Chapter 8

Development and evaluation of fast dissolving film

8.1 INTRODUCTION

Buccal drug delivery has become an important route of drug administration. Various bioadhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches, and more recently films[1-5]. Recently, the use of polymeric films for buccal delivery has been investigated by Peh and Wong[5]. Here, an attempt was made to prepare the fast dissolving film of salbutamol sulphate or ondansetron hydrochloride or lamotrigine containing polyvinyl alcohol for sublingual route.

The sublingual mucosa is relatively permeable due to thin membrane and large veins. It gives rapid absorption and instant bioavailability of drugs due to high blood flow[6-8]. As the fast dissolving film is taken through sublingual route, rapid absorption of drug is possible which finally leads to quick onset of drug action.

8.2 DEVELOPMENT AND EVALUATION OF FAST DISSOLVING SUBLINGUAL FILM OF SALBUTAMOL SULPHATE

The polluted environment and the raising levels of nitrogen dioxide, sulphur dioxide, particulates in the air and fast life of the common man has increased the diseases like asthma[9]. Salbutamol sulphate, (RS)-1-(4-hydroxy-3-hydroxy-methyl phenyl)-2-(tert-butylamino) ethanol sulphate, a β-receptor agonist is most widely used as a sympathomimetic for the treatment of acute as well as chronic asthma. Generally, it is given through inhalation route but is also effective after oral administration[10].

Factorial experimental design, multiple regression analysis, contour plots and desirability function have been proved to be a useful approach for the optimization of the formulations. It was found that amount of polyvinyl alcohol (X_1), amount of glycerol (X_2) and amount of mannitol (X_3) had significantly influence on the mechanical properties of film and % drug release.

Gohel and Panchal[11] has recently proposed a "similarity factor S_d" for the comparison of dissolution profiles which is more simple and flexible than similarity factor f_2 because

data can be expressed either as the amount of drug dissolved or as the percentage drug dissolved. Another advantage is that, unlike the similarity factor f_2, linear interpolation can be used to accurately express the results[12]. The dissolution profiles of optimized batch in distilled water and simulated saliva (pH 6.8) or simulated gastric fluid (pH 1.2) were compared using "similarity factor S_d".

The objective of this work was to formulate and optimize a fast dissolving film of salbutamol sulphate which can be used for the acute and chronic treatment of asthma. Experimental design and desirability function were applied for the optimization of film. As part of the optimization process, the main effect, interaction effects and quadratic effects of amount of polyvinyl alcohol, amount of glycerol, amount of mannitol on % drug release and mechanical properties of film were investigated.

8.2.1 Experimentals

8.2.1.1 *Materials*

Salbutamol sulphate I. P. and strawberry flavor were gift from Relax pharmaceuticals Ltd., Baroda, India. Polyvinyl alcohol (molecular weight-14,000), mannitol (A.R.) and glycerol (A.R.) were purchased from S. D. Fine Chem. Ltd., Mumbai, India. All other chemicals used were of analytical grade and were used without further purification. Deionized double distilled water was used throughout the study.

8.2.1.2 *Preparation of film*

Fast dissolving film of polyvinyl alcohol was prepared by solvent casting method (6). Aqueous solution-I was prepared by dissolving the polymer and glycerol in specific proportion in distilled water and it was allowed to stir for 4 hours and kept for 1 hour to remove all the air bubbles entrapped. Aqueous solution-II was prepared by dissolving the salbutamol sulphate, mannitol and strawberry flavor in specific proportion in distilled water. Both aqueous solution-I and II were mixed and stirred for 1 hour. Then the mixture solution was casted onto a plastic petridish and it was dried in the oven at 50 °C

for 24 hour. The film was carefully removed from the petridish, checked for any imperfections and cut according to the size required for testing (square film: 2 cm length, 2 cm width). The samples were stored in a glass container maintained at temperature of 30 ± 1 °C and relative humidity 60 ± 5 % until further analysis. Thickness of each sample was measured using a thickness tester (Model 110, 0.01mm capacity, Mitutoyo Manufacturing Corporation Limited, Japan) at five locations (center and four corners) and the mean thickness was calculated. Samples with air bubbles, nick or tear and having mean thickness variations of greater than 5 % were excluded from analysis.

8.2.1.3 *Factorial design and the desirability function*

To study all the possible combinations of all factors at all levels, a three factor, three levels full factorial design was constructed and were conducted in a fully randomized order (13). The dependent variables measured were tensile strength, % elongation, elastic modulus and % drug release at 2 minutes in distilled water (Y_{2min}). The composition and responses of the 3^3 design is shown in Table 1. Three independent factors, the concentration of polyvinyl alcohol (X_1), the concentration of glycerol (X_2) and the concentration of mannitol (X_3) were set at three different levels. High and low levels of each factor were coded as 1 and -1, respectively, and the mean value as zero. The range of a factor must be chosen in order to adequately measure its effects on the response variables. This design was selected as it provides sufficient degrees of freedom to resolve the main effects as well as the factor interactions. Stepwise regression analysis was used to find out the control factors that affects significantly on response variables.

Finally the desirability function was used for the optimization of the formulation. During optimization of formulations, the responses have to be combined in order to produce a product of desired characteristics. The application of the desirability function combines all the responses in one measurement and gives the possibility to predict the optimum levels for the independent variables[13].

The combination of the responses in one desirability function requires the calculation of the individual functions. A suitable film should have a moderate tensile strength, high % elongation, low elastic modulus and high % drug release. The individual desirability for each response was calculated using the following methods[13,14].

In this particular study, there were not specific requirements for the tensile strength of the optimum formulation. Therefore the range of the values of the produced formulations was selected. As moderate tensile strength was desired, the formulations that have its value within the range of 6.0-8.0 have a desirability of 1, while the formulations that have values out of this range have a desirability of 0. These can be described by the following equations:

$$d_1 = 0 \quad \text{for } Y_i < Y_{max}$$
$$d_1 = 1 \quad \text{for } Y_{min} < Y_i < Y_{max} \qquad (1)$$
$$d_1 = 0 \quad \text{for } Y_i > Y_{max}$$

Where, d_1 is the individual desirability of the tensile strength.

The % elongation and % drug release values were maximized in the optimization procedure, as suitable film should have high % elongation and high % drug release. The desirability functions of these responses were calculated using the following equation:

$$d_2 \text{ or } d_3 = \frac{Y_i - Y_{min}}{Y_{target} - Y_{min}} \quad \text{for } Y_i < Y_{target}$$
$$d_2 \text{ or } d_3 = 1 \quad \text{for } Y_i > Y_{target} \qquad (2)$$

Where, d_2 is the individual desirability of % elongation and d_3 is the individual desirability of % drug release at 2 minutes.

The values of Y_{target} and Y_{min} for % elongation are 590 and 210 and the values of Y_{target} and Y_{min} for percentage drug release are 97.05 and 65.11 and Y_i is the experimental result.

