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FAST DISSOLVING HPMC E5 BASED ORAL FILM FOR RAPID ABSORPTION OF METOPROLOL TARTRATE

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ABSTRACT

Fast dissolving oral drug delivery system are solid dosage form which disintegrate or dissolve within second when placed in the mouth without need of water or chewing, first developed fast dissolving dosage form consisted in tablet form and the rapid disintegrating properties were obtained through a special procedure or formulation modification, recently fast dissolving film are gaining interest as an alternative to fast dissolving tablet to eliminate fear of chocking. In present investigation, an attempt has been made to develop oral fast dissolving film of Metoprolol Tartrate (25mg), the film were prepared by solvent casting method in which solution was casted on glass surface by using film forming machine, the characterization of film was done by evaluating various film forming polymer and plasticizer, concentration of polymer and plasticizer were optimized by evaluating various physical and chemical properties of film , Metoprolol Tartrate ODF contain HPMC E5 as a polymer, Sucralose as a sweetener and glycerol as a plasticizer proves to be potential, various concentration of HPMC E5 and glycerol used and ODF formulation were made and various mechanical properties were analyzed. Formulation consisting HPMC E5 and glycerol were proving to be better ODF formulation , mechanical property of film like disintegration time, folding endurance were compared with marketed products like ONDEM OF , stability study done by comparing dissolution profile of fresh and stability sample.

KEYWORDS: Metoprolol Tartrate, solvent casting method, film forming machine.

1. INTRODUCTION

1.1. Mouth dissolving drug delivery system (MDDS)

The oral route remains the perfect route for the administration of therapeutic agents `because the low cost of therapy and ease of administration lead to high levels of patient compliance. Oral dosage forms are more popular than other dosage forms because of following reasons: Ease of administration., Accurate dosage, Self- medication, Pain avoidance, Patient compliance.[1, 2]

A new oral fast dissolving dosage form such as the fast dissolving film has been developed which offers the combined advantages 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 & it may produce rapid onset of action. In such cases bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. [24, 31, 33]

Metoprolol Tartrate is a $ß_1$ selective antagonist. It suppresses the activation of the heart by blocking ß adrenoreceptors and they reduce the work of the heart by decreasing cardiac output & blood pressure, Metoprolol Tartrate used in the treatment of hypertension , angina pectoris and arrhythmia where immediate action is required . The absolute bioavailability of Metoprolol Tartrate after oral doses is about 40% - 50%. Metoprolol Tartrate undergoes extensive hepatic metabolism. These pharmacokinetic properties of Metoprolol Tartrate make it ideal for the formulation into fast dissolving oral film. Metoprolol Tartrate Film should offer multiple competitive advantages versus the already marketed pharmaceutical forms of Metoprolol Tartrate : Higher bioavailability, higher compliance, easy to swallow and no need of water To fulfil these needs an attempt was made to formulate and evaluate fast dissolving film of Metoprolol Tartrate using low viscosity polymer and sweetener. The Metoprolol Tartrate Film was especially designed for higher patient compliance and higher bioavailability.

In the present work, we have attempted to formulate Fast Dissolving Film of Metoprolol Tartrate, studied effect of different polymers and plasticizers on the release of Metoprolol Tartrate with special emphasis on, increasing bioavailability of drug by avoiding first pass metabolism and improving dissolution and disintegration of drug.

2. MATERIAL AND METHOD

A gift sample of Metoprolol Tartrate was obtained from HETERO chemicals, India. HPMC E3, E5, E6, E15 were obtained from Colorocon pvt. Ltd. Polyvinyl Alcohol, PVP K 90 was obtained from Merck Ltd.

2.1. Pre-formulation Study

Pre-formulation studies help in studying the physiochemical properties of drug and polymer.

2.1.1. Characterisation of Drug [7, 9]

2.1.2. Description

The Organoleptic properties of drug were determined including colour, solubility and its nature.

2.1.3. Solubility

For the determination of solubility, excess amount of drug was added in the solvent (water, 0.1N HCl, 6.8 pH phosphate buffer) at room temperature and kept for 48hrs with occasional shaking. The supernatant was taken and analyzed by using Shimadzu UV 1800 double beam spectrophotometer.

2.1.4. Determination of λ max

Accurately weighted 10mg of Metoprolol Tartrate was transferred in the 100 mL volumetric flask and volume was made up to 100 ml with 0.1N HCL. From this solution, 1 ml was withdrawn and added to the 10 ml volumetric flask and diluted up to 10 mL with 0.1N HCL. Finally, sample was scanned in the range of 200-400 nm. The wavelength of the maximum absorption was noted and UV spectrum was recorded.

2.1.5. Standard calibration curve of Metoprolol Tartrate:

A stock solution of Metoprolol Tartrate of concentration 100µg/mL was prepared in purified water, 0.1N HCl, pH 6.8 buffer. The UV spectrums were recorded in the range of 200 – 400 nm. The wavelengths of maximum absorption were recorded using Shimadzu UV double beam spectrophotometer. The calibration curves were constructing using standard solutions in the range 5 to 25 µg/mL diluting with appropriate solvent.

