Formulation and Comparative *In-vitro* Evaluation of Fast Disintegrating Mouth Films of Betaxolol Hydrochloride for Hypertension

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***Abstract*:-The present study is aimed at preparing a fast disintegrating oral film of Betaxolol Hydrochloride for the treatment of hypertension using solvent casting method. In the formulation of fast disintegrating mouth films, various trials have been carried out using two grades of HPMC (E15 and E50) as film forming polymer, PEG-4000 as plasticizer, citric acid as saliva stimulating agent, peppermint oil as flavoring agent and sucrose as sweetener.**

The prepared films were evaluated for film thickness, folding endurance, surface pH, morphological properties, %drug content, tensile strength, *In vitro* disintegration time and *In vitro* dissolution studies. The formulation F8 prepared by using HPMC E50 as polymer and PEG-4000 as plasticizer shows the best result with minimum disintegration time of 45.78±0.521, % drug content of 99.03±0.276%, and 96.19±0.51% CDR within 10 minutes, with satisfactory physiological properties. The result of *FT-IR* showed that there is no incompatibility found between the drug and the excipients used in the formulations. This suggests that fast disintegrating mouth films of Betaxolol Hydrochloride could be potentially a useful formulation for the treatment of hypertension where quick onset of action is desired.

Keywords: **Betaxolol HCl, fast dissolving films, solvent casting method, HPMC**

I. INTRODUCTION

Oral drug delivery is the largest and oldest segment of the total drug delivery system. It is the fastest growing and most preferred route for administration of therapeutic agents. [1] It is more acceptable from patient compliance aspects due to low cost and ease of administration. How- ever, significant constraints are associated with oral administration such as hepatic first pass effect and drug degradation due to enzymes.[2,3]The conventional dosage forms given by this route including tablets and capsules suffers from patient non-compliance due to difficulty in swallowing associated with their use. Moreover, the delay in onset of action by this route also calls for a delivery system, which could provide a rapid onset and a quick relief. [4]Fast dissolving dosage forms have acquired great importance in pharmaceutical industry because of their unique properties like dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without need for additional liquid. This convenience provides both a marketing advantage and increased patient compliance. [5]Fast dissolving films is gaining interest as an alternative of fast dissolving tablets, as it is also associated the fear of choking due to the size and shape. [6]

Mouth dissolving oral films offers an attractive route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well-supplied vascular and lymphatic drainage, also large surface area of absorption, easy swallowing and pain avoidance makes the oral mucosa a very attractive and feasible site for systemic drug delivery. [7] The delivery system consist of a very thin oral strip, which is simply based on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto site of application. It then disintegrates and dissolves to release the medication. This route provides the better alternative for the dysphagic patients, children, and geriatrics or to the patients who are mentally retarded, uncooperative, nauseated or on reduced intake of liquids. [8]

Hypertension, also known as high blood pressure defined as having a blood pressure higher than 140 over 90 mmHg, with a consensus across medical guidelines. [9]This means that the systolic reading (the pressure as the heart pumps blood around the body) is over 140 mmHg and / or the diastolic reading (as the heart relaxes and refills with blood) is over 90 mmHg.The higher the pressure in blood vessels the harder the heart has to work in order to pump blood. If left uncontrolled, hypertension can lead to some serious illness and eventually heart attack as well. Hypertension can also lead to stroke, kidney failure, rupture of blood vessels and cognitive impairment. The aim of the study is to prepare fast disintegrating mouth films of Betaxolol Hydrocloride to achieve rapid onset of action as required during the hypertension.

II. MATERIAL AND METHODS

Betaxolol Hcl (purchased from Indian Fine Chemicals, Mumbai-20), Hydroxy Propyl Methyl Cellulose E15 and E50 (Loba Chemie Pvt. Limited, Mumbai), Polyethylene Glycol 4000 (S D Fine-Chem Limited, Boisar), Citric acid (Nice

Chem. Pvt. Limited, Kerala), Sucrose (Thermo Fisher Scientific India Pvt. Ltd. Mumbai) and peppermint oil (Nice Chem. Pvt. Limited, Kerala) were used in preparation of fast disintegrating mouth films.