The elastic modulus value was minimized in the optimization procedure, as suitable film should have low elastic modulus. The desirability functions of this response were calculated using the following equation:

$$d_4 = \frac{Y_{max} - Y_i}{Y_{max} - Y_{target}} \quad \text{for } Y_i > Y_{target}$$

$$d_4 = 1 \text{ for } Y_i < Y_{target} \qquad (3)$$

Where, d_4 is the individual desirability of elastic modulus. The Y_{max} and Y_{target} values are 2.65 and 1.08 and Y_i is the experimental result.

The overall desirability values were calculated from the individual values by using the following equation:

$$D = (d_1 d_2 d_3 d_4)^{1/4} \qquad (4)$$

8.2.1.4 ***Measurement of mechanical properties***

Mechanical properties of film were evaluated using Instron Universal Testing Instrument (Model 1121, Instron Limited, Japan) equipment with a 2 kilogram load cell. Film strips in dimension of 2 cm × 2 cm and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 5 cm. During measurement, the strips were pulled by the top clamp at a rate of 10 cm/min. The force and elongation were measured when the film broke. Results from film samples, which broke at and not between the clamps were not included in calculations. Measurements were run in three replicates for each film.

Four mechanical properties, namely, tensile strength, % elongation and elastic modulus were computed for the evaluation of the film. Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be computed from the

applied load at rupture as a mean of three measurements and the cross sectional area of fractured film as described from the following equation[5.15]:

$$\text{Tensile strength} = \frac{\text{Force at break (N)}}{\text{Initial cross sectional area of the sample (mm}^2\text{)}} \quad (5)$$

Elastic modulus is the ratio of applied stress and corresponding strain in the region of approximately linear proportion of elastic deformation on the load-displacement profile and can be calculated using the following equation[5.15]:

$$\text{Elastic modulus} = \frac{\text{Force at corresponding strain (N)}}{\text{Cross sectional area (mm}^2\text{)}} \times \frac{1}{\text{Corresponding strain}} \quad (6)$$

Percentage elongation can be obtained by the following equation:

$$\% \text{ Elongation} = \frac{\text{Increase in length}}{\text{Original length}} \times 100 \quad (7)$$

8.2.1.5 *Morphology study*

Morphology of the prepared film was observed under a scanning electron microscope (Model JSM 5610LV, Jeol, Japan). The samples were attached to the slab surfaces with double-sided adhesive tapes and the scanning electron photomicrograph was taken at 2000× magnifications

8.2.1.6 *Differential scanning calorimetry (DSC)*

DSC thermograms of pure salbutamol sulphate, drug: polyvinyl alcohol: mannitol (4: 20: 6) physical mixture and optimized film containing 4 mg salbutamol sulphate were measured using differential scanning calorimeter (Model DSC 60, Shimadzu, Japan). The

samples of 5-7 mg were accurately weighted into solid aluminum pans without seals. The measurements were obtained at a heating of 10 °C[16].

8.2.1.7 *In vitro dissolution study*

The dissolution study were conducted using three media, distilled water, simulated saliva which consisted of phosphate buffer saline solution (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4 and 8.00 g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6.8) and simulated gastric fluid[15]. Each square cut film sample (dimension: 2 cm × 2 cm) was placed in a stainless steel wire mesh with sieve opening of approximately 700 µm. The mesh containing film sample was then submerged into the dissolution media. The dissolution study was carried out using USP 25 Paddle apparatus (Model TDT-06P, Electrolab, Mumbai, India) at 37± 0.5 °C and at 50 rpm using 300 ml of deaerated distilled water or 300 ml of simulated saliva (pH 6.8) or 900 ml of simulated gastric fluid (pH 1 2) as a dissolution medium (n=3). Samples (5 ml) were withdrawn at 0, 1, 2, 3, 5, 10 and 20 minutes time intervals and were filtered through 0.45 µm whatman filter paper, diluted suitably and analysed spectrophotometrically at 276 nm (Model UV-1601 UV, Visible spectrophotometer, Shimadzu, Japan). An equal volume of fresh dissolution medium maintained at the same temperature was added after withdrawing sample to maintain the volume. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally ($r^2 > 0.99$). The dissolution test was performed in triplicate for each batch.

8.2.1.8 *Similarity factor S_d*

The similarity factor S_d is defined as

$$S_d = \frac{\sum_{t=1}^{n-1} \left| \mathrm{Log}\left((AUC_{R_t}) / (AUC_{T_t}) \right) \right|}{n-1} \qquad (8)$$

Where n is the number of data points collected during the in-vitro dissolution test and AUC_{Rt} and AUC_{Tt} are the areas under curves of the dissolution profiles of the film in simulated saliva or simulated gastric fluid and in distilled water, respectively, at time t. For the dissolution profiles in simulated saliva or simulated gastric fluid and in distilled water to be identical, the S_d value should be zero[11,12].

8.2.2 Results and Discussion

A statistical model was used in order to estimate the relationship between the response variables and the independent variables. A stepwise multivariate linear regression was performed to evaluate the observations. Before application of the design, a number of preliminary trials were conducted to determine the control factors and their levels. The factors and their levels are shown in table 8.1.

Table 8.1. Composition and responses for 3^3 factorial design (Each value indicates the mean of three replicates).

Batches	Variables			Response values				Overall desirability
	X_1	X_2	X_3	Tensile strength (N/mm^2)	% Elongation	Y_{2min}	Elastic modulus (N/mm^2)	
V_1	-1	-1	-1	6.96	257.00	89.07	2.65	0.00
V_2	-1	-1	0	5.10	210.00	93.31	2.45	0.00
V_3	-1	-1	1	4.12	282.00	97.05	1.37	0.00
V_4	-1	0	-1	6.37	383.00	86.06	1.67	0.66
V_5	-1	0	0	5.30	346.00	92.94	1.47	0.00
V_6	-1	0	1	3.73	293.00	94.22	1.27	0.00
V_7	-1	1	-1	6.37	411.00	81.01	1.57	0.65
V_8	-1	1	0	5.49	378.00	86.76	1.37	0.00
V_9	-1	1	1	4.31	289.00	91.33	1.47	0.00
V_{10}	0	-1	-1	8.53	316.00	75.27	2.65	0.00

V_{11}	0	-1	0	6.28	285.00	84.02	2.16	0.44
V_{12}	0	-1	1	5.30	247.00	87.75	2.06	0.00
V_{13}	0	0	-1	8.24	482.00	71.63	1.67	0.00
V_{14}	0	0	0	6.37	468.00	76.50	1.37	0.67
V_{15}	0	0	1	5.30	415.00	84.42	1.27	0.00
V_{16}	0	1	-1	9.02	511.00	70.08	1.77	0.00
V_{17}	0	1	0	7.35	476.00	75.11	1.57	0.62
V_{18}	0	1	1	5.79	325.00	71.13	1.77	0.00
V_{19}	1	-1	-1	7.75	520.00	66.12	1.47	0.37
V_{20}	1	-1	0	6.77	480.00	76.32	1.37	0.67
V_{21}	1	-1	1	6.37	421.00	84.57	1.47	0.71
V_{22}	1	0	-1	8.24	535.00	65.11	1.57	0.00
V_{23}	1	0	0	7.55	502.00	75.44	1.47	0.66
V_{24}	1	0	1	6.37	483.00	84.31	1.27	0.79
V_{25}	1	1	-1	8.53	590.00	65.70	1.47	0.00
V_{26}	1	1	0	7.94	576.00	77.94	1.27	0.76
V_{27}	1	1	1	5.79	566.00	80.11	1.08	0.00

