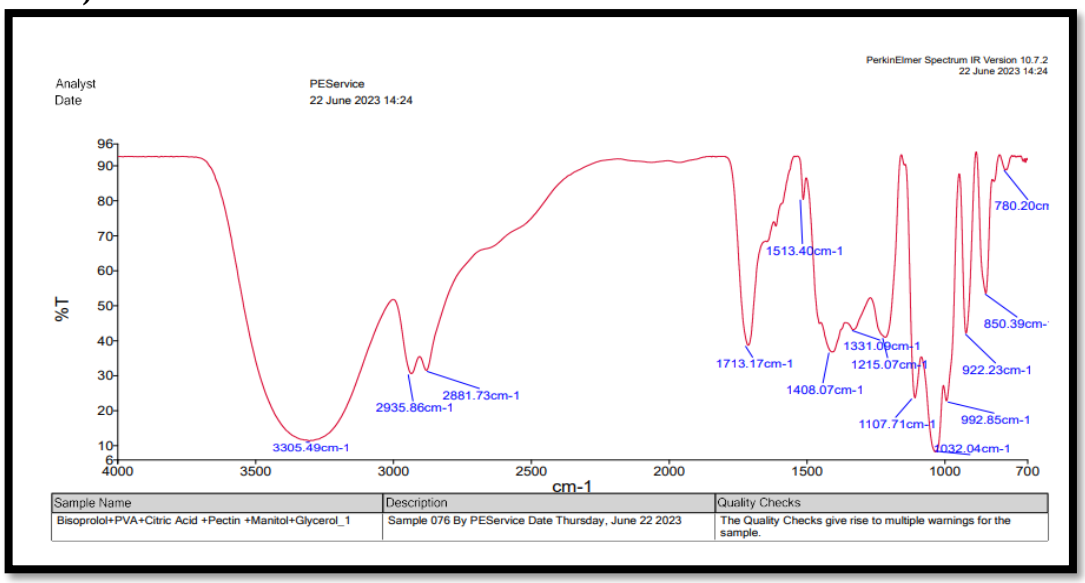


Fig. 3 FT-IR spectra of Bisoprolol Fumarate+PVA+Citric Acid+Manitol+Glycerol

e) DSC study: Differential Scanning Calorimetry of Bisoprolol fumarate was recorded between 30.0°C to 300.0°C at the rate of 20.0°C per minute under the atmosphere of nitrogen.

