FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM OF BISOPROLOL FUMARATE

POONAM A. PADAMWAR[*1], POONAM P. PHASATE[1]

[1]Department of Quality Assurance,
Shri Bhagwan College of Pharmacy, Aurangabad- 431001, Maharashtra, India.
Email id - poonampadamwar@gmail.com
Contact No. 9404379554.

ABSTRACT:

Bisoprolol Fumarate is an antihypertensive agent used in the management of hypertension and prophylaxis treatment of angina pectoris and heart failure. Present work aimed at preparing quick onset of action which is beneficial in hypertension, aiding in the enhancement of bioavailabity and is very convenient for administration without the problem of swallowing and using water. The film were prepared by using polymers such as hydroxypropyl methyl cellulose (HPMC) and Maltodextrin, plasticizer such as PEG 400, by a solvent casting method. They were evaluated for physical characteristics such as thickness, uniformity of weight, folding endurance, drug content, surface ph, percentage elongation and tensile strength and give satisfactory results. The formulations were subjected to disintegration, in-vitro drug release test. The in vitro disintegration time of the optimized batch F4 was found to be 20 sec. The optimized batch was found to be stable for 1 month under specified stability conditions.

KEYWORDS:

Bisoprolol Fumarate, Fast dissolving film, HPMC, Maltodextrin, Solvent casting method, 3^2 factorial design.

INTRODUCTION:

A variety of pharmaceutical research has been conducted to develop new dosage forms, considering quality of life, most of these efforts have been focused on ease of medication. Fast dissolving film is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for mucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. Oral dissolving films can be administered without water, anywhere, any time.

Bisoprolol Fumarate is beta blocking agent, which is used for the management of hypertension and prophylaxis treatment angina pectoris and heart failure. The aim of present research work was to formulate the fast dissolving oral film of Bisoprolol Fumarate, using film forming polymers which responsible for the strength of the film, plasticizers helps to improve the flexibility of the film and reduces the brittleness of the film, saliva stimulating agent aids in the faster disintegration of film. Prepared dissolving film has minimum disintegration time and faster dissolution rate giving quick onset of action.

Justification and novelty behind this research work is following:

- No Marketed Bisoprolol Fumarate film is available in India.
- Less excipients are required to manufacturing of film, ultimately cost of film decreases.
- In case of high blood pressure quick onset of action required because uncontrolled high blood pressure create Strokes, Heart attack, Kidney Problem.
- Hypertension markedly reduces functional ability and extremely restlessness in such cases rapid onset of action required.
- Specially intended to geriatric patients who have problem of dysphagia.
- Administered without water, anywhere, any time (after or before meal).
- Avoid the problem of disintegration.

MATERIALS AND METHODS:

Bisoprolol Fumarate was obtained as a gift sample from Unichem Laboratories Ltd, Raigad, Maharashtra, India. HPMC E5, E15, Maltodextrin was obtained from Lupin Research Park (Lupin Ltd). PEG 400, glycerin, aspartame, PVA was obtained from Research Lab Fine Chem Industries, Mumbai, India.

Preparation of Mouth Dissolving Film by Solvent Casting Method:

The fast dissolving oral film of the Bisoprolol Fumarate by using HPMC E15 and Maltodextrin is prepared by solvent casting method. In this first aqueous solution of the HPMC E15 and Maltodextrin is prepared by dissolving the HPMC E15 and Maltodextrin in distilled water. Bisoprolol Fumarate is added to the aqueous solution after that citric acid is added to the above solution followed by addition of the sweetener and plasticizer. The solution was casted on the casting surface (mould, Petri dish) and dried at room temperature for 10 hours or dried into a Hot air oven for 6 hrs. Then film removed from the surface and cut into the desired size (2x2) of equivalent dose of Bisoprolol Fumarate. This preparation method was followed till completion of work.

Figure 1 Prepared Teflon Mould for Film Casting

Preparation of Fast Dissolving Film of Bisoprolol Fumarate by Using 3^2 Full Factorial Designs

It is enviable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man-hours and raw materials. Traditionally pharmaceutical formulations after developed by changing one variable at a time approach. The method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to develop an ideal formulation using this classical technique since the joint effects of independent variables are not considered. It is therefore very vital to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design. In addition to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interactions. The number of experiments required for these studies is dependent on the number of independent variables selected. The response (Y_1) is measured for each trial.