	Levels		
Independent Variables	Low	Medium	High
X_1 = amount of polyvinyl alcohol (mg)	10.00	15.00	20.00
X_2 = amount of glycerol (mg)	2.00	3.00	4.00
X_3 = amount of mannitol (mg)	4.00	5.00	6.00

The statistical evaluation of the results was carried out by analysis of variance (ANOVA) using Microsoft Excel Version-2000. The ANOVA results (p value) effect of the variables on mechanical properties and % drug release of film is shown in table 8.2.

Table 8.2. ANOVA results (P value) effect of the variables on mechanical properties and % drug release of film.

Factors	Tensile strength		% Elongation		Y_{2min}		Elastic modulus	
	Coeffi-cient	P	Coeffi-cient	P	Coeffi-cient	P	Coeffi-cient	P
X_1	0.9756	<0.0001*	101.3330	<0.0001*	-7.5627	<0.0001*	-0.1583	0.0056*
X_2	0.1894	0.0587	61.3330	<0.0001*	-3.0172	0.0002*	-0.2394	0.0002*
X_3	-1.274	<0.0001*	-38.0000	0.0009*	5.8244	<0.0001*	-0.1922	0.0013*
X_1^2	-0.6278	0.0013*	26.222	0.1283	5.3083	0.0002*	-0.2694	0.0063*
X_2^2	0.1572	0.3439	-37.444	0.0359*	-0.4783	0.6724	0.2739	0.0057*
X_3^2	0.0439	0.7889	-6.444	0.6987	-1.7633	0.1318	0.0289	0.7407
X_1X_2 ...	0.1150	0.3280	-1.5000	0.8983	1.4225	0.0888	0.1309	0.0466*
X_2X_3	-0.0483	0.6771	-15.7500	0.192	-1.0941	0.1825	0.1150	0.0762
X_1X_3	0.1291	0.2738	-1.0000	0.9321	2.1333	0.0152*	0.0908	0.1538
$X_1X_2X_3$	-0.2675	0.0734	27.270	0.0677	-0.7975	0.4191	-0.1962	0.0178*
Constant	6.7748	<0.0001*	420.9250	<0.0001*	78.8177	<0.0001*	1.6081	<0.0001*
r^2	0.9529		0.9212		0.9464		0.8436	

Regression coefficients *, statistically significant (P<0.05)

The significant factors in the equations were selected using a stepwise forward and backward elimination for the calculation of regression analysis. The terms of full model having p value non significant (p>0.05) have negligible contribution in obtaining dependent variables and thus neglected[12].

The equations representing the quantitative effect of the formulation variables on the mechanical properties and % drug release are shown below:

$$\text{Tensile strength} = 6.909 + 0.976X_1 - 1.274X_3 - 0.628X_1^2$$
$$(R^2 = 0.9196; DF = 3,23; F = 87.66; P < 0.05) \quad (9)$$

$$\%\,\text{Elongation} = 434.111 + 101.333X_1 + 61.333X_2 - 38.000X_3 - 37.444X_2^2$$
$$(R^2 = 0.8797; DF = 4,22; F = 40.239; P < 0.05) \quad (10)$$

$$Y_{2\,min} = 77.323 - 7.562X_1 - 3.017X_2 + 5.824X_3 + 5.31X_1^2 - 2.133X_1X_3$$
$$(R^2 = 9175; DF = 5,21; F = 46.75; P < 0.05) \quad (11)$$

$$\text{Elastic modulus} = 1.627 - 0.158X_1 - 0.239X_2 - 0.192X_3 - 0.269X_1^2$$
$$+ 0.273X_2^2 + 0.130X_1X_2 - 0.196X_1X_2X_3$$
$$(R^2 = 0.7853; DF = 7,19; F = 9.93; P < 0.05) \quad (12)$$

Coefficients with one factor represents the effect of that particular factor while the coefficients with more than one factor and those with second order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively. Positive sign in front of the terms indicates positive effect while negative sign indicates negative effect of the factors. It can be concluded from equations that only polyvinyl alcohol showed positive effect on tensile strength while only mannitol showed positive effect on % drug release. But polyvinyl alcohol and mannitol had negative effect on % drug release and tensile strength, respectively.

Contour plots were obtained for the measured response based on the model using Sigma Plot® software. The relationship between the independent variables and the response can be further explained by using these contour plots. Figure 8.1, 8.2 and 8.3 shows the contour plots for tensile strength, % drug release at 2 minutes and over all desirability as a function of any two factors among X_1 (amount of polyvinyl alcohol), X_2 (amount of glycerol) and X_3 (amount of mannitol) while other factor is kept constant.

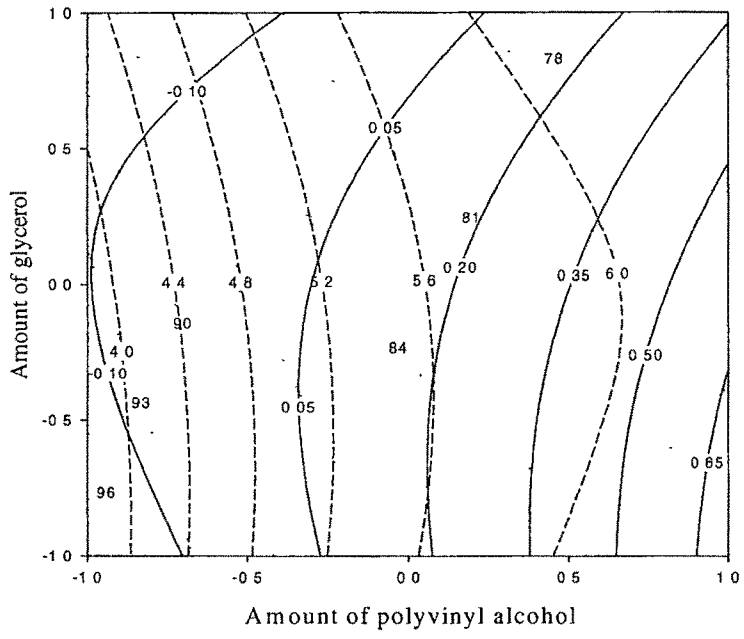


Figure 8.1. Contour plot for tensile strength (----), % drug release at 2 minutes (·····) and over all desirability (—) keeping amount of mannitol at 0 level.

