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Research Article

Formulate and Evaluate, Fast Dissolving thin Film of Metoprolol Succinate

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Abstract:

Objective: Metoprolol succinate, which is used to treat cardiovascular disorders, is a strong beta-1 adrenoreceptor blocker with cardio-selective effect but is heavily metabolised in the liver during the first pass. Our goal is to minimise hypertension by creating a film of metoprolol succinate that dissolves quickly.

Methods: Metoprolol succinate films that dissolve in the mouth were made utilising a solvent casting technique. HPMC E5 was used as the film-forming agent, PEG400 was used as the plasticizer, and honey was included as the film-modifying agent in the final formulation. HPMC E15 (X1) and honey (X2) concentrations were used as independent variables, whereas disintegration time (DT), tensile strength (TS), and % cumulative drug release (CDR) were used as dependent variables in a 32-full factorial design. Thickness, folding endurance, tensile strength, disintegration time, and drug release were among the criteria used to assess the manufactured films. Results showed that HPMC E15 and honey both positively impacted DT and TS while negatively impacting CDR.

Results: The optimum formulation was determined to be the one with a DT of 58.0 ±1.01 seconds, an in vitro drug release of 105.32± 1.55, and a tensile strength of 73.55 ± 1.37 g/cm2.

Conclusion: Thus, employing a solvent casting method, a fast-dissolving thin film of Metoprolol succinate was created with effective taste masking and prompt in vitro drug release.

Keywords: Metoprolol succinate, Fast dissolving oral film, HPMC E5, Honey, Solvent casting

Introduction

Oral administration provides various benefits, including injectable simplicity, absence of discomfort, adaptability, absence of sanitation requirements, lower cost, and patient compliance. For this reason, new methods for oral delivery have been

developed. It is a sort of medication that, as the name suggests, dissolving or breaks down quickly in the mouth without requiring any kind of liquid. This dose form is extremely accommodating for patients with dysphagia caused by conditions such as stroke, Shaking palsy, AIDS, neurological illness, and cerebral palsy. FDF is extremely useful for elderly and kid patients, as well as those who are travelling and do not have immediate access to water. FDF, also known as oral wafers, is a collection of thin polymeric film that is gaining increasing attention in the pharmaceutical business. It is a unique formulation that is now widely recognised for delivering vitamins and personal care items. Currently, systemic distribution of over-the-counter medications is permitted and trials are underway for prescription drugs [1] .

Metoprolol succinate, a powerful beta-1 adrenoreceptor blocker with cardio-selective activity, is typically used to treat cardiovascular diseases such angina pectoris and hypertension. Metoprolol has no effect on beta-2 receptors but inhibits cardiac beta-1 adrenergic receptors. By producing negative chronotropic and inotropic effects in the absence of membrane stabilising or intrinsic sympathomimetic activity, this inhibition lowers cardiac output. when taken orally, it is around 50 percent for the tartrate derivative and 40 percent for the succinate variant available in blood. Metoprolol undergoes substantial first-pass hepatic metabolism [2].

Materials and Methods

Metoprolol succinate sample obtain from Dr. Reddys Laboratories, Hyderabad. HPMC E3, HPMC E5, HPMC E15, PEG 400, Propylene Glycol, Glycerol, Aspartame, Methanol, Ethanol obtained from chemical room of jaipur college of pharmacy. All chemicals and reagents used were of AR grade.

Analytical method

Weigh accurately 100mg of pure durg, then mixed in phosphate buffer pH 6.8 and make up the volume to 100ml to give a concentration of 1mg/ml. Then transfer 10ml of this solution corresponding to 10mg/10ml to 100ml volumetric flask and dilute to 100ml to give a stock solution of 0.1mg/ml i.e. 100 µg/ml. Then 10ppm solution was prepared using this stock solution. The above stock solution was used to prepare various dilutions 2, 4, 6, 8, 10, 12, 16, and 20 µg/ml in phosphate buffer pH 6.8. Then the absorbances of dilutions are measured on UV-spectrophotometer at the 222nm using phosphate buffer pH 6.8 as blank solution. The average absorbance value and standard deviation were computed for the triplicate runs of this experiment in order to produce the calibration curve of Concentration in g/ml vs. Absorbance at max and the equation for the line of best fit[3].

Drug and Excipient Compatibility Study

Analysis of Drug-Excipient Compatibility using FTIR

For this experiment, a combination of the pure drug and potassium bromide (1:20) in a dry condition was created to test the two substances' compatibility. Then, using an IR pellet maker, pellets were made from each of the resulting mixes. A spectral scan was then performed on the pellet using a wavelength range of 4000 to 4000-cm-1.