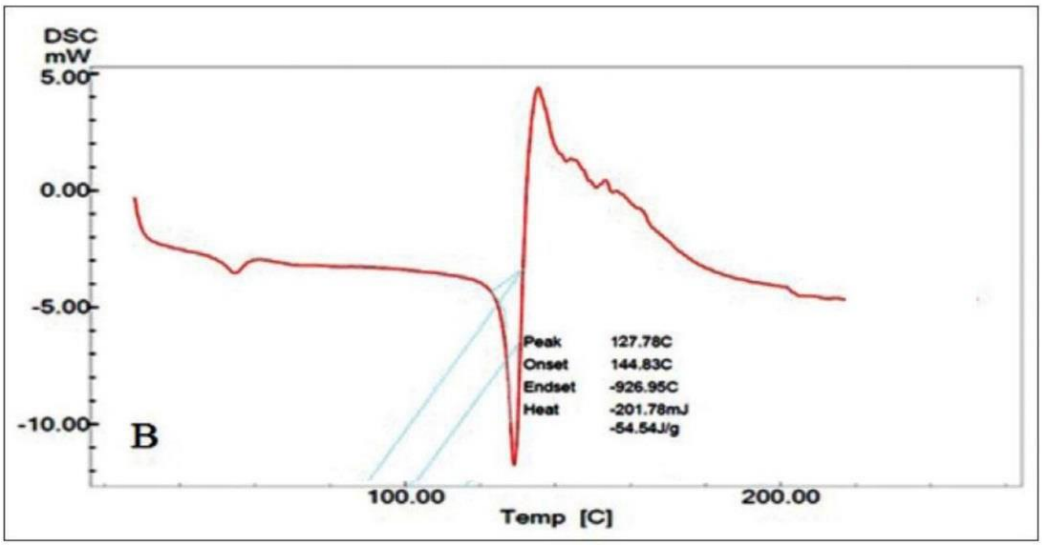


Fig. 4 DSC thermo gram of Bisoprolol fumarate

EVALUATION PARAMETERS OF FORMULATION –

a) Scanning Electron Microscope –

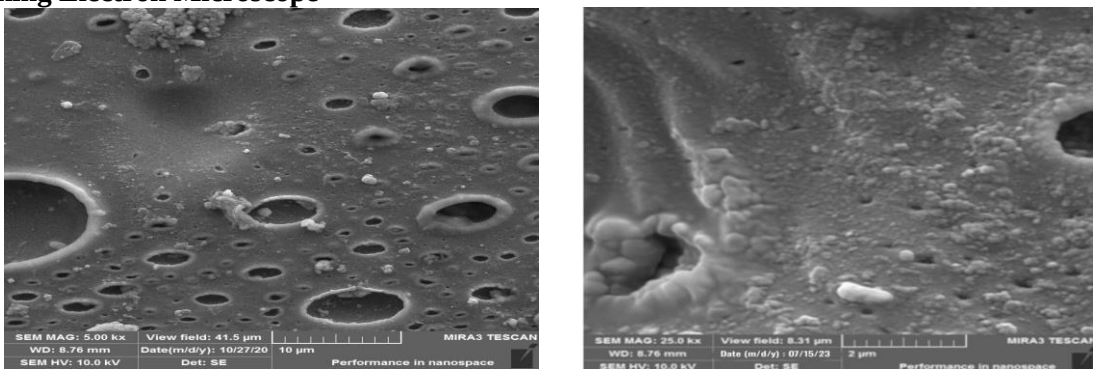


Fig.5 SEM image of film at magnification 5000X and 25000X

b) Variation-A result showed that as the conc. of polymer increase weight of also increases. The weight variation of the formulations was in the range of 27.00±2.1 to 39.36±1.3 mg, which was acceptable.

Table 2 Weight Variation (mg) of film

S.No.	Formulation	Weight Variation (mg))± SD
1.	F1	27.00±2.1
2.	F2	29.67±1.2
3.	F3	30.33±1.6
4.	F4	30.9±1.8
5.	F5	35.2±1.6
6.	F6	39.36±1.3

c) Thickness of Films-Thickness of mouth dissolving film depends on conc. of polymer. Thickness of all mouth dissolving film was measured with manual Vernier caliper showed thickness value in range 92±5 to 102±5 µm**.**

Table 3

S.No.	Formulation	Thickness (µm)± SD
1.	F1	92±5
2.	F2	102±5
3.	F3	93±3.6
4.	F4	85±2.5
5.	F5	99±1
6.	F6	94.7±1.5

f) Folding endurance- Folding endurance gives an indication of brittleness of the It was shown that as the concentration of polymer and plasticizer increases, folding Endurance of mouth dissolving film increases. The folding endurance value of the prepared films ranged from 21±3to 108±2

Table 4 Folding endurance-

S.No.	Formulation	Folding endurance
1.	F1	21±3
2.	F2	33±1
3.	F3	48±2
4.	F4	70±1
5.	F5	98±3
6.	F6	108±2

e) Drug content- All the mouth dissolving film was found to contain an almost uniform quantity of the drug, as per content uniformity studies indicating reproducibility of the technique. Drug content in the films was evaluated and the values were found to be between 95.2±0.8 to 99.5±0.1%, for three different cuts from each film, results were shown in Table 4.12.