Drug excipents compatibility studies

The interaction study between drug and polymer was carried out using FTIR. The KBr discs of drug and polymer in the ratio of 1:1 was prepared and spectra were obtained

UV Spectrum Analysis of Betaxolol hydrochloride

The solution of Betaxolol hydrochloride in phosphate buffer pH 6.8 was prepared and scanned in the range of 200-400 nm to get the maximum wave length and UV spectrum was obtained (Figure 1).

Standard plot of Betaxolol hydrochloride in Phoshphate buffer pH 6.8

Preparation of Standard stock solution

Stock solution I

Standard drug solution of Betaxolol hydrochloride was prepared by dissolving 100 mg of pure Betaxolol hydrochloride in a small amount of 6.8 phosphate buffers in 100ml volumetric flask and then the volume was adjusted with the same buffer as a solvent. The resultant solution gives the concentration of 1mg/ml. ie.1000µg/ml.

Stock solution II

From stock solution I: 10 ml solution was taken and then diluted up to100 ml with the same solvent in a volumetric flask and then concentration of this stock was 100µg/ml.From this stock solution II, 0.2,0.4,0.6,0.8 and 1 ml solutions were pipetted out and volum was made to 10ml with phosphate buffer pH 6.8 to give concentration of 2,4,6,8 and 10ug/ml respectively. The absorbance of these solutions were measure at 224 nm (lambda max of BetaxololHCl). The standard calibration curve was obtained from data of concentration v/s absorbance.

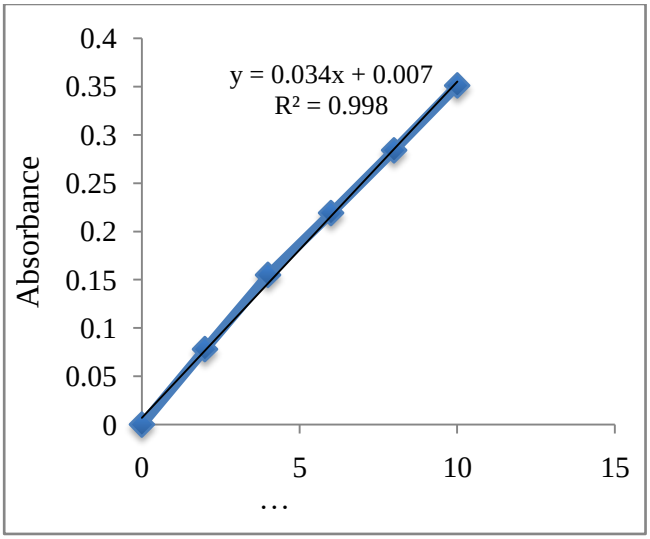

Figure 1: Standard curve of Betaxolol HCl in phosphate buffer pH 6.8

Preparation of Fast dissolving Oral Films by solvent casting method

Fast dissolving Oral films were prepared by using solvent casting method. Here, solution I is prepared by dissolving required quantity of HPMC E15 or HPMC E50 in little water (ratio1:1) and keep it aside for 4 hours to remove the air bubbles.

Solution II is prepared by adding accurately weighed drug, polyethylene glycol 4000, citric acid, sucrose and sufficient peppermint oil. Solution II is added to solution I and mixed well on a magnetic stirrer. It is then casted on to a Petri dish plate and dried at room temperature for overnight. After drying, the films were carefully removed from plates and cut into required size (2×2) cm^2.The prepared films are wrapped in aluminum foil and kept in desiccator for further evaluation test. Eight formulations were prepared using two polymers and labeled them as F1, F2, F3, F4, F5, F6, F7 and F8. But in formulation F1 the film was not formed and it was not used for further studies. The samples were evaluated for various tests.