Analysis of Drug-Excipient Compatibility Using DSC

DSC was used to investigate medication excipient compatibility. Differential scanning calorimetry was utilised to carry out the experiment. Scanners in a nitrogen environment examined thermograms of the drug and its combination at temperatures ranging from minus one hundred degrees Celsius to four hundred degrees Celsius.

Procedure for Film Preparation

Film making involved the use of a solvent casting technique. Overnight, the polymer had been soaked in three-fourths of the solvent. For around 30 minutes, the mixture of polymers was blended on the magnetic stirrer to achieve uniform dispersion. Following the addition of each ingredient, the plasticizer, film modification, and sweetening agent were added and mixed for 10 minutes. For 60 minutes, a stirrer with magnets was used to combine the polymer solution. To get rid of any air bubbles, the polymer solution had been sonicated for 30 minutes. Then a circular glass petriplate with a 9.0cm diameter was filled with polymer solution. Glycerin was used to lubricate the petri plates. The films were air dried at room temperature, then cut into 2 cm by 2 cm films, peeled, and put in the desiccant after being covered with butter paper[4].

Preliminary Screening for best film

Carageenan, xanthan gum, polyvinyl alcohol, and high molecular weight polyethylene (HPMC) were among the many polymers evaluated for their film-forming abilities. Among all the different types of polymers tested, HPMC was shown to be the most effective film-forming agent. Using a solvent casting technique, swiftly dissolving films were manufactured. HPMC E3, E5, and E15 may be used to make a good transparent, non-sticky film. The polymer was chosen based on its look, folding durability, film disintegration time, and stickiness.

Formulation and optimization of Fast dissolving metoprolol succinate thin film using 3^2 Factorial Design.

A design of experiment was employed to improve the metoprolol succinate Fast dissolving Film. With two factors at three levels and nine formulations, a full factorial experiment design was created as shown in table 3. The independent variables were numerical factors with the names X1 for HPMC E15 concentration and X2 for honey concentration. The responses Y1- disintegration time in seconds, Y2- tensile strength of films in g/cm2, and Y3- drug release in % at 9 minutes were chosen for statistical optimisation[5].

Evaluation of Fast Dissolving film of metoprolol succinate

Physical attributes such as microscopy, weight, thickness, surface pH, folding endurance, disintegration time, tensile strength, drug release, and stability were assessed for the produced films.

Weight and thickness

The produced films were trimmed into 2cm X 2cm size before being weighed on an electronic balance. We measured the weight of all three films and calculated their mean and standard deviation. The thickness of the film was determined in three different spots using a micrometre, and the mean as well as the standard deviation of these measurements were recorded[6].

Folding Endurance

The individual film was manually folded in the same plane for the duration of the test, producing a break that could be seen. The number of folds necessary to cause a crack to appear is recorded as the film's folding endurance [7].

Tensile Strength

The formula below is used to compute tensile strength, which is the greatest stress that can be applied to a film before it breaks.

$$\text{Tensile strength} = \frac{\text{Load at fracture X 100}}{\text{Film thickness X film width}}$$

An average and standard deviation of three reading was recorded using Tensile strength tester.

Disintegration test

Disintegration test was done using disintegration test apparatus IP with phosphate buffer pH 6.8 as the medium and 37±2 temperature [8].

Invitro Drug Release

The invitro drug release was measured using customised dissolving apparatus. The dissolving medium was a buffer made of phosphate with an equilibrium pH of 6.8. A dissolving flask containing the films was inserted into a 50 ml beaker containing 20 ml of phosphate buffer pH 6.8. We used the Dissolving Apparatus II, and ran the stirrer at 50 rpm without the basket. Spectrophotometric analysis at a maximum spectrum of 248 nm using UV 1800 indicated the concentration of the sample sampled at 3, 6, 9, 12, 15, 18, and 21 minutes[9].

Statistical Optimization

The statistical optimisation will be performed using Design Expert 11.0--a demo version of the software developed by Stat Ease Inc. X1 and X2 demonstrate how the film's disintegration time in seconds is affected by the independent variables of HPMC E15 and honey concentration, respectively. The Y2 strength (in g/cm2) and Y3 drug release of the film were evaluated at 9 minutes. The significance of the effect of each independent variable on the dependent variables was determined using two-way ANOVA at the $P<0.05$ level.

Stability Study

For the ideal film formulation, the stability study will be carried out. The manufactured films were then placed in a desiccator for 90 days at room temperature and ambient humidity. After this time, the films were tested for different parameters.