Table 5

S.No.	Formulation	Conc. in mg	Drug content (%)
1.	F1	1.007	97.4±0.2
2.	F2	1.03	98.3±0.3
3.	F3	0.998	96.6±1.1
4.	F4	1.003	99.5±0.1
5.	F5	1.0076	98.3±0.3
6.	F6	0971	95.2±0.8

f) Surface pH-

Surface pH of all mouth dissolving films prepared by different polymers was found to be in the range of 6.24±0.05 to 6.88±0.05 pH, which was close to the neutral pH, which indicated that films may have less potential to irritate sublingual mucosa & hence, more acceptable by the patients (Table 4.13).

Table 6

S.No.	Formulation	Surface pH± SD
1.	F1	6.24±0.05
2.	F2	6.35±0.10
3.	F3	6.7±0.08
4.	F4	6.80±0.02
5.	F5	6.88±0.05
6.	F6	6.75±0.05

g) *In- vitro* dissolution study: The *in-vitro* dissolution study of mouth dissolving film was performed USP dissolution testing apparatus type II with a paddle stirrer. The speed of rotation of paddle was set at 50 rpm. Dissolution study was performed using 900 ml of phosphate buffer pH 6.8 maintained at a temperature of 37 ± 0.5 °C. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium or phosphate buffer pH 6.8 at maintained temperature of 37 ± 0.5 °C. The samples withdrawn were analyzed, for drug release and release kinetics, spectrophotometrically using UV spectrophotometer (after suitable dilutions)

Table *in-vitro* dissolution study of different formulations of Bisoprolol fumarate fast dissolving film (F1-F6)

Time (minutes)	Cumulative percentage release of Bisoprolol fumarate fast dissolving film					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
2	5.99	5.35	5.56	6.42	6.10	5.99
4	15.73	14.77	14.45	19.06	15.96	15.74
6	29.65	26.56	26.35	37.06	29.99	27.52
8	48.07	43.81	43.70	58.38	47.99	43.81
10	69.71	64.70	64.70	83.23	70.40	64.91
12	95.85	89.34	89.56	97.16	95.04	90.41