2.1.6. FTIR Spectroscopy

Drug was characterized by FTIR spectroscopy. The spectrum was recorded using FTIR Spectrophotometer (Agilent). The scanning range was 4000 to 600 cm-1. The spectrum of Metoprolol Tartrate is shown in figure no. 1.

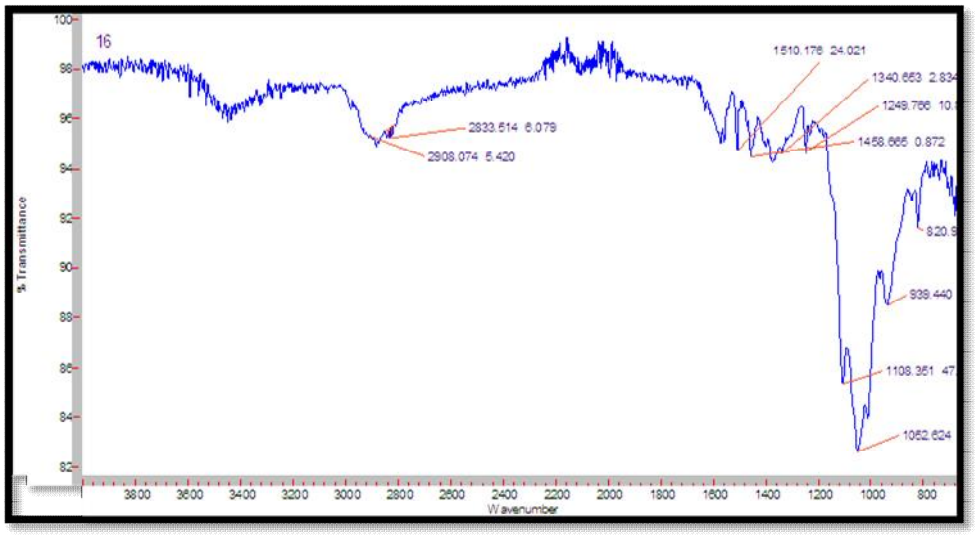

Figure no.1. IR spectra of Metoprolol Tartrate

2.1.7. Differential scanning calorimetry

The DSC study was carried out for obtained sample of Metoprolol tartrate to confirm its purity. The DSC patterns were recorded on a METTLER TOLEDO (Stare SW 920) System 1.5mg of drug was heated in crimped aluminium pans at a scanning rate of 400C/min in an atmosphere of nitrogen gas flow 40 ml/min using the range of 40-3500C.

2.1.8. Compatibility study of drugs with polymers

These studies were performed in order to confirm the drug-excipients compatibility.

2.1.9. FTIR spectroscopy study

FTIR spectra of pure Metoprolol Tartrate, HPMC E5, PEG 400 and physical mixtures of these excipients with drug were recorded on Agilent FTIR spectrophotometer. The instrument was operated under dry air purge and the scans were collected with resolution of 4cm-1 over the region 4000-400 cm-1. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction, shown in Figure 3.

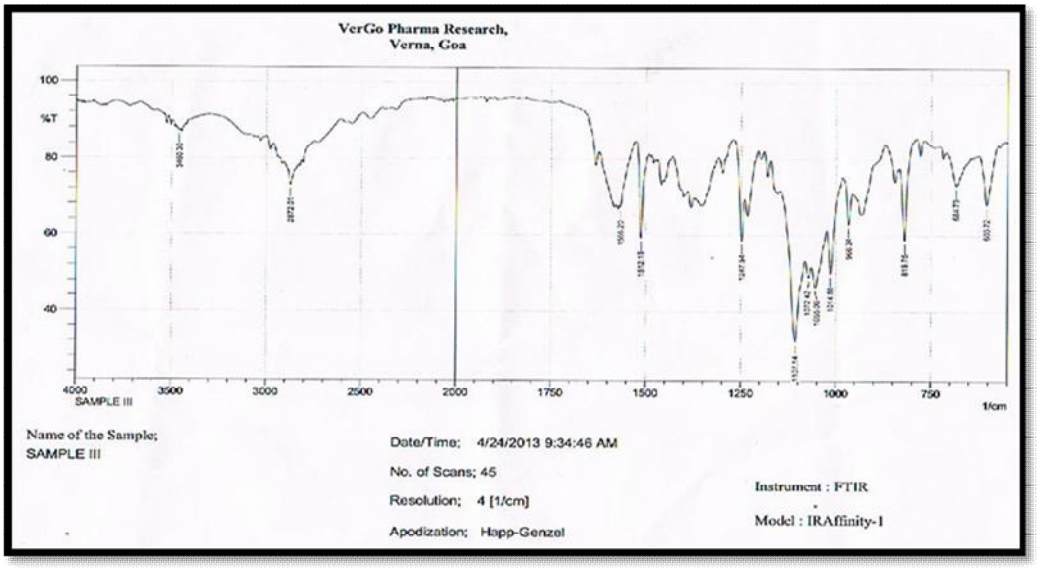

Figure no.3. IR spectra of Metoprolol Tartrate +HPMC E5

2.1.10. Differential scanning calorimetry (DSC) study

The DSC thermograms were obtained for pure Metoprolol Tartrate, HPMC E5, PEG 400 and their physical mixture. In physical mixture those excipient were added that were expected to be used in the development of formulation. The DSC patterns were recorded on a METTLER TOLEDO (Stare SW 920). Each sample (1-2mg) was heated in crimped aluminium pans at a scanning rate of 400C/min in an atmosphere of nitrogen using the range of 40mL/min. The temperature calibrations were performed periodically using indium as a standard and thermograms obtained were observed for any interaction. The DSC thermograms are shown in figure 7.9, 7.10