Results and Discussion

Analytical method

The range for metoprolol succinate was discovered to be 2.0 to 20.0 g/ml. Standard deviation (SD) and the average absorbance value across three readings were calculated (Table 1 and Fig. 1).The regression coefficient was found to be 0.997 and the slope to be 0.0281. The value of the co-efficient of correlation, which indicates linearity between the plotted values of absorbances and concentration, was discovered to be 0.998.

Table 1: Standard Calibration Curve of Metoprolol Succinate In Phosphate Buffer Ph 6.8

Sr. No.	Concentration (µg/ml)	Absorbance (n=3) at 222nm	SD
1	2	0.087	0.001
2	4	0.142	0.01
3	6	0.21	0.012
4	8	0.255	0.012
5	10	0.313	0.01
6	12	0.381	0.013
7	14	0.424	0.01
8	16	0.466	0.01
9	18	0.544	0.012
10	20	0.6	0.012

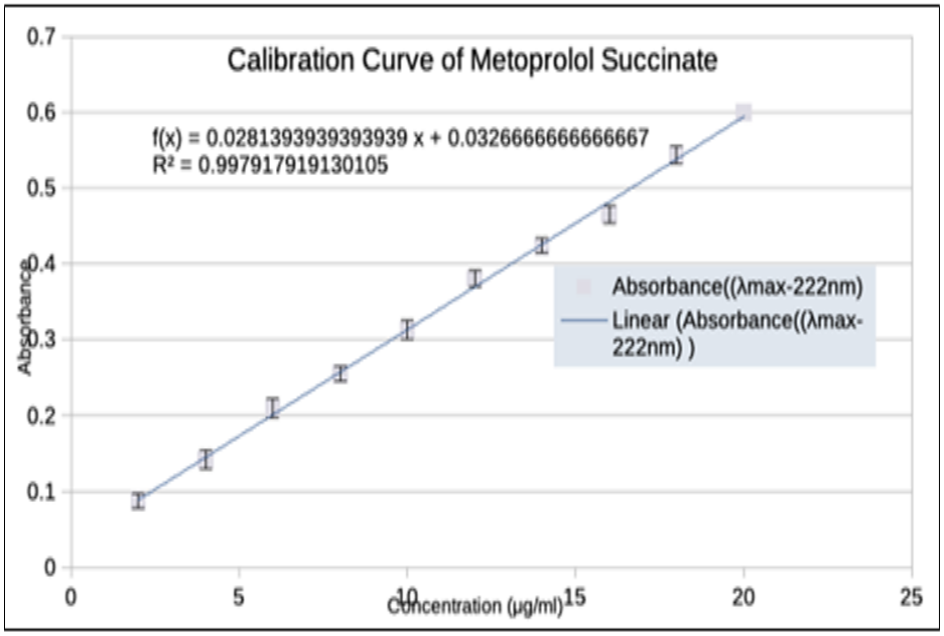

Figure 1: Calibration Curve for Metoprolol Succinate in phosphate buffer pH 6.8

Drug-Excipient Compatibility using FTIR

The spectra of pure drug and formulation were compared shown in figure 2 (A) & (B)[9] for presence of any unusual shift or appearance of peak. The spectra of both the pure drug and of drug and excipient combination are compared. Since there is no shift or appearance of any peak in the spectra, it can be concluded that there is no drug and excipient interaction in the formulation of thin film of metoprolol succinate.

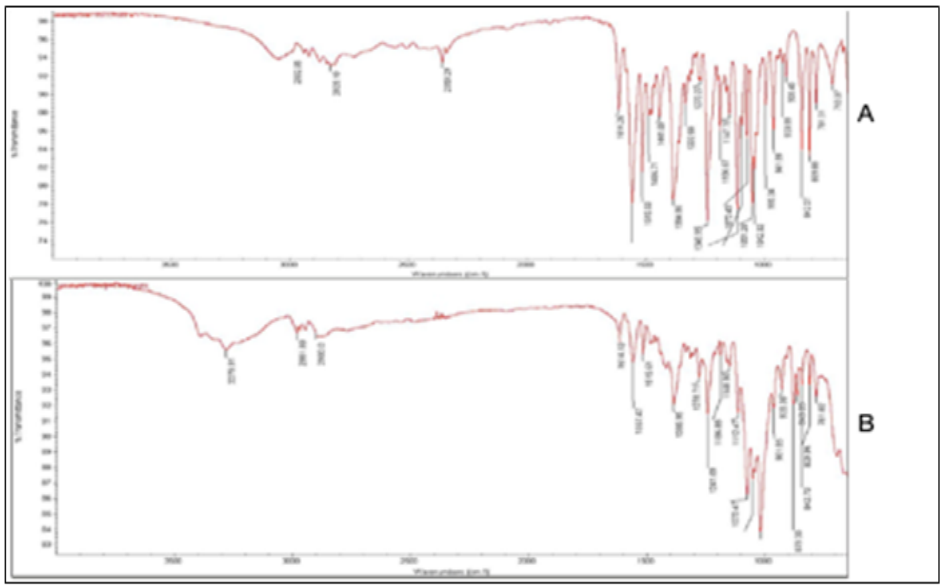

Figure 2: Infra-Red Spectra (A) metoprolol succinate (B) Combination of metoprolol succinate and Excipients