Table 1: The composition of different formulations (F1-F8)

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
BetaxololHcl (mg)	20	20	20	20	20	20	20	20
HPMC E15 (mg)	-	100	150	-	-	-	-	-
HPMC E50 (mg)	80	-	-	100	150	100	120	150
PEG 4000 (mg)	100	100	100	100	100	120	120	120
Sucrose (mg)	15	15	15	15	15	15	15	15
Citric acid (mg)	10	10	10	10	10	10	10	10
Tween 80 (ml)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Peppermint Oil (ml)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Water (ml)	10	10	10	10	10	10	10	10

Weight variation

An area of 2x2cm^2 of the film was cut at three different places from the casted film. The weight of each film was taken thrice and average weight variation was calculated.

Thickness

The thickness of the film was measured using micrometer Screw gauge. The thickness of each film was determined at different locations and standard deviation was calculated.

Folding endurance

The folding endurance is expressed as the number of folds required to break the specimen or to develop visible cracks. This gives an indication of the brittleness of film. Folding endurance was determined manually by repeatedly folding the film at the same place several times till it breaks. [9]

Tensile strength

Tensile strength was measured by using the apparatus fabricated in the laboratory. A film of area 2x2cm^2 was cut which did not contain any air bubble. The film was fixed to the assembly and the weight that was required to break the film was noted as well as film elongation was noted using the pointer fixed to the assembly. Tensile strength was measured using the formula given below:

Tensile strength = Load at break / strip thickness × strip width. [10]

Percentage elongation

It was determined by the increase in the length of the film just before the breaking of the film. The formula used for calculating% Elongation is as shown below:

%Elongation = [Final length–Initial length]/Initial length x100. [11]

Moisture absorption

The prepared films were cut into 2 x2cm^2, weighed and placed in a desiccators containing 100 ml of saturated solution of Aluminum chloride at 75±5% RH. After three days the films were taken out and re-weighed. The percentage moisture absorption was calculated using the following formula.

%Moisture absorption =Final weight - Initial weightx100/ Initial weight

Table 2: Physicochemical Parameters of formulation F2-F8

Formulation Code	Weight Variation* (mg)	Thickness* (mm)	Folding endurance*	Tensile Strength* (kg/cm^2)
F2	236±0.29	0.16±0.02	21±1.527	0.259 ±0.008
F3	254±0.68	0.14±0.005	25±0.577	0.934±0.002
F4	252±0.44	0.15±0.006	57±1.21	0.903±0.020
F5	290±0.16	0.13±0.005	84±0.573	0.871±0.13
F6	272±0.181	0.17±0.026	92±1.577	1.133±0.026
F7	290±1.42	0.12±0.003	67 ±1.527	1.232±0.422
F8	315±1.42	0.14±0.005	96 ±0.612	1.332±0.315

Table 3: Physicochemical parameter of formulation F2-F8

Formulation Code	%Moisture absorption	Surface pH*	%Drug Content*	Disintegration time* (sec.)
F2	11.1± 0.21	6.80±0.015	95.84±0.023	60.33±0.57
F3	10.3± 0.12	6.76±0.036	97.40±0.034	45.33±0.54
F4	14.25± 0.76	6.81±0.010	98.70±0.167	90.65±1.11
F5	16.45± 0.59	6.80±0.17	96.75±0.286	40.68±1.57
F6	20.70± 0.52	6.68±0.015	96.23±0.037	90.47±2.046
F7	21.44 ±0.71	6.75±0.01	97.14±0.121	120.66±0.581
F8	22.83± 0.30	6.78±0.035	99.03±0.276	45.78±0.521

Surface pH

The oral film was slightly wetted with the help of water. Then the pH of film was measured by bringing the electrode in contact with the surface of the oral film. This study was performed for each formulations and mean ± S.D were calculated.