$Y= b_0+ b_1 x_1+b_2x_2+b_{12}x_1x_2+b_{11}x_1^2+b_{22}x_2^2$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. For factorial design the solvent casting method was selected. In this design 2 factors were evaluated each at 3 levels, and experimental trials were performed at all 9 possible combinations. The amount of polymer HPMC E15+ Maltodextrin (X_1) and amount of plasticizer, PEG 400 (X_2) were selected as independent variables and each factor being studied at -1, 0, +1 level. Percent drug release was selected as dependent variable. The following table lists the design variables with its coded values and actual values, and second table provides the factorial design layout i.e. all possible 9 combinations respectively.

Table 1 Design Variables

Coded values	**Actual values (mg)**	
	X_1	**X_2**
-1	400+50	50
0	400+100	60
+1	400+150	70

Table 2 Full Factorial Design Layout

Formulation code	Variable level	
	X_1 (Polymers)	X_2 (Plasticizer)
F1	**-1**	**-1**
F2	**-1**	**0**
F3	**-1**	**+1**
F4	**0**	**-1**
F5	**0**	**0**
F6	**0**	**+1**
F7	**+1**	**-1**
F8	**+1**	**0**
F9	**+1**	**+1**

Table 3 Factorial batches composition

	F1	F2	F3	F4	F5	F6	F7	F8	F9
DRUG (mg)	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
HPMC + MALTODEXTRIN (mg)	400 +50	400 +100	400 +150	400 +50	400 +100	400 +150	400 +50	400 +100	400 +150
PEG 400 (mg)	50	50	50	60	60	60	70	70	70
ASPARTAME (mg)	50	50	50	50	50	50	50	50	50
CITRIC ACID (mg)	18	18	18	18	18	18	18	18	18
MENTHOL	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
COLOUR	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
WATER (ml)	10	10	10	10	10	10	10	10	10

Figure 2 Prepared Bisoprolol film and after cutting in desired size

FACTORIAL BATCHES EVALUATION OF FAST DISSOLVING ORAL FILMS:

Weight Variation

The weight variation test is determined by measuring the weight of the individual film of 2 cm x2 cm area. For the measurement of the weight digital analytical balance was used. The weight of three films was measure and mean is taken.

Thickness

The thickness of strip was measured by digital vernier caliper at different locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip.

Folding endurance

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value.

Tensile strength

Tensile strength of films was determined using an apparatus fabricated in laboratory. A small film strip (2 × 2 cm^2) was cut and fixed to assembly. The weight required to break the film was noted and simultaneously film elongation was measured with the help of pointer mounted on the assembly. Measurements were done in triplicate for each batch. The mechanical properties tensile strength and % elongation were calculated for the fast dissolving film from the above measurements. Tensile strength is the ratio of maximum stress applied to a point at which the film specimen breaks and can be computed from the applied force at rupture to the cross sectional area of the fractured film as a mean of three measurements and described in the equation-

$$Tensile\ strength = \frac{\text{Load at failure } \times \ 100}{\text{Strip Thickness } \times \text{ Strip Width}}$$

Percent elongation

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases.

$$\%\ elongation = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

P^H Value

The pH value can determine by dissolving one oral film in 10ml distilled water and measuring the pH of the obtained solution. It is necessary that film should have nearly uniform pH value.

Drug content

For determination of the drug content Bisoprolol Fumarate oral film equivalent to dose of 2.5 mg was dissolved in 50 ml of pH 6.8 buffer .The solution was sonicated for 10 minutes and then filtered through Whatmann filter paper no. 41, to separate out the insoluble excipients. 1ml of filtrate was diluted to 100 ml with pH 6.8 buffer. The absorbance of resultant solution was measured using U. V. spectrophotometer at 225 nm and drug content was calculated.