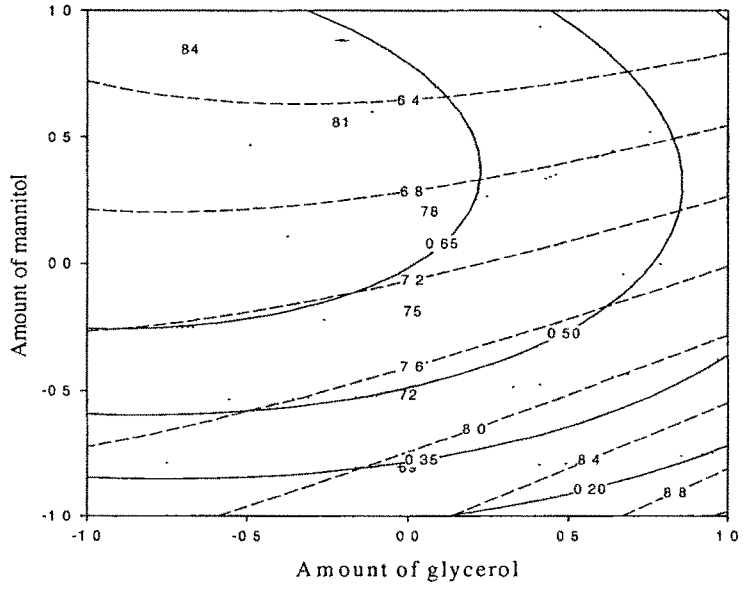


Figure 8.2. Contour plot for tensile strength (----), % drug release at 2 minutes (·····) and over all desirability (—) keeping amount of poly vinyl alcohol at 0 level.

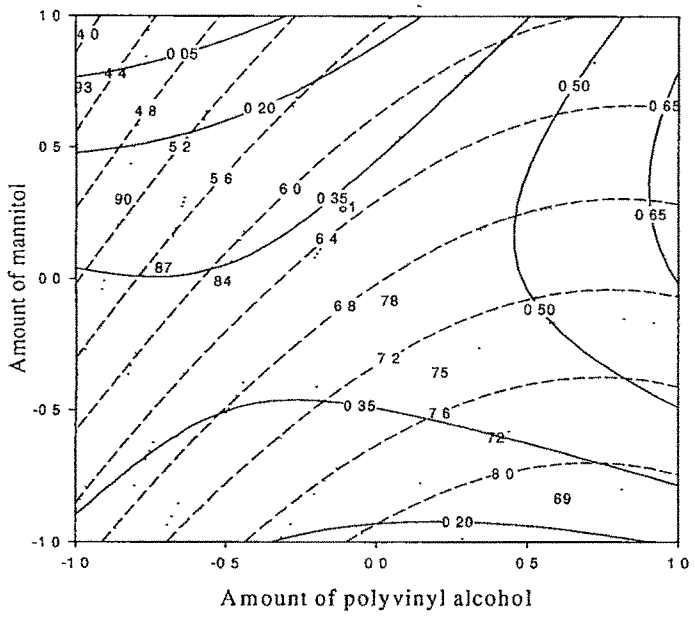


Figure 8.3. Contour plot for tensile strength (----), % drug release at 2 minutes (·····) and over all desirability (—) keeping amount of glycerol at 0 level.

The contour lines indicated that the addition of a higher amount of polyvinyl alcohol showed a higher tensile strength, lower % drug release and higher overall desirability while addition of amount of glycerol showed a lower tensile strength, lower % drug release and higher overall desirability. The reason is that more plasticizer modifies the physical properties of the polymer to improve film forming behavior[15]. Addition of higher amount of mannitol showed lower tensile strength, higher % drug release and higher overall desirability. The optimum level of mannitol was desired because more amount of mannitol made film more brittle.

In order to assess the reliability of the equations that describe the influence of the factors on the % drug release and mechanical properties of film, three additional check points experiments (batch C_1, batch C_2 and batch C_3) were conducted in triplicate using the amount of X_1, X_2 and X_3 at 0 level[14]. The experimental values and predicted values of each response are shown in table 8.3.

Table 8.3. Comparison between observed and predicted results of check point batches.

Responses	Batch ($X_1 = 0, X_2 = 0, X_3 = 0$)	Predicted values	Experimental values	Relative error (%)
Tensile strength	Batch C_1	6.914	7.146	3.355
	Batch C_2	6.914	7.036	1.764
	Batch C_3	6.914	6.828	1.243
% Elongation	Batch C_1	434.118	473.000	8.956
	Batch C_2	434.118	459.000	5.731
	Batch C_3	434.118	438.000	0.894
Y_{2min}	Batch C_1	77.321	74.823	3.230
	Batch C_2	77.321	79.039	2.221
	Batch C_3	77.321	80.263	3.804
Elastic modulus	Batch C_1	1.638	1.729	5.555
	Batch C_2	1.638	1.688	3.052
	Batch C_3	1.638	1.552	5.250

The % relative error between predicted values and experimental values of each response was calculated using the Following equation:

$$\%\,\text{Relative error} = \left(\left|\text{Predicted value} - \text{Experimental value}\right| / \text{Predicted value}\right)\times 100 \quad (13)$$

The % relative error obtained from checkpoint batch was in range of 0.89-8.95. It can be seen that in all cases there was a reasonable agreement of predicted values and experimental values, since low values of the relative error were found. This confirmed the role of a derived reduced polynomial equation, proved the validity of model and ascertained the effects of polyvinyl alcohol, glycerol and mannitol on % drug release and mechanical properties of the film.

Desirability function was utilized to find out the best batch out of 27 batches. The batch V_{24} showed the highest overall desirability of 0.785. Therefore, this batch was considered as the best batch and the values of independent variables of this batch were considered as optimum values for the preparation of film. The final formulation of film containing salbutamol sulphate is given in table 8.4.

Table 8.4. Final formulation of film containing salbutamol sulphate.

Independent variables	Optimum values (mg per film of 4 cm^2 area)
Salbutamol sulphate	4.00
Polyvinyl alcohol	20.00
Glycerol	3.00
Mannitol	6.00
Strawberry flavor	0.02

Mechanical properties of the film of final formulations of salbutamol sulphate such as tensile strength, elongation, elastic modulus were measured which is given in table 8.3.

Table 8.5. Mechanical properties of the film of salbutamol sulphate.

Tensile strength (N/mm^2)	% Elongation	Elastic Modulus (N/mm^2)
6.37 ± 0.05	421.00 ± 1.99	1.27 ± 0.02

The prepared film containing salbutamol sulphate was clear and colorless. The scanning electron photomicrographs of the film at 2000× magnifications and 4500× magnification showed smooth surface with some little pores and with out any scratches or transverse striations (figure 8.4 and figure 8.5).