Content Uniformity

The film of 2x2cm^2 was cut and dissolved in phosphate buffer pH6.8 and volume was made to 100ml in a volumetric flask. 1ml was withdrawn from this solution and made upto10ml with phosphate buffer pH 6.8. The absorbance of this solution was measured at 224nm using UV visible spectro-photometer and the concentration was calculated. By correcting the dilution factor, the drug content was calculated. The test was performed in the triplicates and the standard deviation was calculated. [12]

Disintegrating time

Disintegration time was performed to ensure the disintegration of film in phosphate buffer pH 6.8. One film from each formulation was introduced into tube of disintegration apparatus. The apparatus was operated until the film disintegrated and disintegration time was noted. The test was performed in triplicate. [13]

In vitro dissolution study

In-vitro dissolution study of prepared films was performed in USP dissolution apparatus II (Paddletype) using 300ml phosphate buffer pH 6.8 as dissolution medium at 50rpm speed and the temperature maintained at 37±0.5°C. The samples were withdrawn at the time intervals of 30 seconds and analyzed spectrophotometrically at 224 nm. [14]

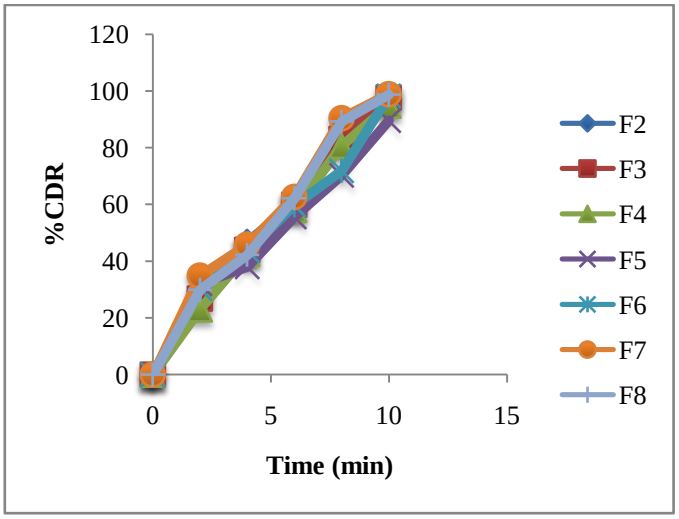

Figure 2: Comparison of *In-vitro* Drug Release profile of formulations F2-F8

Stability studies

The stability study of the formulated film was carried out under different experimental conditions as per ICH guidelines. The film was wrapped in butter paper and then packed in aluminum foil and kept in stability chamber at 40±2°C and 75%RH for the period of 3 months. At each month interval the films were taken and analyzed for any changes in weight uniformity, Folding endurance, %Moisture absorption, %Drug content and *In-vitro* dissolution study. [15]