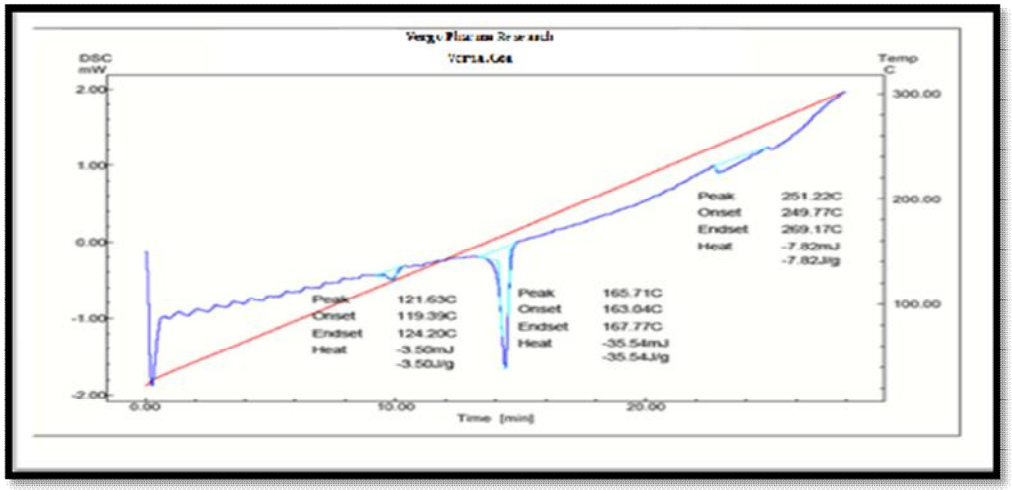

Figure no 4. DSC thermogram of physical mixture of drug + HPMC E5

2.2. FORMULATION DESIGN OF ORAL FAST DISSOLVING FILMS

2.2.1. General Procedure for Preparation of Oral fast dissolving films

The Fast dissolving films were prepared by solvent casting technique. Various polymers were used as a film forming polymer. The oral fast dissolving films was prepared by dissolving film forming polymer (10% w/v) in the distilled water, then solution was continuously stirred up to an hour on magnetic stirrer and kept for an hour to remove all the air bubbles entrapped. The formulation was casted on a suitable platform by using film forming machine and dried to form a film. Then the film was carefully removed and cut into suitable size i.e. 3cm x 2cm. [36, 49] We optimized the batches as S1, S2, S3, S4,S5, S6, S7, S8, S9 (Table no.1) and evaluated them by using Film Forming machine (V J Instrument) (figure no 1)

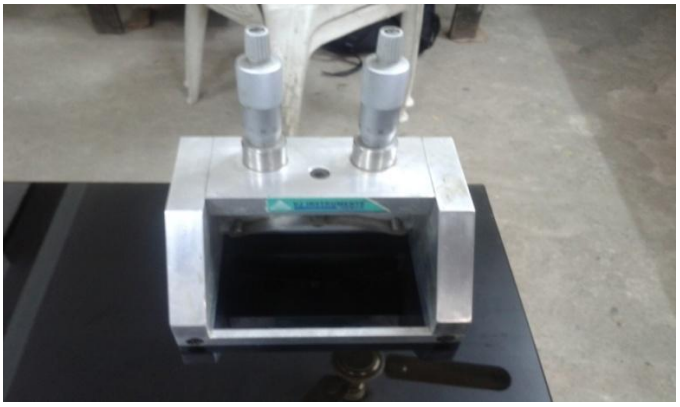

Figure no.1. Film Forming machine (V J Instrument)

Table no. 1. Formulation design as per factorial layout

Sr.No.	Components	S1	S2	S3	S4	S5	S6	S7	S8	S9
1	Metoprolol Tartrate	25	25	25	25	25	25	25	25	25
2	HPMC E5	22.5	22.5	22.5	25	25	25	27.5	27.5	27.5
3	Glycerol	6	7.5	9	6	7.5	9	6	7.5	9
4	Sucralose	1.71	1.71	1.71	1.71	1.71	1.71	1.71	1.71	1.71
5	Distilled water	q.s	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Area of the Final film- 3cm X 2cm, Dose of drug per film-25 mg

2.3. EVALUATION OF ORAL FAST DISSOLVING FILMS [11, 14, 34]

2.3.1. Folding endurance

All the polymers were able to give the acceptable folding endurance values. The observed folding endurance was in the range of 7-28.

2.3.2. Drug content per sq. cm area

The average content of Metoprolol Tartrate per film (3cn x 2cm) was found to be 25.68 mg. The values were almost uniform in all S1-S9 formulations. (Table no.3)

2.3.3. Thickness

The thicknesses of formulated films were found to be in range of 0.07 to 0.09 ± 0.01 mm. The values were almost uniform in all S1-S9 formulations.