Disintegration time

The disintegration for orally disintegrating tablets described in CDER guidance can be applied to oral film. Although, no official guidance is available for FDOF, this may be used as a qualitative guideline for quality control test or at development stage. But for the present work disintegration was measured by taking the 25 ml of distilled water in 50 ml beaker and individual film is dipped into that solution and disintegration time was recorded.

In Vitro Dissolution study

The in vitro release of drug from all formulations was determined using USP apparatus type II (Paddle method). The following conditions were followed to study the in-vitro dissolution study of Bisoprolol Fumarate Oral Film.

1. USP dissolution apparatus: Type II (Paddle method)
2. Volume of dissolution medium: 900 ml
3. Speed: 50 rpm
4. Temperature: 37±0.50 C
5. Dissolution medium: pH 6.8 buffer
6. Sampling interval: 1 min
7. Quantity of sample withdrawn: 5ml

Aliquots of dissolution medium of 5 ml were withdrawn at 1 min interval for 4 min. The volume withdrawn was replaced by fresh volume of dissolution medium. The filtered samples were analyzed spectrophotometrically at 225 nm and absorbance was noted. Cumulative percent drug release was calculated.

Accelerated stability study of optimized batch

Stability of a drug has been defined as the ability of a particular formulation in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. Recommended storage conditions, re-test periods and shelf-lives are to be established. The International Conference of Harmonization (ICH) Guidelines titled, "stability testing of New Drug substance and products" (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions

Long-term testing: - 25^0 C ± 2^0 C / 60 % RH ± 5% for 12 months.

Accelerated testing: - 40 ^{0}C ± 2^0 C/ 75 % RH ± 5% for 6 months.

Accelerated Stability studies were carried out at 40^0 C / 75 % RH for the best formulations for 1 month.

Method: The best formulation was assessed their accelerated stability with respect to their appearance, in-vitro disintegration time, surface pH & drug release characteristics after storing them at 40 ± 2^0 C / 75 ± 5 % RH for 1 month.

RESULT AND DISCUSSION:

Drug Excipients Compatibility study

Infra-red studies

IR spectrum of Bisoprolol Fumarate and physical mixture was recorded, and it was in accordance with the reported peaks. It is shown in Following Figure.no.3. The IR spectra of Bisoprolol Fumarate comply with its chemical structure and show peaks for principal group's .The structural assignments for the characteristics absorption bands are listed in Following Table no.4.