Drug-Excipient Compatibility Using DSC

The thermograms that were recorded were examined for any odd peak shifts or appearance changes. The DSC thermogram of metoprolol succinate in conjunction with excipients is shown in Fig. 3 (A)and (B) below,[10] respectively. Endothermic peak at 138°C was seen in the curve of the DSC of the pure drug, with the onset of peak at 134.42 °C and the endset peak at 153.04 °C, whereas Endothermic peak at 135.7°C and 167.10 °C was observed in the DSC curve of the combination of the drug and the excipients. The presence of polymers likely accounted for the minor change in the endothermic peak. Since the endothermic peak did not significantly move, inconsistency between the medicine and the excipient could not have occurred.

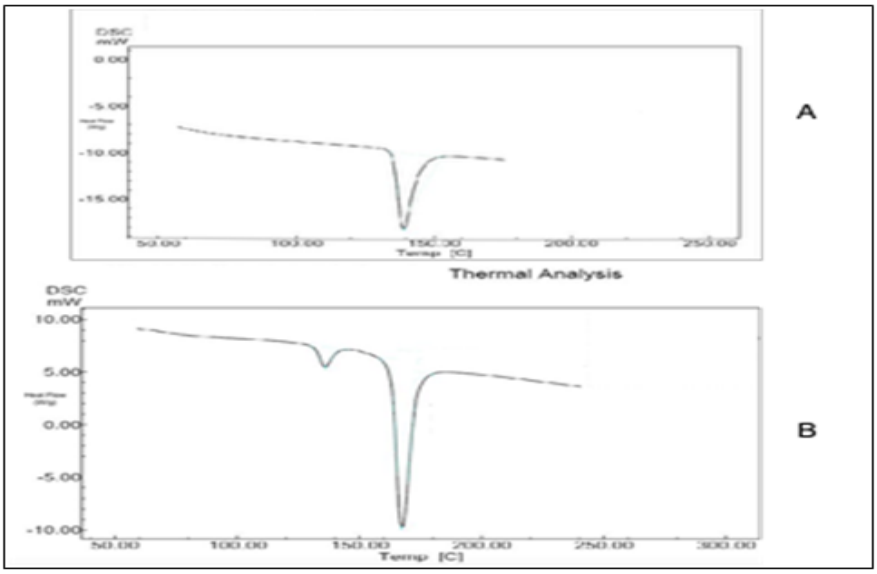

Figure 3: DSC Study (A) Metorolol succinate (B) Metoprolol succinate and Excipients

Preliminary Screening and optimization of various plasticizers, film modifier, and film forming agent.

Research was done beforehand to determine the best combination of film forming polymer, plasticizer, and sweetener concentration for making films with the desired mechanical property and dissolving characteristics.

It was discovered that HPMC E15 is a great film forming polymer that can make translucent, rigid, easily pealable films. high firmness, low stickiness, and a silky texture. Good peelable films were obtained using a 5% concentration of HPMC E3. In order to create a smooth and clear placebo film, HPMC E5 was used. As can be seen in table 2, HPMC E5 concentrations lower than 3% did not produce films, whereas concentrations of 5% produced readily peelable films.

The results of feasibility trials indicated that HPMC E15 with plasticizer PEG400 produced the finest films. The table 2 below shows the results of adding honey as a film modifying agent and lowering the PEG 400 concentration in order to create less flexible films. The films were discovered to become stiff when treated with honey, allowing for clean removal with little damage.