2.3.4. Surface pH study

The surface pH values of the formulations are given in Table no.3. All the polymers resulted in the formulations that have neutral surface pH. The surface pH of the strips was ranging from 6.8 to 7. The neutral values of surface pH of films assured that there will be no irritation to the mucosal lining of the oral cavity.

2.3.5. Disintegration time

The D.T. of film was in the range 22-39 seconds. It was observed that as the solid contents of the film increased, D.T. also increased. The increase concentration of HPMC also increases the disintegration time. As shown in Table no. 3.

Table no.3 Evaluation of Factorial Batches of Fast Dissolving Oral Films

Sr. no.	Batch code	Weight of the film (mg)*	Thickness (mm)	Surface pH*	Disintegration Time (sec)	Folding Endurance	Drug content
1	S1	55.21	0.07-0.08	6.85	22	28	94.25
2	S2	57.71	0.07-0.08	6.89	24	37	91.29
3	S3	60.21	0.08-0.08	6.94	24	48	97.24
4	S4	57.71	0.07-0.08	6.84	28	32	103.26
5	S5	60.21	0.08-0.09	6.90	29	42	98.25
6	S6	62.71	0.08-0.09	6.86	30	50	94.23
7	S7	61.21	0.08-0.09	7.0	34	35	90.24
8	S8	63.71	0.08-0.09	6.86	39	52	97.36
9	S9	66.21	0.08-0.09	6.92	39	52	107.25

2.3.6. In-Vitro Dissolution Studies [8, 19]

The different dissolution medium like 0.1 N HCl and Simulated saliva were used for the dissolution study of optimized S3 formulation. The cumulative % drug release of S3 formulation indicated the 95.25 % drug release in 0.1 N HCl and 94.27 % drug release in simulated saliva in 5 min (table no.4 and 4.1). There is no significant difference on drug release by both the dissolution media. Also 0.1N HCl is the recommended dissolution

medium for Metoprolol Tartrate by US FDA so it was selected as a dissolution medium for present study. Hence all the dissolution studies were carried out in 0.1 N HCl only.

Table no. 4. Dissolution data of factorial batches of fast dissolving oral films

Time (min)	S1	S2	S3	S4	S5	S6	S7	S8	S9
1	57.14± 1.67	51.16± 0.98	50.14± 2.04	47.38± 1.87	45.36± 1.64	44.56± 0.78	39.25± 1.69	37.14± 1.45	34.64± 1.42
2	70.13± 2.05	67.35± 1.75	61.84± 1.52	54.23± 2.14	57.25± 3.41	55.24± 1.47	46.27± 2.41	45.20± 2.14	48.36± 2.14
3	83.01± 1.62	85.25± 2.35	79.25± 0.98	68.24± 1.36	69.24± 1.46	74.35± 2.10	60.49± 0.97	59.12± 2.07	63.27± 2.16
4	86.08± .098	88.58 ±1.45	84.37± 3.04	78.25± 2.17	74.34± 1.20	78.87± 1.84	68.34± 1.96	69.46± 1.47	74.32± 1.98
5	92.13± 2.41	99.14± 2.51	94.27± 0.98	84.48± 1.56	85.14± 2.63	87.36± 1.48	72.34± 1.47	75.24± 0.98	81.36± 2.04
6	94.13± 3.04	-	100.28± 1.5	90.24± 0.88	91.14± 2.45	96.28± 2.36	78.21± 2.54	79.26± 1.78	79.24± 1.36
7	-	-	-	95.14± 3.05	95.20± 1.64	97.21± 3.04	84.32± 1.95	85.38± 2.86	88.24± 1.42
8	-	-	-	-	-	-	89.36± 2.10	94.52± 1.47	104.2± 2.98
9	-		-	-	-	-	94.21± 3.45	99.34± 3.04	-

*All values are expressed as mean ± S.D. (n=3)