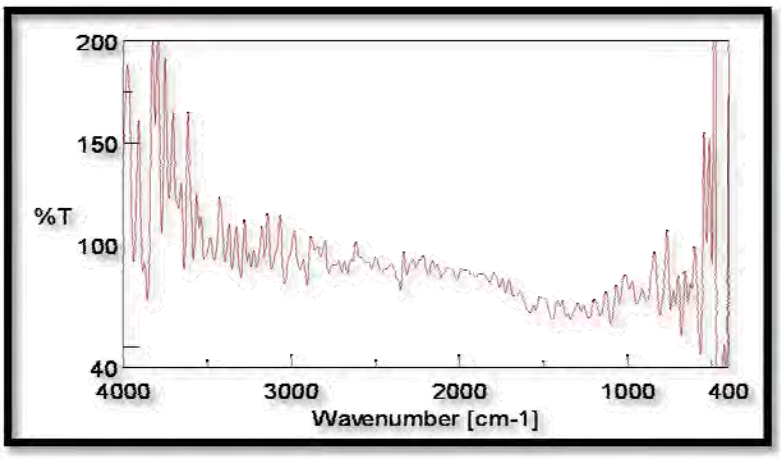

Figure 3 IR Spectrum of Bisoprolol Fumarate

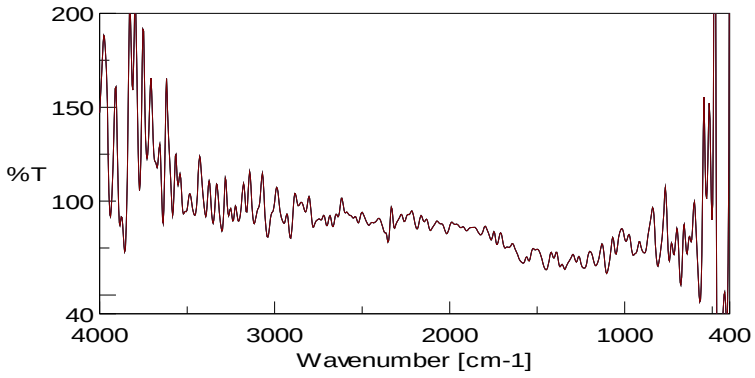

Figure 4. IR Spectrum of Bisoprolol Fumarate and Polymers

Table 4 Infrared Spectral assignment for Bisoprolol Fumarate

Type	Pure Drug	Formulation
C-O Stretching	1049.09	1103.08
C-H Stretching	2946.7	2946.7
N-H stretching	3301.54	3351.54
O-H stretching	3637.09	3647.09

In physical mixtures of drug and polymer, there was neither masking of single characteristic peak nor existence of additional peak in drug spectra. So it was concluded that drug and HPMC E 15, Maltodextrin were compatible with each other.

Weight Variation

The weight of all batches observed between 31.15 to 35.60 mg with standard deviation less than 0.2% for all batches which indicates uniformity in the weight.

Thickness

The thickness of the film lies between 0.09 to 0.12 mm with uniformity in the thickness. It was observed that increase in the polymer concentration the thickness of film increases with 0.01 mm.

Folding Endurance

The folding endurance of all batches observed between 90-155 .For the batches F4, F7, F9 the folding endurance observed 155,130,135 respectively. From the evaluation of folding endurance it was concluded that with increase in polymer concentration folding endurance decreases and with increase in plasticizer concentration folding endurance increases.

Tensile strength and % elongation

The tensile strength gives an indication of the strength and elasticity of the film. Tensile strength of all formulations showed better tensile strength and % elongation. Tensile strength was found in range 0.432±0.007 to 0.554±0.004 kg/mm^3. There is no significant change in the tensile strength of all prepared formulations. The nature of polymer affects tensile strength and % elongation. Soft and brittle polymer increases TS and decreases % elongation, while hard and tough polymer increases TS and % elongation. The % elongation is found in range of 4±0.004 to 6.12±0.001.

Surface pH

The Surface pH of all formulation observed between 6 to 6.8. It was observed that after addition of the plasticizer the pH moves slightly towards basic pH. The pH between 6 to 6.8 indicates the pH of formulation near to ph of saliva.

% Drug content

The percent drug content observed between 97 to 99 %. The values ensure good uniformity in the drug content in Fast Dissolving oral Film of Bisoprolol Fumarate.

In Vitro Disintegration Time

The in vitro disintegration time for all batches measured between 16 to 20 seconds which indicated faster disintegration time as compared to the fast dissolving tablet which have normal disintegration time 30 seconds in many reported literature.

Evaluation of physico-mechanical parameters of fast dissolving film

Batches	Weight (mg)	Thickness (mm)	Folding Endurance	Tensile Strength(kg/ mm^2)	% Elongation at break	Surface pH	%Drug Content	In-vitro disintegration time (s)
F1	31.15±.005	0.010±0.00	106.33±9.2	0.444±0.005	4.67±0.003	6.54±0.12	98.16±.001	18±00
F2	33.14±.005	0.010±0.00	97.33±6.02	0.457±0.003	5.12±0.003	6.62±.03	99.16±.003	18.5±2.08
F3	35.16±.011	0.013±0.00	90.33±2.08	0.471±0.001	5.23±0.001	6.64±.09	99.17±.001	18.6±1.15
F4	31.38±.005	0.09±0.00	155±2.0	0.554±0.004	6.12±0.00	6.49±.07	99.18±.005	16.3±0.00
F5	33.36±.015	0.012±0.00	105.33±7.23	0.412±0.001	5.63±0.003	6.49±.035	99.14±.003	17.5±1.00
F6	31.56±.007	0.014±0.00	92.66±17.18	0.434±0.002	4.79±0.004	6.53±.073	98.17±.002	18±2.64
F7	33.59±.015	0.09±0.00	130±10.58	0.510±0.00	4.86±0.001	6.71±.020	97.19±.001	19±1.5
F8	34.59±.03	0.010±0.00	105.33±12.09	0.469±0.003	5.10±0.002	6.87±.020	99.12±.007	18.6±1.52
F9	35.6±.02	0.015±0.00	135±11.53	0.457±0.005	5.59±0.001	6.77±.015	99.13±.007	19±2.00