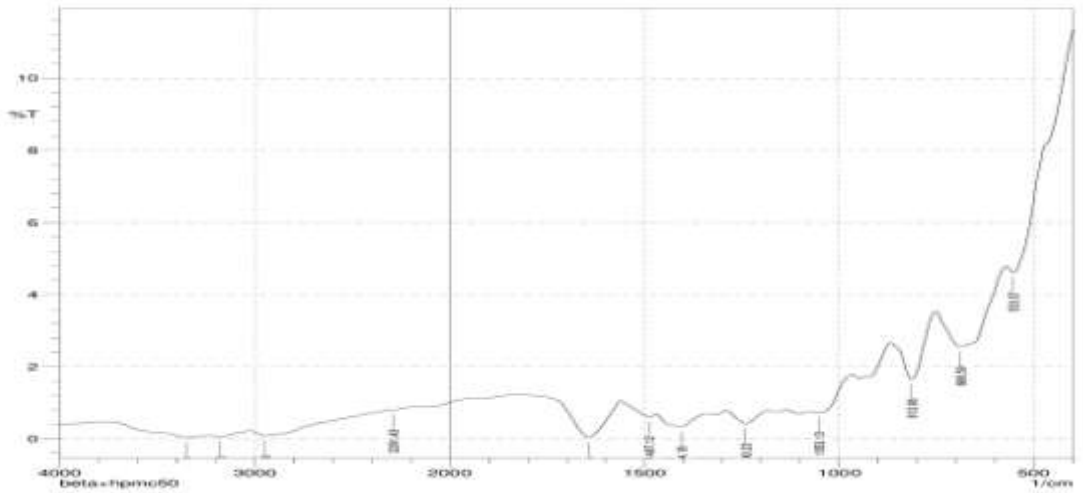

Figure 3: *FT-IR* spectrum of Betaxolol HCl

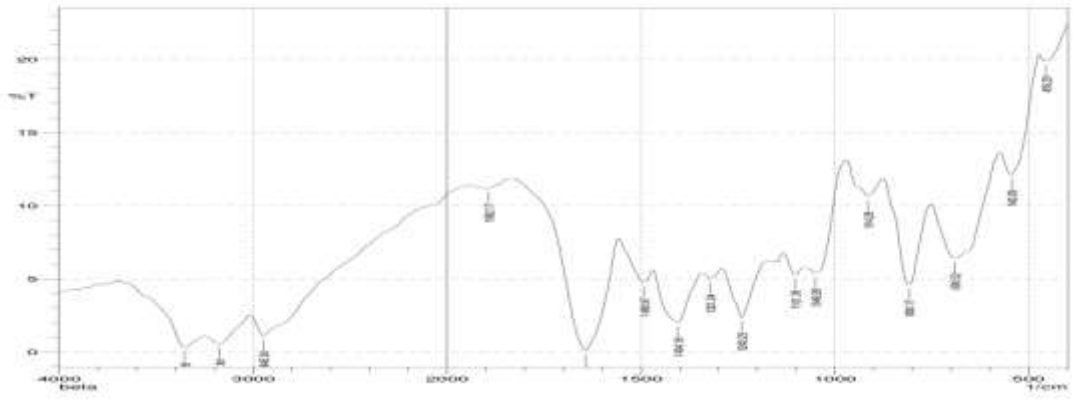

Figure 4: *FT-IR* spectrum of Betaxolol HCl and HPMC E_{50}

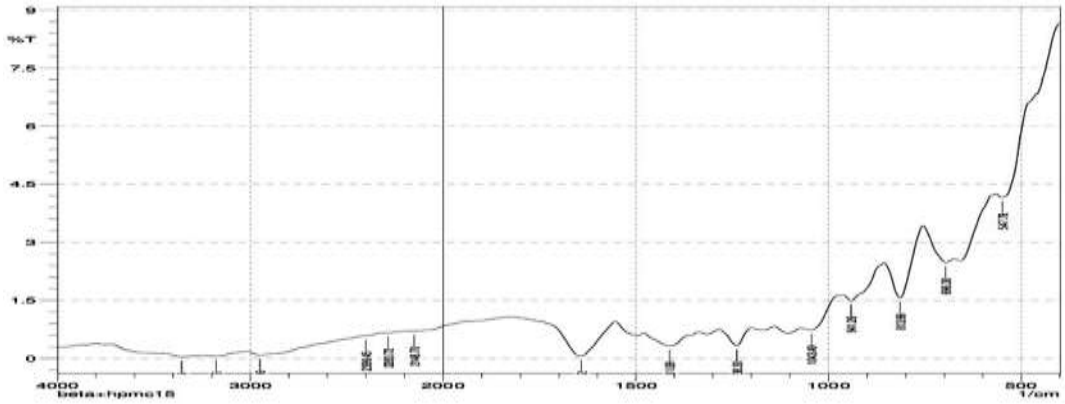

Figure 5: *FT-IR* spectrum of Betaxolol HCl and HPMC E 15

Table 4: Physicochemical evaluations during stability study for formulation F8

Parameters	Condition(40± 2°C / 75%RH)		
	30 days	60 days	90 days
Weight uniformity(mg)	316.37±0.02	316.98±1.25	317.43±0.26
Folding endurance	96±1.00	95±1.00	93±0.57
%Drug content	99.81±0.021	99.75±0.95	98.95±0.89
%Moisture absorption	23.13.±0.07	23.54±0.69	23.69±0.28