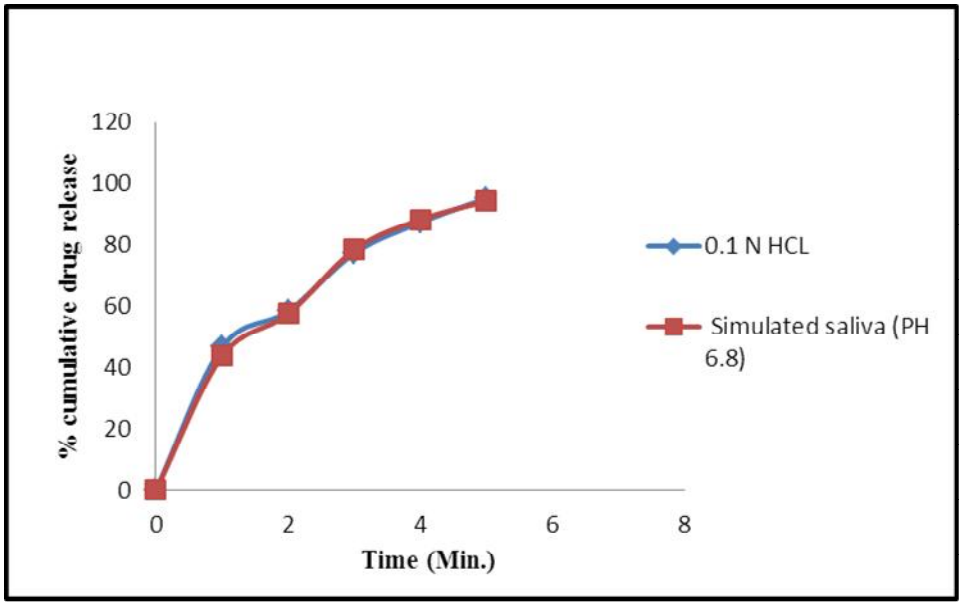

Figure no.2. Dissolution data of S3 formulation in different dissolution medium

2. 3.7. Permeation study through buccal mucosal membrane

Permeation study through oral mucosa indicated that the extent of permeation of Metoprolol tartarte from formulation S3 observed 84% 30 min. (table no. 5. And figure no. 8)

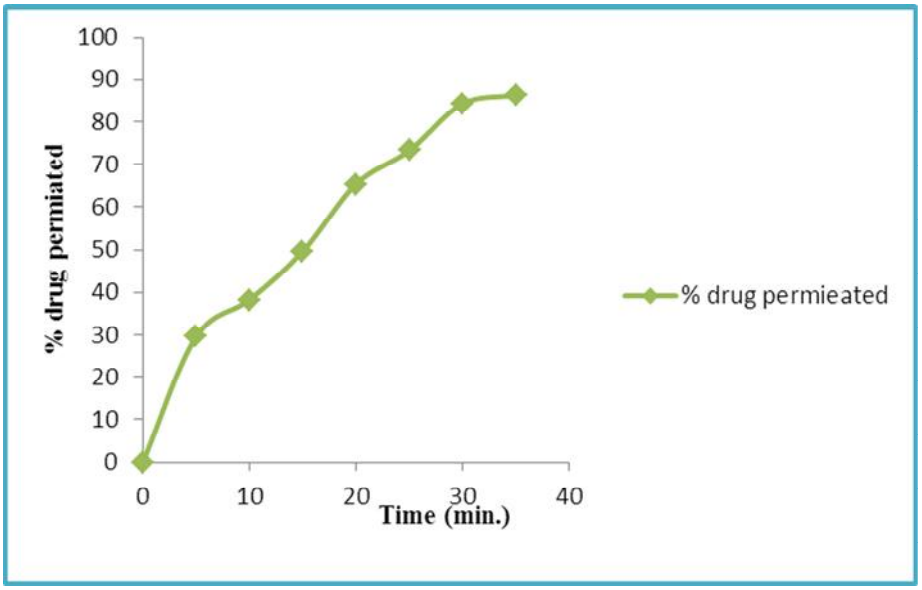

Figure no.3 Permeation study of formulation S3

2.3.8. Stability studies

The optimized S3 formulation was selected for stability studies on the basis of high cumulative % drug release, results of *in vitro* disintegration time and results of folding endurance. The results obtained were tabulated in Table no 4 &5. From these results it was concluded that, formulations S3 is stable and retained their original properties with minor differences. The *in vitro* release profile of S3 at 40 °C/ 75% RH condition after 30 days was 98.90 ± 0.94 which indicated that there is no or minor alteration of original properties after storage.

Table no. 4. Stability studies of optimized formulation

Parameters	Initial	After 30 days stability studies
Folding endurance	48	46
Drug content (%)	96.54 ± 0.84	95.88 ± 0.56
Surface pH	6.8 ± 0.05	6.8 ± 0.08
Disintegration time (sec)	24 ± 0.56	25 ± 0.59

Table no. 5. Drug release profile of formulation S3 after stability studies

Time (min)	% CDR before stability study	% CDR after stability study
0	0	0
1	50.14 ± 0.67	47.26± 0.24
2	61.84 ± 0.32	64.48± 1.42
3	79.25 ± 0.72	76.25± 0.81
4	94.27 ± 0.49	91.68± 0.67
5	97.28 ± 0.54	95.90 ± 1.44

2.3.9. Response surface plots

Response surface plot were generated for each response as shown in Figure No. 26-31. As the concentration of HPMC E5 from 22.5 to 27.5, there was a decrease in cumulative % drug release. So the polymer retards the drug release. When the polymer were present in less concentration (formulation S1)then the cumulative % drug release at 5 min was 96.25, while when we increased the concentration to highest (formulation S9) then the cumulative % drug release at 5 min was 79.80 only. When we kept HPMC E5 constant and the concentration of glycerol increased from 6 to 9 then the cumulative % drug release was slightly increase. The disintegration time increases with increase in concentration of HPMC E5 and When we kept HPMC E5 constant and the concentration of glycerol increased from 6 to 9 then there is very slight change in disintegration time, as the concentration of HPMC E5 was increased from 22.5 to 27.5 it showed increase in folding endurance from 28 to 35. When we increased the concentration of glycerol from 6 to 9 then it also increased the folding endurance from 28 to 48. Hence the HPMC E5 and Glycerol increase in folding endurance but effect of HPMC E5 lower as compared to Glycerol as shown in equation (figure no 8-11).