Dissolution Study

% Drug release of formulation F1 to F9

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0 min	0%	0%	0%	0%	0%	0%	0%	0%	0%
1 min	27%	28.5%	28.5%	34.5%	25.5%	27%	25%	26.85%	24.45%
2 min	49.5%	69%	73.5%	63%	57%	66%	60.5%	68.55%	64.5%
3 min	94.35%	96%	96.3%	99%	96.75%	97.35%	94.2%	97.95%	98.85%

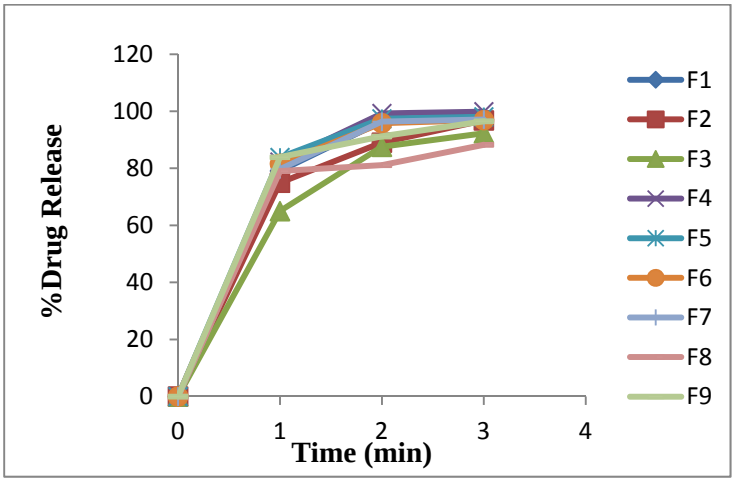

Figure 2 Dissolution profile of batches F1 to F9

The *in-vitro* drug release from film of all formulation was performed in triplicate using USP apparatus II (paddle method). Dissolution study was performed in pH 6.8 phosphate buffer. In case of F4 and F9 formulations about 99 % and 98.85 % of drug was released in 3 min. In case of F1, F7 formulation about 94.35 % and 94.2 % of drug released in 3 min. This drug release pattern indicates that the increased concentration of polymer decreases drug release and increased concentration of plasticizer increases drug release.

Accelerated Stability Study for optimized formulation

Accelerated stability study was performed as per ICH Guideline Q1 (A) for optimized formulation i.e., F4 was selected on the basis of % cumulative drug release and also results in in-vitro disintegration time. From these results it was concluded that, formulation F4 is stable and retained their original properties with minor differences. The in vitro release profile of f4 at $40^{O}C$/75% RH conditions after 1 month was 99% and 97% respectively, has indicated that there is no or minor alteration after storage.

Table 4 Results of Accelerated stability study

Batch	Appearance	Folding Endurance	Weight (Mg)	Disintegration Time (Sec)	Tensile Strength(N/Mm$^{2)}$	%Drug Content
Initial	Transparent	155	31.38	16.3	0.554	99.18
After 1 Month	Transparent	150	29.23	17	0.500	98

Table 5 in vitro drug release profile of F4 batch after accelerated stability study

Time (min)	Initial	After 1 month
0	0%	0%
0.5	34.5%	31.04%
1.5	63%	60.3%
2.5	99%	97%

CONCLUSION:

In current research work, an effort has been made to prepare Fast dissolving Bisoprolol Fumarate oral film by solvent casting method. The fast dissolving films of Bisoprolol Fumarate were prepared by solvent casting technique using film forming polymers HPMC E15 and Maltodextrin. The prepared film disintegrates within twenty second which releases drug rapidly and gives antihypertensive action. As compared to that conventional dosage form, Fast dissolving Film has rapid onset of action. The optimized batch F4 was found to be stable for a period 1 months accelerated stability study at $40^{o}c$ /75% RH.

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