Table 2: Preliminary Trial Screening for Film with Different Polymer

Batch	Film forming polymer	Plasticizer	Film properties	Tachyness	Folding endurance	DT (s)
FDF1	HPMC E15 (3%)	Glycerin (10%)	Stiff	Very Sticky	343±2.61	100±1.51
FDF2	HPMC E15 (4%)	Glycerin (10%)	Stiff	Very Sticky	343±2.61	166±2.6
FDF3	HPMC E15 (3%)	PEG 400(10%)	Stiff	Non Sticky	379±2.5	103±4.5
FDF4	HPMC E15 (4%)	(10%)	Stiff	Non Sticky	391±1.01	170±1.05
FDF5	HPMC E3 (1%)	PEG 400(10%)	**No result**	**No result**	Film not Prepared	Film not Prepared
FDF6	HPMC E3 (2%)	PEG 400(10%)	**No result**	**No result**	Film not Prepared	Film not Prepared
FDF7	HPMC E3 (3%)	PEG 400(10%)	Thin	**No result**	257±4.5	140±4.5
FDF8	HPMC E3 (4%)	PEG 400(10%)	Thin	Non Sticky	323±3.6	152±1.05
FDF9	HPMC E3 (5%)	PEG 400(10%)	Stiff	Non Sticky	390±4.5	160±1.05
FDF10	HPMC E5 (1%)	PEG 400(10%)	**No result**	**No result**	Film not Prepared	Film not Prepared
FDF11	HPMC E5 (2%)	PEG 400(10%)	**No result**	**No result**	Film not Prepared	Film not Prepared
FDF12	HPMC E5 (3%)	PEG 400(10%)	Very Thin	**No result**	234±3.5	134±2.5
FDF13	HPMC E5 (4%)	PEG 400(10%)	Thin	Non Sticky	456±2.6	150±1.05
FDF14	HPMC E5 (5%)	PEG 400(10%)	Stiff & Good	Non Sticky	565±1.5	160±1.05
FDF15	HPMCE15 (3%)	PEG 400(1%) + Honey(2%)	Stiff & Good	Non Sticky	643±2.61	75±1.51
FDF16	HPMCE15 (4%)	PEG 400(1%) + Honey(4%)	Stiff & Good	Non Sticky	844±1.01	120±1.05

Evaluation of Fast Dissolving thin film of metoprolol succinate

The experimental design arrangement in, the metoprolol succinate thin film used is described in Table 3.The results of evaluation of nine formulations of metoprolol succinate thin film prepared using design of experiment are shown in figure 4 and table 4. .The weight of the films was found to be in the range of 41.24±2.5mg to 80.00±1.01 mg. The thickness of film was found to be between 0.093±0.006 mm to 0.139±0.005mm. The folding endurance of the film was found to be in the range of 712±2.5 to 945±2.01.The disintegration time was found to be between 58.0 ±1.01 s and 109.0 ±2.41. The tensile strength was found to be between 73.55 ± 1.37 g/cm2 to 112.04 ± 2.45 g/cm2. The film's thickness, folding durability, and disintegration time all improve with a higher polymer content. The development of strong hydrogen bonds between polymer and plasticizer may be responsible for imparting flexibility to survive rupture, as shown by the combination of maximum tensile strength and maximum folding endurance.The drug release at 9 min was found to be between 61.02 ± 0.56 % to 105.32 ± 1.55 %. The data for in vitro release of metoprolol succinate from the formulation is given in Table 4 and compared in Fig 5.

Table 3: Composition of 3^2 Factorial Fast Dissolving thin film of metoprolol succinate.

Name of Material	MSF1	MSF2	MF3	MSF4	MSF5	MSF6	MSF7	MSF8	MSF9
Metorolol succinate(mg)	100	100	100	100	100	100	100	100	100
HPMC E15 (%)	3.5	3.75	4	3.5	3.75	4	3.5	3.75	4
Ethanol(ml)	5	5	5	5	5	5	5	5	5
Honey (%)	2	2	2	3	3	3	4	4	4
PEG400(%)	1	1	1	1	1	1	1	1	1
Methyl Paraben(%)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Ascorbic Acid	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Citric Acid (%)	1	1	1	1	1	1	1	1	1
Aspartame (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Propylene Glycol(%)	1	1	1	1	1	1	1	1	1
Water qs (ml)	10	10	10	10	10	10	10	10	10