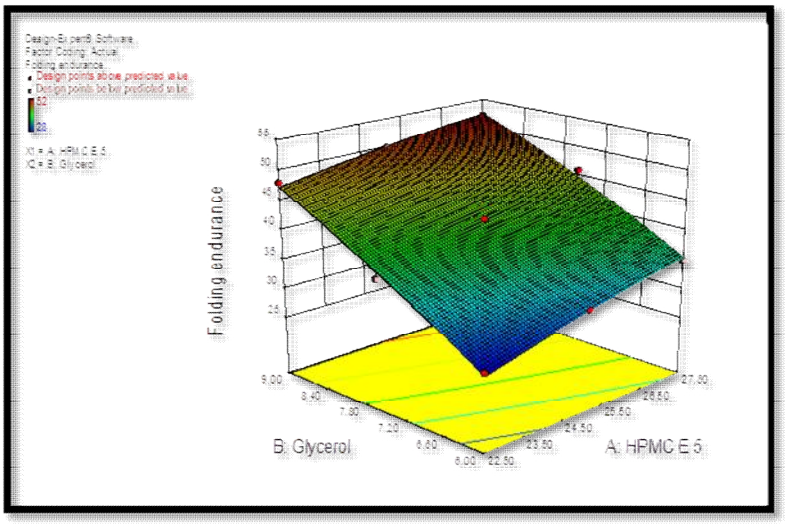

Figure no. 4. Response surface plot for folding endurance

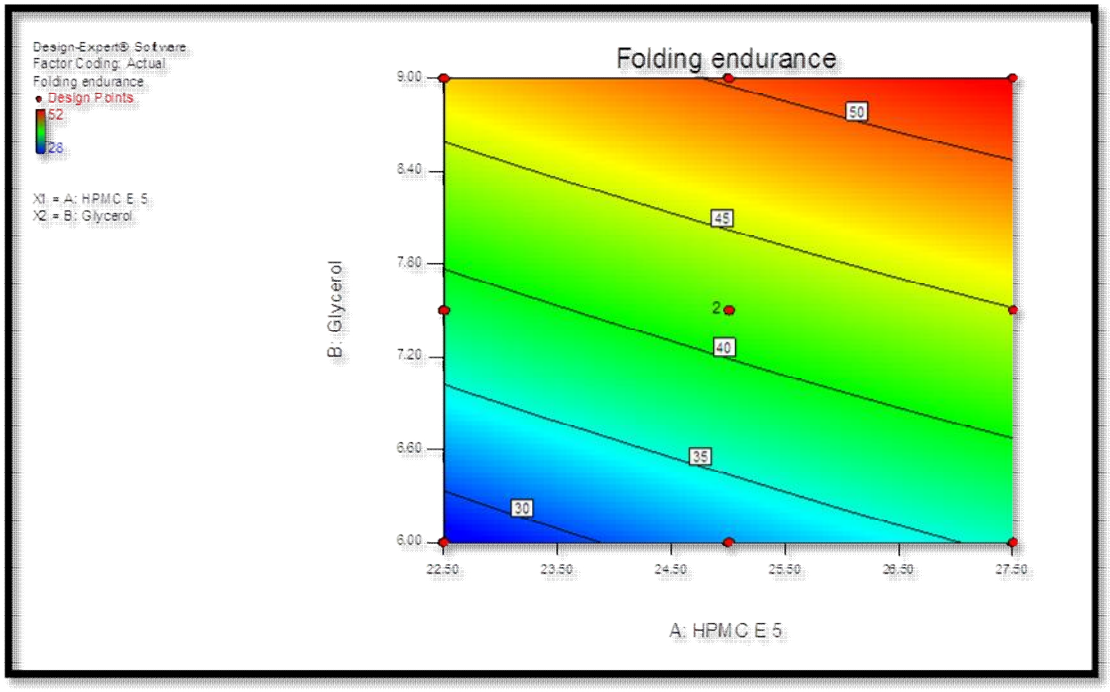

Figure no. 5. Counter plot for folding endurance

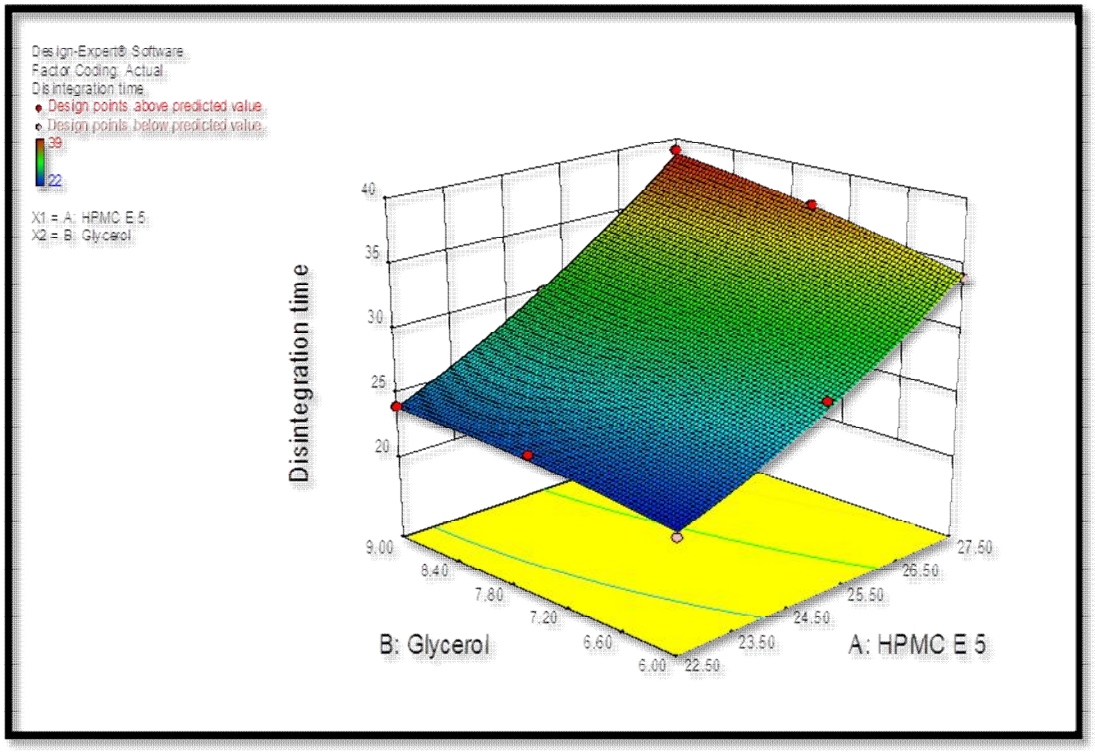

Figure no. 10. Response surface plot for disintegration time

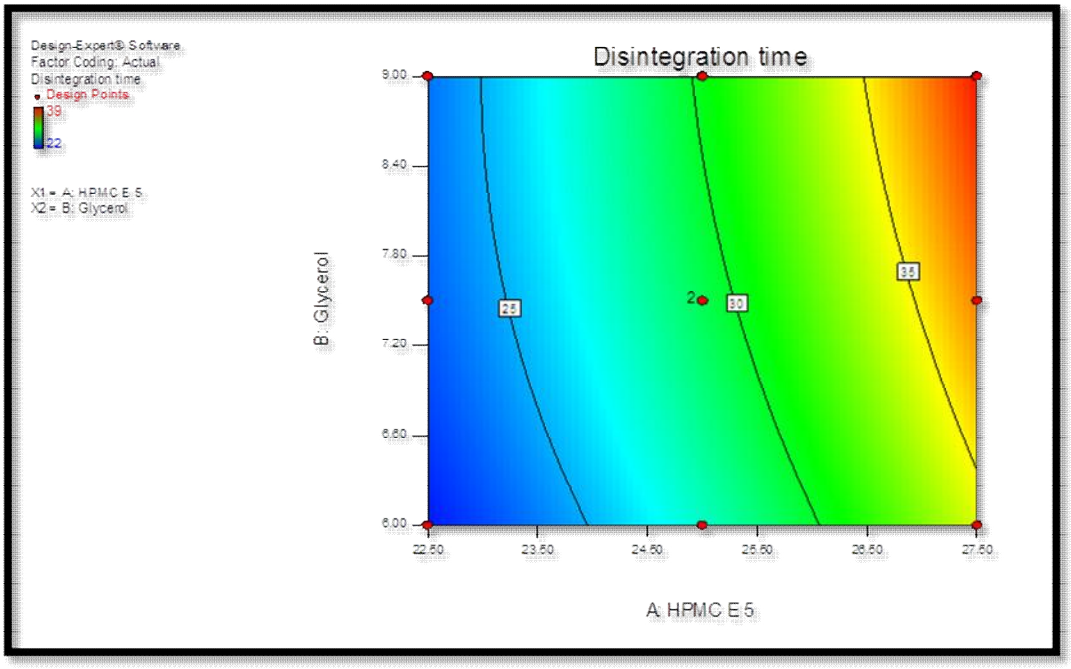

Figure no. 6. Counter plot for disintegration time

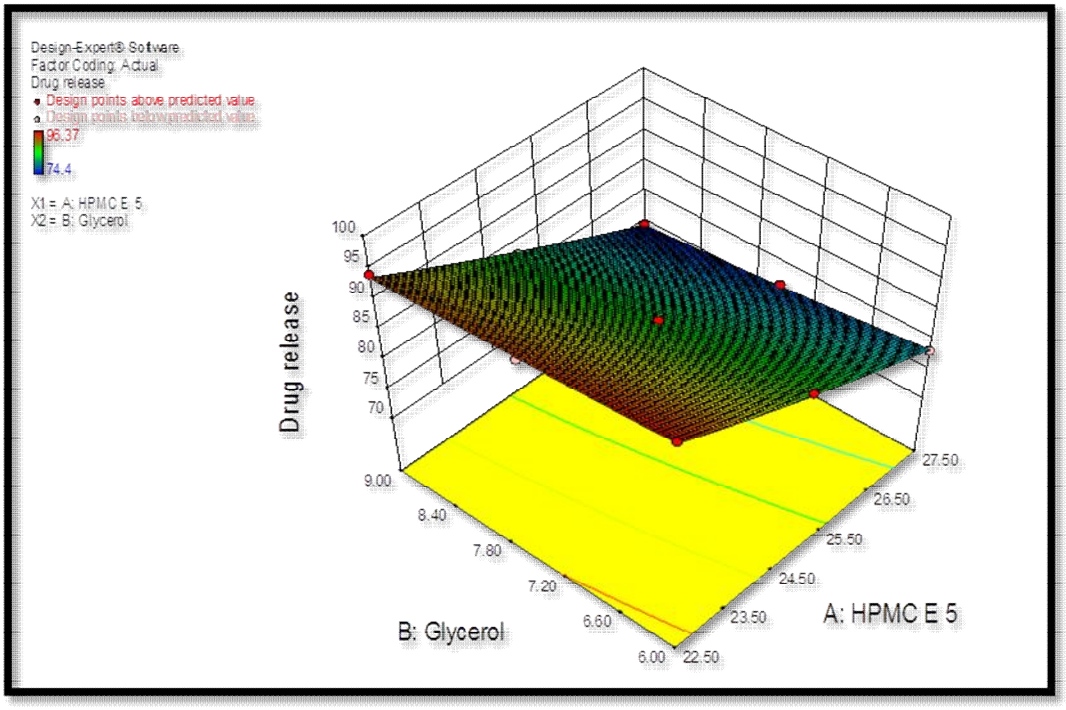

Figure no. 7. Response surface plot for cumulative % Drug release

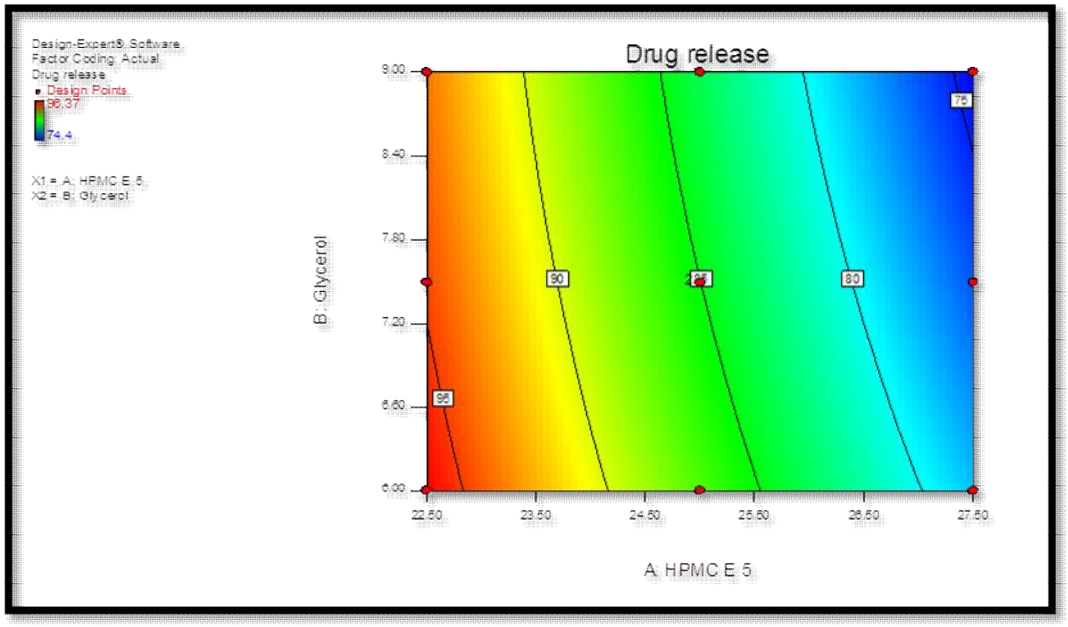

Figure no. 8. Counter plot for cumulative % Drug release

3. RESULT AND DISCUSSION

For the present study, Metoprolol tartrate was selected as a model drug candidate as no marketed film of Metoprolol tartrate is available in India. Moreover, the conventional tablet leading to patient noncompliance. The developed formulation which disintegrates in oral cavity in less than 40 seconds without the need of drinking water; and improved patient compliance particularly for those who have difficulty in swallowing.