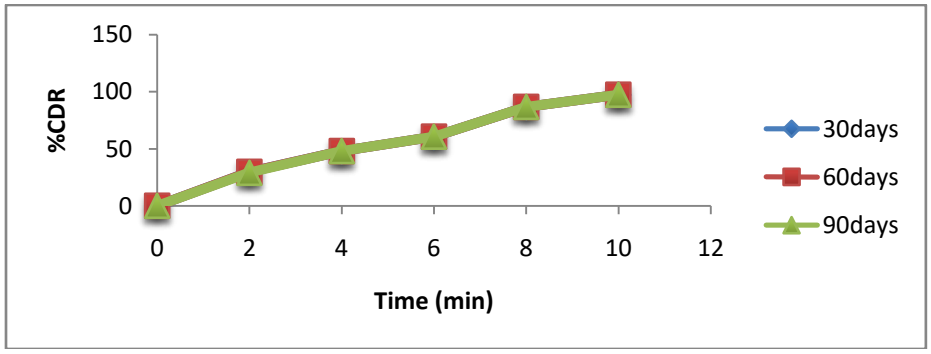

Figure 6: *In-vitro* dissolution study for formulation F8 after 1, 2 and 3 months

III. RESULTS AND DISCUSSION

In the present study, fast disintegrating films of Betaxolol hydrochloride were prepared by solvent casting method using HPMC E50 and HPMC E15 as film forming polymer, and Polyethylene glycol 4000 as plasticizers in various ratios, Sucrose as sweetener and Peppermint oil as flavoring agent. The effect of different concentration of polymer and plasticizers of film formulations was studied.

The films were evaluated for the various evaluation parameters. They were prepared by using varying concentrations of different polymers and plasticizers. All the prepared films were transparent, non-sticky, flexible and good in appearance except F1, which is not accepted.

The slight difference in the thickness of films could be attributed to the uneven surface of the plate. The individual weight of the films was measured and weight variation was calculated. The slight difference in the weight could be proportionately related to the variation in the film thickness. The pH of all the formulations was found in the range of 6.68 to 6.80. This shows that all the films prepared were of saliva pH (7.4).

All the films showed good folding endurance and most of them showed folding endurance of more than 50. The tensile strength of formulation F8 was found to be highest with the highest % elongation. The disintegration time of the films was found to be in the range of 45– 120sec. The higher disintegration time of could be attributed to higher concentration of film forming polymer as well as the muco-adhesive nature of this polymer.

The formulations F3, F4, F7, and F8 showed better drug content of above 97%. The reason of slight variation in the drug content of the prepared film can be attributed to the difference in the thickness of the film. Almost all amount of drug was found to be released from the formulations within 10 minutes. Formulations F2, F5, F6 and F7 showed the best drug release of more than 97% within 10 minutes. Thus it could be said that F8 is the best formulation according to all the evaluation parameters.

The selected film F8 showed good stability at both RT and accelerated conditions for the period of 3 months. There was no significant change in mechanical properties, drug content and drug release of the film. This shows that the film will remain stable to the wear and tear that occurs during its handling and transportation.

IV. CONCLUSION

The results of the studies indicated that HPMC E50 and HPMC E15 could be used as a film-forming polymer for the formulation of mouth disintegrating film of Betaxolol hydrochloride. All the films prepared showed acceptable mechanical properties. The in vitro disintegration time of all the formulation batches was found to be within 45-120 sec. On the basis of tensile strength, drug content and *in vitro* dissolution, formulation F8 was found to be the promising formulation showing better strength and good drug release profile. Also this formulation was stable for a period of 3 months with no significant change in drug content and drug release profile. Thus it could be said that the fast disintegrating mouth film of Betaxolol hydrochloride could be a better option for treatment of hypertension where quick onset of action is desired.

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