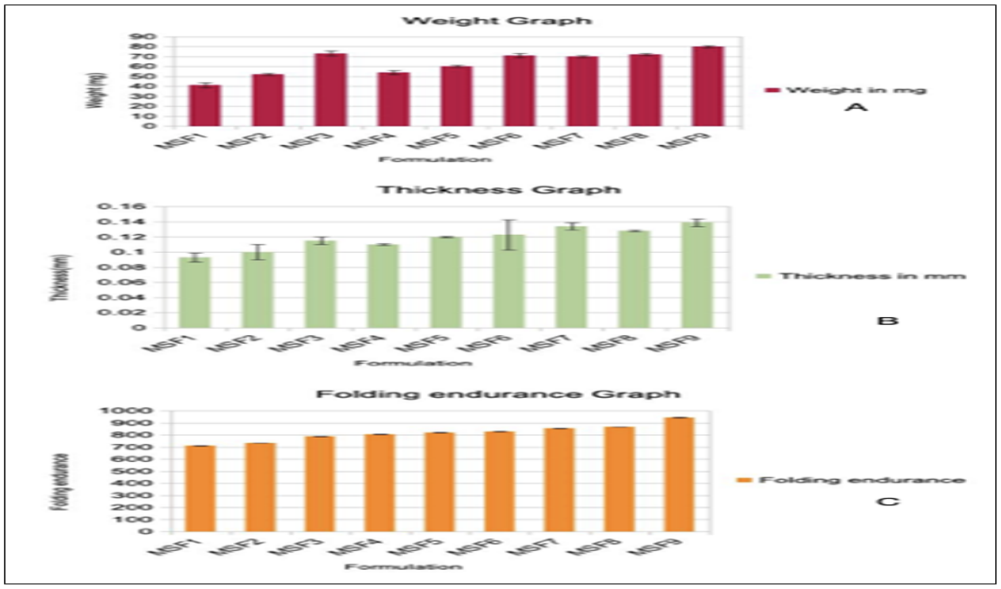

Figure 4: Bar graph of (A) weight of thin film (B) thickness of thin film (C) folding endurance of thin film

Table 4: Physicochemical Evaluation of metoprolol succinate thin film

Formulation	Disintegration (s)	Tensile Strength(g/cm^2)	Drug Release
MSF1	58.0 ±1.01	73.55 ± 1.37	105.32 ± 1.55
MSF2	64.0 ±1.21	80.65 ± 2.17	102.32 ± 1.35
MSF3	71.0 ±1.51	90.65 ± 1.30	90.24± 2.55
MSF4	69.0 ±2.01	84.65 ± 2.13	89.12± 1.24
MSF5	75.0 ±2.01	93.65 ± 2.51	79.02 ± 1.56
MSF6	86.12 ±1.31	99 ± 1.37	73.02 ± 1.18
MSF7	90.02 ±2.51	94 ± 2.13	82.02 ± 2.54
MSF8	92.0 ±2.11	102.12 ± 1.12	79.02 ± 1.58
MSF9	109.0 ±2.41	112.04 ± 2.45	61.02 ± 0.56

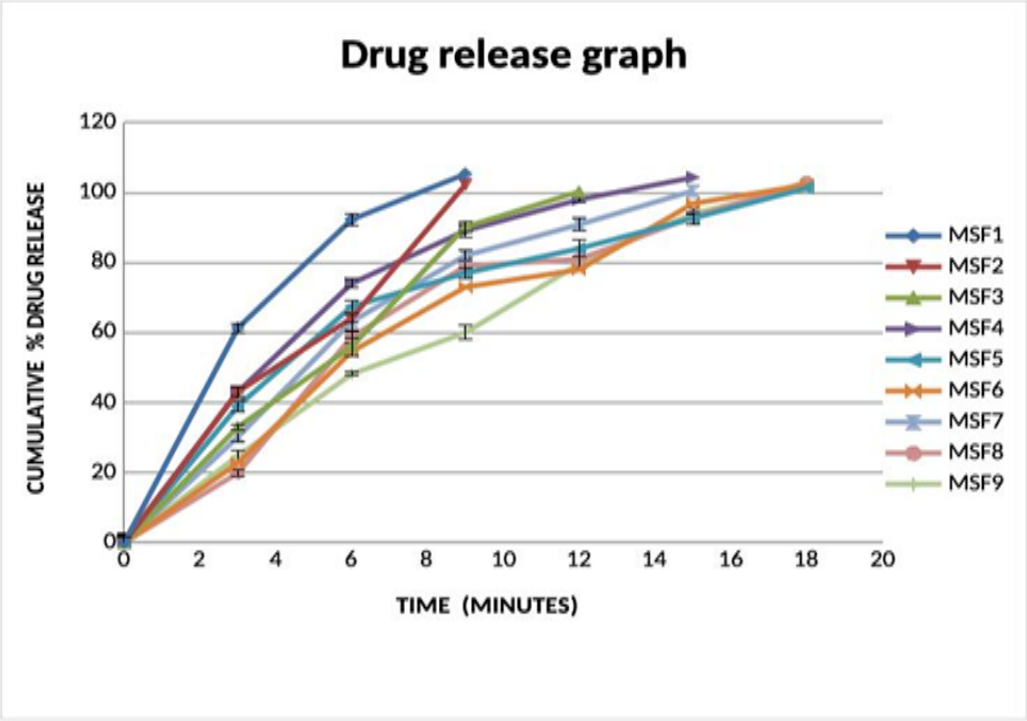

Figure 5: Comparative in- vitro release of fast dissolving metoprolol succinate film

ANOVA Analysis

The impact of independent factors on dependent variables may be understood via the mathematical connections created by multivariate linear regression analysis. The reaction is enhanced when the coefficient is positive, and it is suppressed when the coefficient is negative. According to a Design Expert's recommendation, we used ANOVA with a 5% significance level to estimate the model's efficacy. If the probability of an error is less than 0.05, the model is deemed to be significant. Table 5 displays the results of an ANOVA.