A Preformulation study was carried out during the early stages of this work. It has found that Metoprolol tartrate is having maximum absorption at wavelength 223 nm. The drug-polymer compatibility study was carried out to determine the interactions between the drug and the polymers used in the study. The FTIR and DSC study revealed that, polymers and excipients used were compatible with drug. The Fast dissolving films were formulated by solvent casting technique using film forming machine. Different polymers were screened for the preparation of Fast dissolving films. Amongst all the formulations, formulation containing HPMC E5 combine with glycerol as plasticizer has shown excellent *in vitro* disintegration time and *in vitro* cumulative percent dissolution, compared to other formulations. The two variables were studied at three levels thus, a 3^2 full factorial design was applied and nine different formulations were developed by solvent casting method and evaluated.

The films prepared using HPMC E5 and Glycerol showed the best result among all other films. Formulation S5 (HPMC E5: glycerol, 150:100) disintegrated in 29 seconds and

released 90% of drug within 3 minutes and was considered as the best formulation. As the concentration of film forming polymers gets increased it also increases the film forming capacity of the films.

4. CONCLUSION

From above discussion, it can be concluded that the successful formation and optimization of fast dissolving films of Metoprolol tartrate using HPMC E5 as film forming polymer and glycerol as a plasticizer Hence Metoprolol tartrate can be conveniently administered orally in the form of films.

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