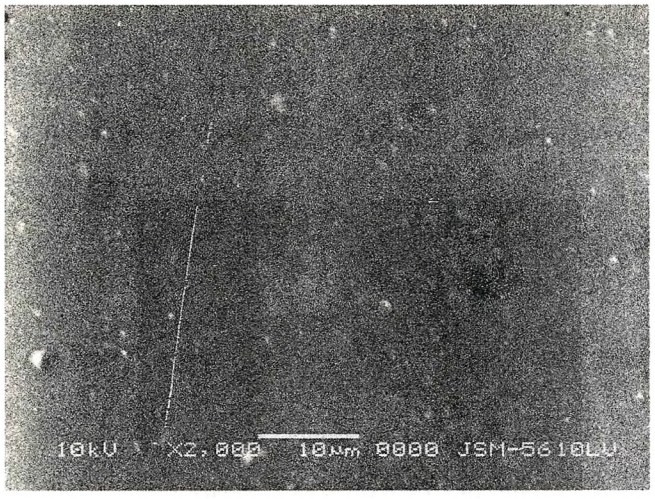


Figure 8.4. SEM micrograph of salbutamol sulphate film at 2000X magnification.

Figure 8.5. SEM micrograph of salbutamol sulphate film at 4500X magnification.

The DSC curves of pure drug, drug: polyvinyl alcohol: mannitol physical mixture and film containing salbutamol sulphate is shown in figure 8.6. Salbutamol sulphate showed an endothermic peak at 168.09 °C corresponding to its melting point. Drug: polyvinyl alcohol: mannitol (4:20:6) physical mixture showed two endothermic peaks one at 165.90 °C and another at 213.63 °C corresponding to polyvinyl alcohol and mannitol mixture. The film containing salbutamol sulphate showed two peaks one at 123.59 °C

corresponding to drug and another at 193.99 °C corresponding to excipients. The intact DSC peak of drug in the physical mixture and film indicated that the drug did not interact with the excipients used in the film.

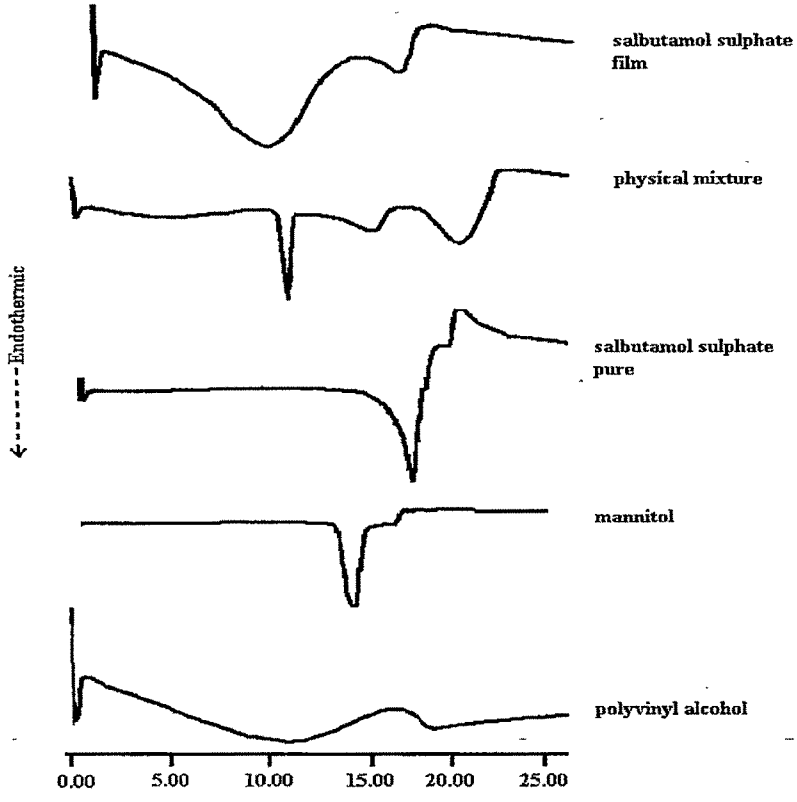


Figure 8.6. DSC of thermograms of salbutamol sulphate optimized film.

Dissolution studies of all batches were carried out using distilled water as a dissolution medium. Dissolution study of optimized batch was also carried out in simulated saliva (pH 6.8) and simulated gastric fluid (pH 1.2) as absorption of drug from the film is through sublingual mucosa, esophagus and stomach. Table 8.6 shows the % drug release of the film in different dissolution media. Figure 8.7 depicts the dissolution profiles of batch V_{24} in different media. The dissolution data of this batch in distilled water were compared with the dissolution data in simulated saliva and simulated gastric fluid using S_d statistics[12, 16-18]. An S_d value of 0.006323 for simulated saliva and 0.01421 for simulated gastric fluid indicates that the release profile of batch V_{24} in distilled water and simulated saliva and simulated gastric fluid are comparable. In simulated gastric fluid, %

drug release at 2 minute was 92.11% which revealed high efficacy of the film for rapid drug release.

Table 8.6. % Drug release of the film of salbutamol sulphate in different dissolution media (n=5).

Time (minute)	% Drug release in distilled water ± S.D. (reference)	% Drug release in simulated saliva ± S.D. (test)	% Drug release in simulated gastric fluid ± S.D.
0	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00
0.5	36.78 ± 0.07	45.93 ± 0.63	30.62 ± 0.05
1	78.54 ± 0.105	63.96 ± 0.38	58.9 ± 0.41
2	89.63 ± 0.36	92.84 ± 0.44	93.01 ± 1.12
3	97.75 ± 0.53	97.32 ± 0.07	95.12 ± 0.83
5	98.37 ± 0.66	99.74 ± 0.52	95.4 ± 0.36
10	99.65 ± 0.74	99.12 ± 0.84	97.1 ± 0.68
20	99.88 ± 1.02	99.32 ± 0.98	99.84 ± 0.74

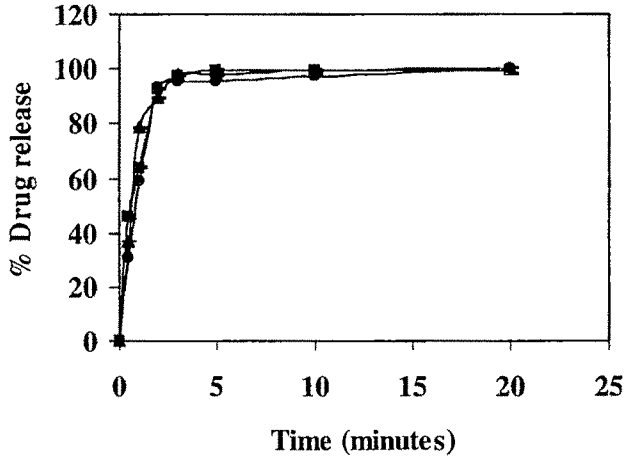


Figure 8.7. Comparative dissolution profiles of salbutamol sulphate film in distilled water (▲), simulated saliva (pH 6.8) (■) and simulated gastric fluid (pH 1.2) (●).

Figure 8.8 shows the dissolution of the film in distilled water in beaker at different time interval. It showed that the film was completely dissolved within 2 minutes in distilled water.