Table 5: ANOVA Analysis for 3^2 experimental design

Outputs	**Disintegration Time.**		**Tensile Strength.**		**Drug Release**	
	F value	**P-value Prob > F**	**F value**	**P-value Prob > F**	**F value**	**P-value Prob > F**
HPMC E15	43.05	0.0006	794.29	< 0.0001	16.50	0.0066
Honey	138.96	< 0.0001	1429.11	< 0.0001	16.50	0.0012
R^2	0.9671		0.9973		0.8912	
Adjusted R^2	0.9564		0.9963		0.8540	
Predicted R^2	0.9214		0.9933		0.8012	

The reduced model was created by leaving out the factors that were found to be statistically unimportant ($p>0.05$). Below, we provide the condensed models for each answer:

Disintegration Time (Y1) = 81.14 + 9.0 X1+16.16 X2

Tensile Strength Y2 = 93.71+ 8.00X1+10.69X2

% Cumulative drug release (%CDR) Y3 = 85.78-8.92X1 -12.42X2

The disintegration period (Y1) of the film lengthens as the concentration of HPMC E15 and honey increases, according to the response surface plot in Figure 6. Additionally, it was shown that factor honey & HPMCE15 had a bigger impact on disintegration, were discovered to be important variables and to have an agonistic effect on the disintegration time.

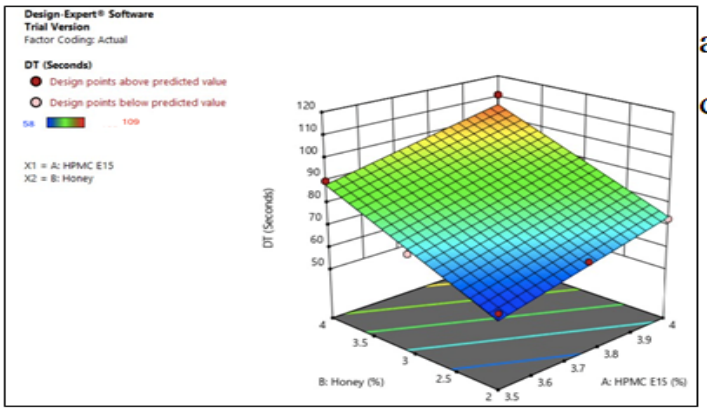

Figure 6: Response Surface Plot for Response Y1 Disintegration Time

Response surface plot Figure 7 revealed that a rise in HPMC E15 and honey concentrations improved the film's tensile strength. The mechanical strength of the cast films was not impacted by any interaction effect or second-order interaction. Possible explanation: PEG chain penetration into HPMC E5 causes crosslinking and mechanical strength. Honey and HPMCE15 were identified as agonistic factors that contributed significantly to the tensile strength.

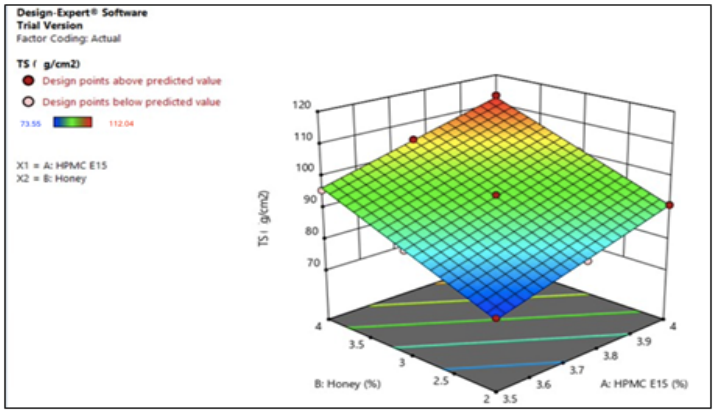

Figure 7: Response Surface Plot for Response Y2 Tensile Strength

Percent of medication release According to the response surface plot, decreasing drug release from the film was seen when the concentrations of HPMC E15 and honey were increased. Fig. 8. Honey and HPMC E15 are both significant components that are counteracting the drug's release, as shown by their estimated coefficients having negative values of -8.90 and -12.52, respectively.