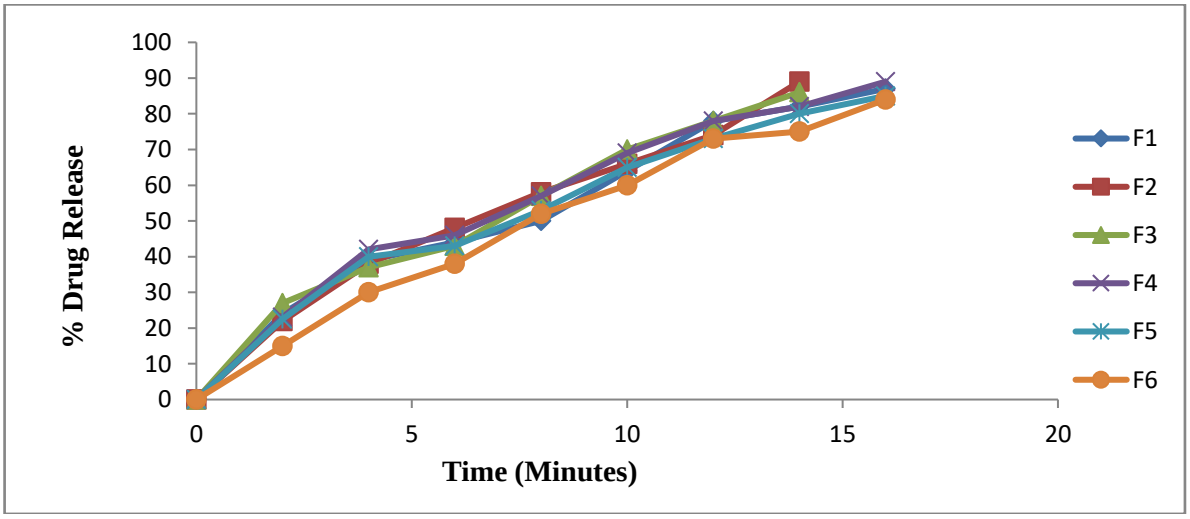


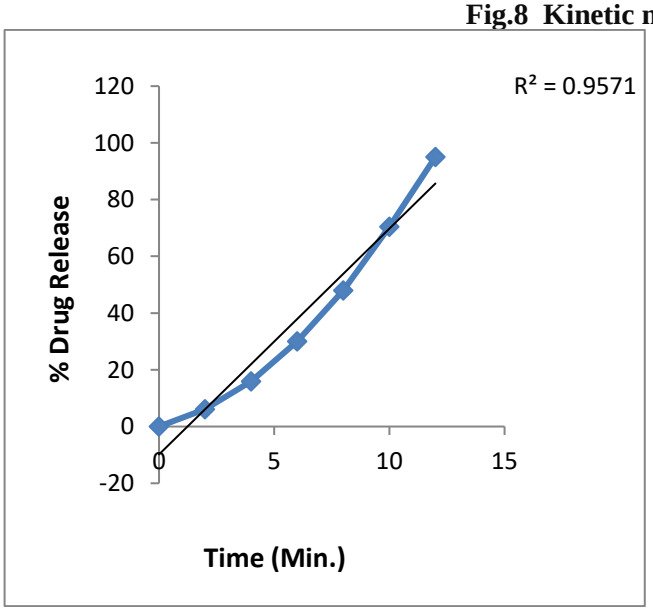
Fig.7 % Drug release of Formulation F1 to F6

h) Kinetics of drug release *in vitro* - In order to find out the mechanism of drug release, the *in-vitro* dissolution data were applied to various kinetics models. The best fit with highest regression coefficient values (R^2) predicted by first order kinetic model, second order kinetic model Higuchi model and Korsemeyer-peppas models.

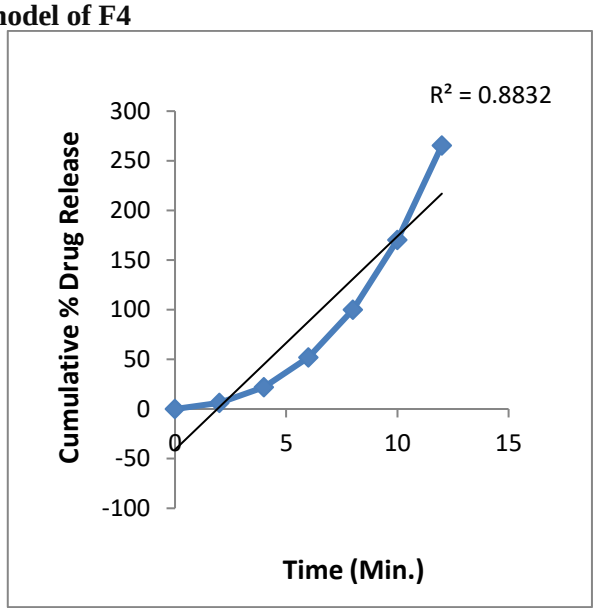
Table 7 Kinetic analysis of *in-vitro* drug release data o formulations F1-F6

S.No.	Formulation code	Zero order R^2	First order R^2	Higuchi model R^2	Korsemeyer- peppas equation R^2
1.	F1	0.9544	0.8815	0.9913	0.7924
2	F2	0.9502	0.8788	0.9894	0.7849
3.	F3	0.948	0.8777	0.9907	0.7814
4.	F4	0.9764	0.8970	0.9913	0.8470
5.	F5	0.9571	0.8832	0.9924	0.7972
6.	F6	0.9511	0.8829	0.9927	0.7878