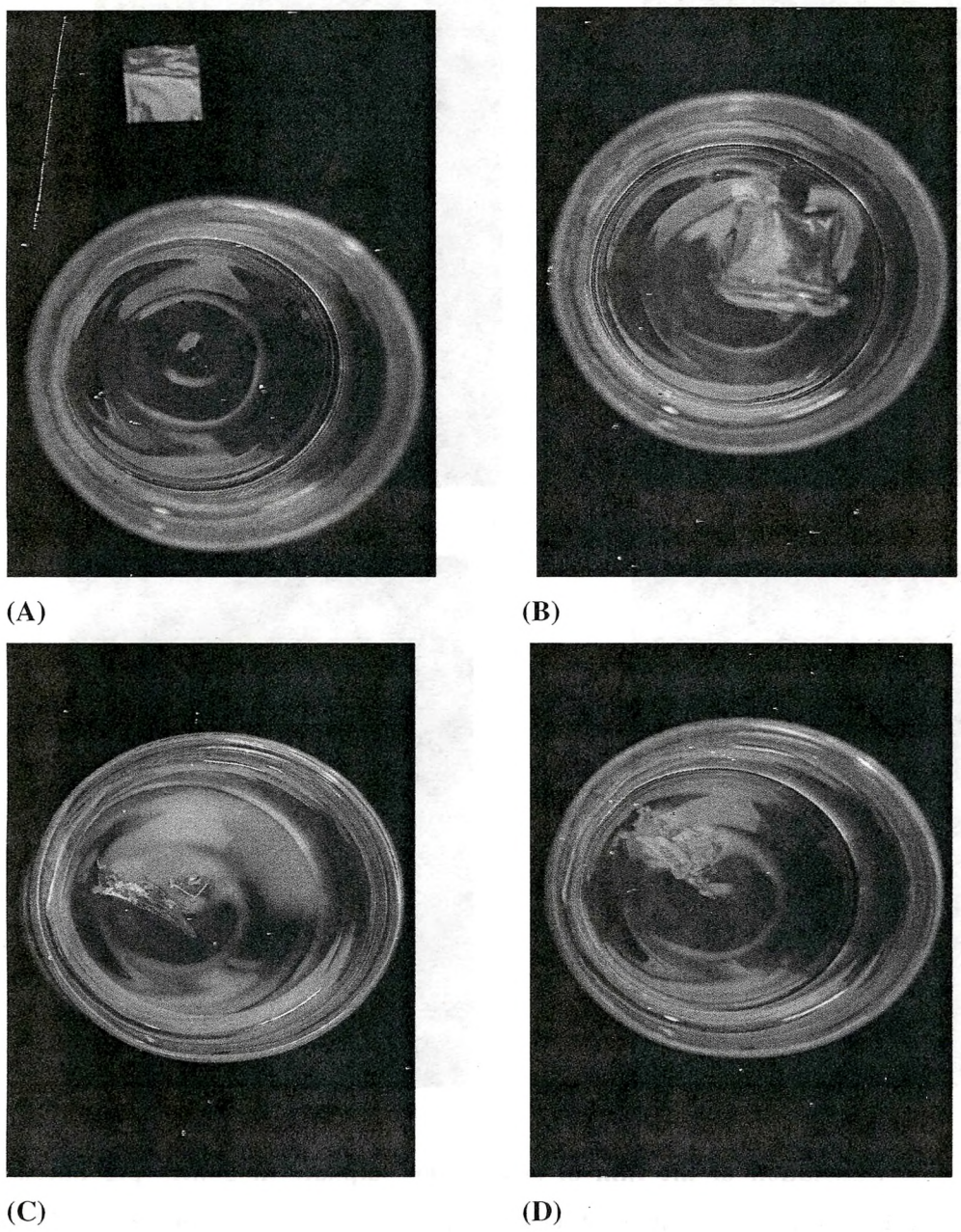
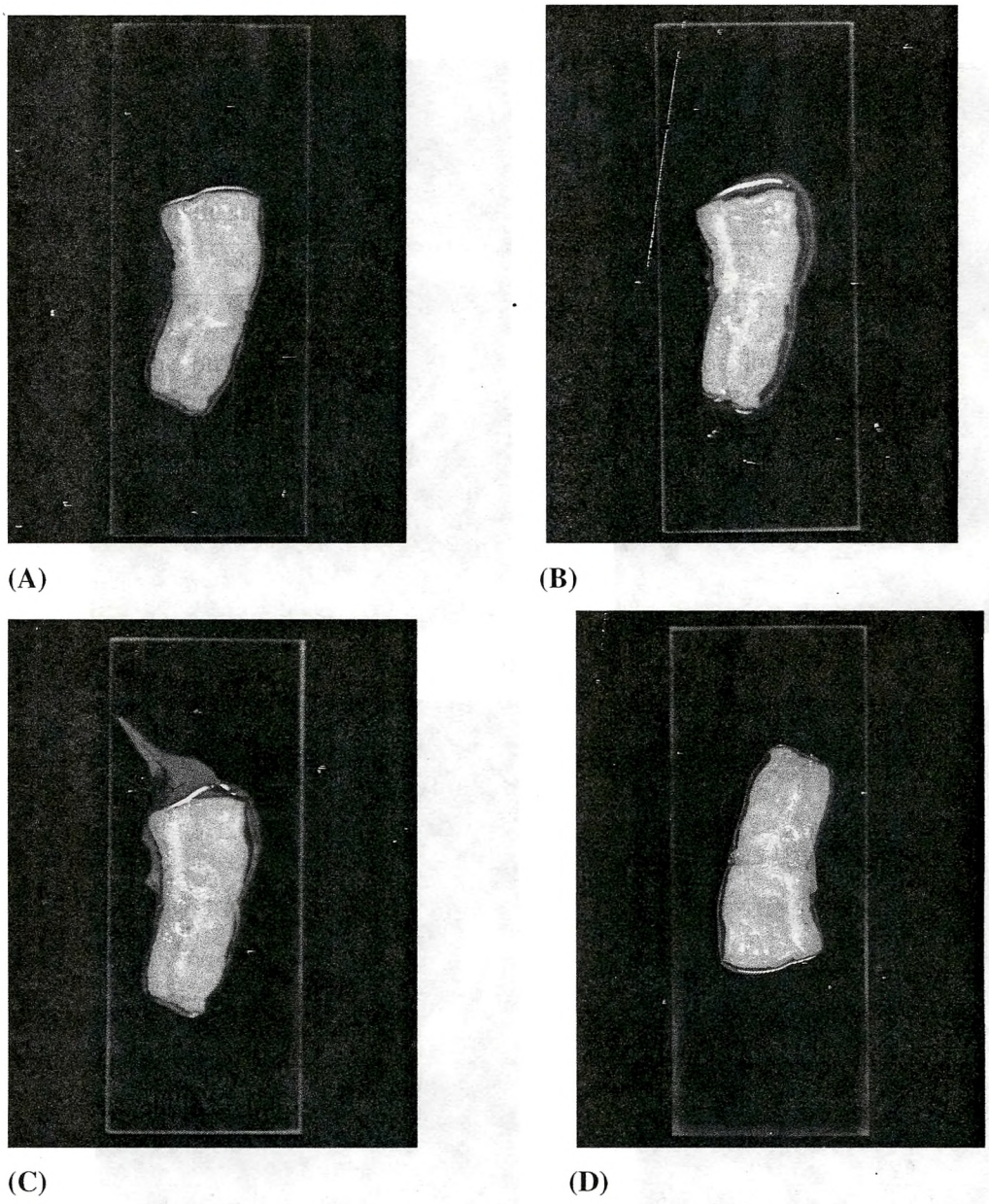


Figure 8.8. Dissolution of the film of salbutamol sulphate in distilled water in beaker (A) film outside the beaker, (B) film in distilled water (C) film in distilled water after 30 seconds, (D) film distilled water after 60 seconds.