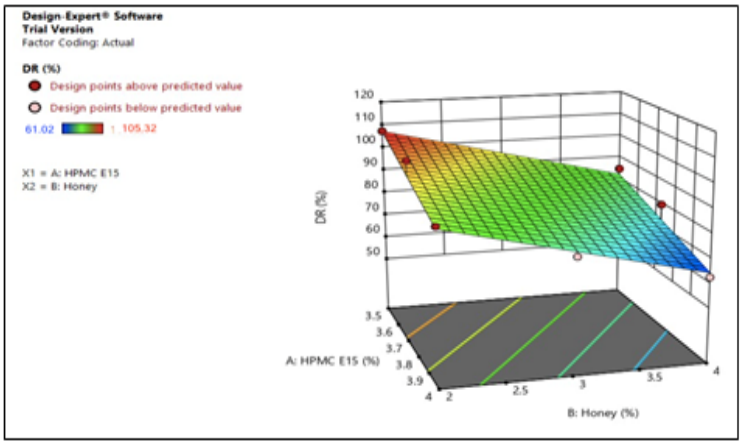

Figure 8: Response Surface Plot for Response Y3 Drug Release in 9 min

Goals for Optimization

The goals considered for optimization of Fast dissolving metoprolol succinate thin film were to reduce the disintegration time and maximize the drug release of the films. The software provided solutions out of which one solution that gave desirability and it was formula of batch MSF1. So batch MSF1 was considered as the best formulation that would give minimum disintegration time and maximum drug release.

Microscopy of the Optimized Formulation.

Fast dissolving metoprolol succinate thin film 2cm X 2cm were placed under the Scanning Electron Microscope to view the surface topography of the film is given in Figure 9 and the films surface topography was found to be smooth and satisfactory.

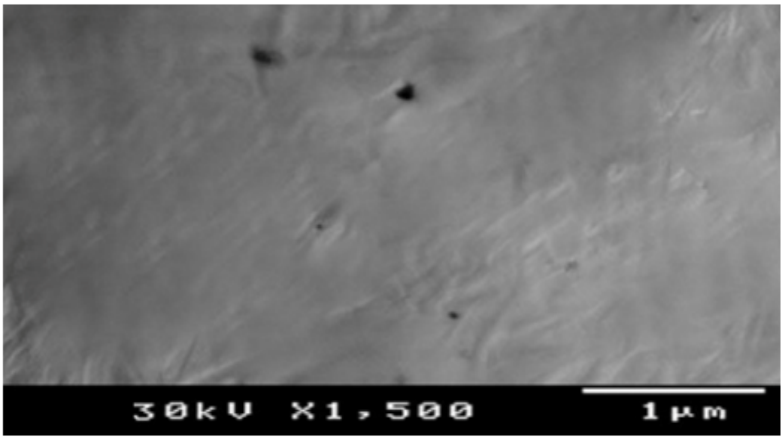

Figure 9: Microscopy of the Optimized Formulation.

Stability Study

The stability study for Fast dissolving metoprolol succinate thin film was done at room temperature and ambient humidity conditions for 90 days for the optimized batch MSF1. The results of the stability studies are as given below in Table 6: The results of the stability studies showed that there is no any interaction; no degradation and formulation were stable.

Table 6: Stability Results of Optimized Formulation MSF1

Evaluation parameters	30 days	60 days	90days
Weight(mg)	41.24±2.5	41.02±2.5	41.02±2.5
Thickness (mm)	0.093±0.006	0.093±0.006	0.093±0.006
Folding endurance	712±2.5	715±2.5	717±2.5
In vitro disintegration time (s)	58.0 ±1.01	58.0 ±1.01	59.0 ±2.01
% Drug release at 9 min	105.32 ± 1.55	105.32 ± 1.55	104.32 ± 1.32

Conclusion

As a result of combining HPMC E15 and PEG 400 at the concentrations of 4% w/v and 1% w/v with the combination of honey (2%), the resulting MSF exhibited increased dissolving and adequate flavour masking. PEG 400, a hydrophilic polymer, may have facilitated better medication solubility. The e-tongue sensor verified that the flavour was well masked. The metoprolol succinate film has the desired rapid disintegration leading to rapid therapeutic action, and its mechanical strength is sufficient enough that it can be used as an alternative to the commercially available immediate-release tablets for controlling hypertension. Metoprolol Succinate films with a rapid onset of action were shown to be effective in the treatment of hypertension.

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