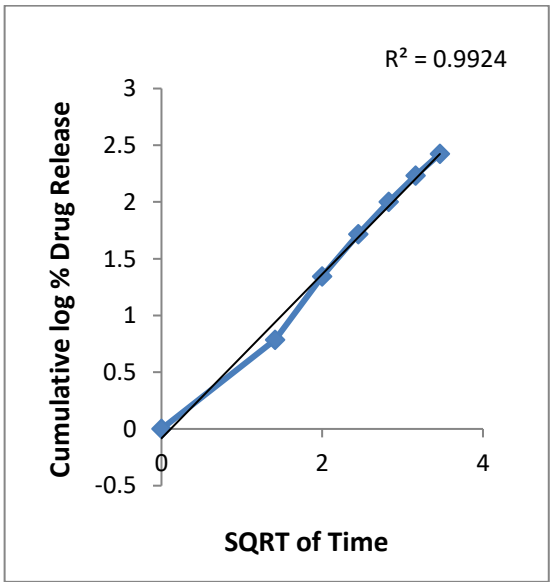
Fig.8 Kinetic model of F4



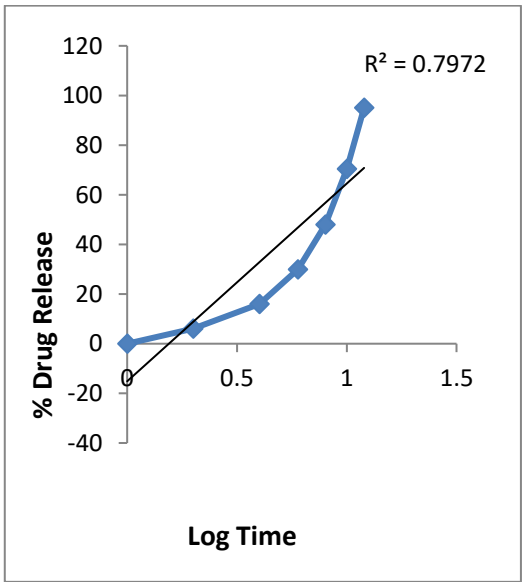
Zero order Kinetic models



First order Kinetic models



Higuchi models



Korsemeyer-Peppas models

It was analyzed that the most effective formulation F4, which had the best R^2 value using the Korsemeyer-Peppas system, follows the zero order kinetics model.

i) Stability study Stability study was conducted by storing the film at 40±2°/75±5% Relative humidity for three months. The content, hardness, weight variation and release behavior from mouth dissolving film were tested after three month (ICH guidelines).

Table 8 Stability study of optimized formulation (F4) Mouth dissolving film-

S.No.	Parameter	Initial	3 month
1.	Thickness(µm)	85±2.5	82±3
2.	Folding endurance	70±1	70±4
3.	Weight variation (mg)	30.9±1.8	28.9±1.8
4.	*In-vitro* Disintegration time(sec)	30±2	31±3
5.	*In-vitro* Dissolution study (%)	97.85	97.16
6.	Drug content (%)	99.5±0.1	98.5±0.1
7.	Surface pH	6.80±0.02	6.60±0.02

CONCLUSION-

The mouth dissolving film formulations are one of the innovative approaches in the pharmacy field in future it may become one of the promising dosage forms for treatment of disease or disorders. In present study, Bisoprolol fumarate was selected as modern drug candidate. The developed formulation disintegrates in the oral cavity within 30 seconds and improves the patient compliance particularly for those having difficulty in swallowing. F4 Formulation films were evaluated for weight variation and thickness showed satisfactory results. Disintegration time of the films was increased with increase in the concentration of the polymers, as more fluid is required to wet the film in the mouth. Content uniformity study showed that the drug is uniformly distributed in the film. Present study reveals that F4 formulated films showed satisfactory film parameters. It can be concluded that, mouth dissolving film containing Bisoprolol fumarate can be prepared by solvent casting method. PVA and Pectin film exhibited required folding endurance, disintegration time and in vitro dissolution study. Formulation F4 disintegrated in 30 sec and released 97.85% of drug within 10 min and considered as best formulation.

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Authors' contributions

All the authors have contributed equally.

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