Figure 8.9 shows the dissolution of the film in guinea pig buccal mucosa. The results showed that the film was completely dissolved within 2 minutes in guinea pig buccal mucosa.



(A) **(B)**

(C) **(D)**

Figure 8.9. Dissolution of the film of salbutamol sulphate in guinea pig buccal mucosa (A) buccal mucosa without film (B) film put over the buccal mucosa (C) film over the buccal mucosa after 30 seconds, (D) film over the buccal mucosa after 60 seconds.

8.2.3 Conclusions

The fast dissolving film of salbutamol sulphate obtained by solvent casting method showed acceptable mechanical characteristics and satisfactory % drug release. The prepared film was transparent with smooth surface without any interactions between drug and polymer. The multiple regression analysis of the results led to equations that describe adequately the influence of the selected variables on the responses under study. The desirability function resulted to the optimum values of the factors at which the produced film showed fast drug release and suitable mechanical properties. The high % drug release of the film in simulated saliva and simulated gastric fluid indicated that it could be helpful for the treatment of acute and chronic asthma where quick bioavailability of the drug is desired.

8.3 DEVELOPMENT AND EVALUATION OF FAST DISSOLVING SUBLINGUAL FILM OF ONDANSETRON HYDROCHLORIDE

8.3.1 Experimentals

8.3.1.1 *Materials*

Ondansetron hydrochloride, aspartame and strawberry flavor were gift from Skymax Laboratories, Rajkot, India. Polyvinyl alcohol (molecular weight-14,000), mannitol (A.R.) and glycerol (A.R.) were purchased from S. D. Fine Chem. Ltd., Mumbai, India. All other chemicals used were of analytical grade and were used without further purification. Deionized double distilled water was used throughout the study.

8.3.1.2 *Preparation of film of ondansetron hydrochloride*

The fast dissolving sublingual film of ondansetron hydrochloride was prepared according to the same procedure of salbutamol sulphate final formulation with slight variation of addition of aspartame. Aqueous solution-I was prepared by dissolving the polymer and glycerol in specific proportion in distilled water and it was allowed to stir for 4 hours and

kept for 1 hour to remove all the air bubbles entrapped. Aqueous solution-II was prepared by dissolving the ondansetron hydrochloride, mannitol, aspartame and strawberry flavor in specific proportion in distilled water. Both aqueous solution-I and II were mixed and stirred for 1 hour. Same as that of preparation of salbutamol sulphate film. The final formulation of the film of ondansetron hydrochloride is given in table 8.7.

Table 8.7. Final formulation of film containing ondansetron hydrochloride.

Independent variables	**Optimum values (mg per film of 4 cm^2 area)**
Ondansetron hydrochloride	8.00
Polyvinyl alcohol	30.00
Glycerol	4.50
Mannitol	7.00
Strawberry flavor	0.02
Aspartame	0.05

8.3.1.3 *Mechanical properties*

Mechanical properties of the film such as tensile strength, elongation, elastic modulus were measured same as that of salbutamol sulphate film. Scanning electron microscopy and differential scanning calorimetry study of the film were carried out in same manner as that of sabutamol sulphate.

8.3.1.4 *In vitro dissolution study*

The dissolution studies were conducted similarly as that of salbutamol sulphate film with change in the analysis by measuring absorbance spectrophotometrically at 249 nm. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally ($r^2 > 0.98$). The dissolution test was performed in triplicate.

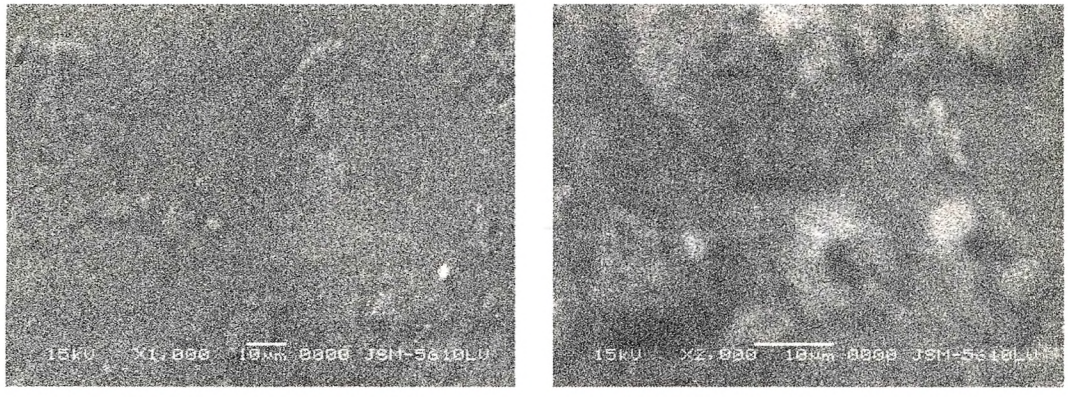
8.3.2 Results and Discussion

The mechanical properties of film of ondansetron hydrochloride such as tensile strength, % elongation and elastic modulus is given in table 8.8.

Table 8.8. Mechanical properties of the film of ondansetron hydrochloride.

Tensile strength (N/mm^2)	% Elongation	Elastic Modulus (N/mm^2)
8.22 ± 0.06	561.00 ± 2.87	0.95 ± 0.01

The prepared film containing ondansetron hydrochloride was clear and colorless. The scanning electron photomicrograph of the film at 1000× magnifications and 2000× magnifications showed smooth surface with some little pores and with out any scratches or transverse striations (figure 8.10).



(A) **(B)**

Figure 8.10. SEM micrographs of ondansetron hydrochloride film at (A) 1000X (B) 2000X magnification.

The DSC curves of pure drug, drug: polyvinyl alcohol: mannitol physical mixture and film containing ondansetron hydrochloride is shown in figure 8.11. Ondansetron hydrochloride showed an endothermic peak at 180.00 °C corresponding to its melting

point. Drug: polyvinyl alcohol: mannitol (8:20:6) physical mixture showed three endothermic peaks, at 104.36 °C and 168.31°C corresponding excipients and another at 186.64 °C corresponding to drug. The film containing ondansetron hydrocholide showed three peaks, at 100.44°C and 151.56 °C corresponding to excipients and another at 187.94 °C corresponding to drug. The intact DSC peak of drug in the physical mixture and film indicated that the drug did not interact with the excipients used in the film.

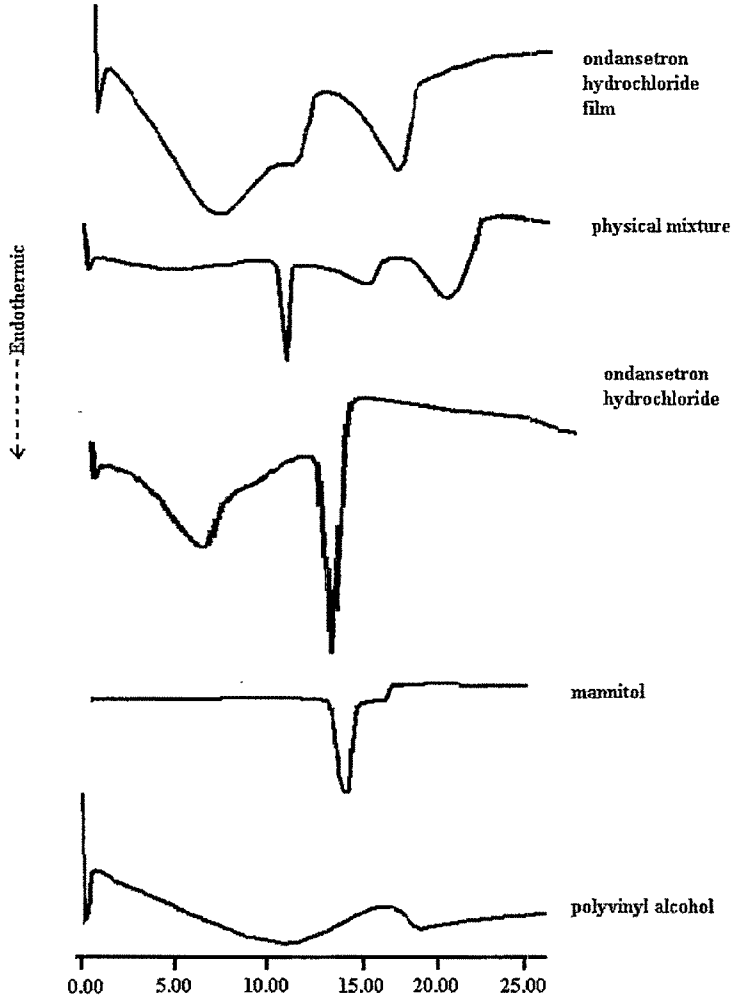


Figure 8.11. DSC of thermograms ondansetron hydrochloride film.

Dissolution studies of film was carried out using distilled water, simulated saliva (pH 6.8) and simulated gastric fluid (pH 1.2) as absorption of drug from the film is through sublingual mucosa, esophagus and stomach. Table 8.9 shows the % drug release of the

film in different dissolution media. Figure 8.12 depicts the dissolution profiles of the film of ondansetron hydrochloride in different media. The dissolution data of film in distilled water were compared with the dissolution data in simulated saliva and simulated gastric fluid using S_d statistics. An S_d value of 0.005441 for simulated saliva and 0.01795 for simulated gastric fluid indicates that the release profile of film in distilled water and simulated saliva and simulated gastric fluid are comparable. In simulated gastric fluid, % drug release at 2 minute was 89.11% which revealed high efficacy of the film for rapid drug release.

Table 8.9. % Drug release of the film of ondansetron hydrochloride in different dissolution media (n=5).

Time (minute)	% Drug release in distilled water ± S.D. (reference)	% Drug release in simulated saliva ± S.D. (test)	% Drug release in simulated gastric fluid ± S.D.
0	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00
0.5	32.25 ± 0.55	41.37 ± 0.07	31.04 ± 0.24
1	73.33 ± 0.69	61.68 ± 0.32	53.73 ± 0.11
2	85.11 ± 0.74	87.82 ± 1.96	89.11 ± 0.07
3	94.82 ± 0.47	94.33 ± 0.47	93.81 ± 1.48
5	97.03 ± 0.84	98.05 ± 0.15	94.71 ± 0.59
10	99.48 ± 0.09	99.26 ± 0.38	98.38 ± 0.63
20	99.83 ± 1.07	99.48 ± 0.54	99.41 ± 0.88

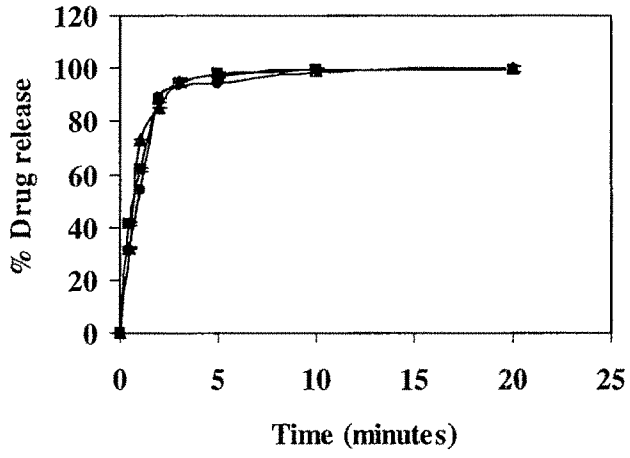


Figure 8.12 Comparative dissolution profiles of ondansetron hydrochloride film in distilled water (▲), simulated saliva (pH 6.8) (■) and simulated gastric fluid (pH 1.2) (●).

8.3.3 Conclusions

The fast dissolving film of ondansetron hydrochloride obtained by solvent casting method showed acceptable mechanical characteristics and satisfactory % drug release. The prepared film was transparent with smooth surface without any interactions between drug and polymer. The film showed fast drug release and suitable mechanical properties. The high % drug release of the film in simulated saliva and simulated gastric fluid indicated that it could be useful for patient suffering from post operative or chemotherapy induced sever nausea and vomiting where quick onset of drug action is desirable.

8.4 DEVELOPMENT AND EVALUATION OF FAST DISSOLVING SUBLINGUAL FILM OF LAMOTRIGINE

8.4.1 Experimentals

8.4.1.1 *Materials*

Lamotrigine and strawberry flavor were gift from Torrent Pharmaceuticals Ltd., Rajkot, India. Polyvinyl alcohol (molecular weight-14,000), mannitol (A.R.) and glycerol (A.R.) were purchased from S. D. Fine Chem. Ltd., Mumbai, India. All other chemicals used were of analytical grade and were used without further purification. Deionized double distilled water was used throughout the study.

8.4.1.2 *Preparation of film of lamotrigine*

The fast dissolving sublingual film of lamotrigine was prepared according to the same procedure of lamotrigine. The final formulation of film of lamotrigine is given in table 8.10.

Table 8.10. Final formulation of film containing lamotrigine.

Independent variables	**Optimum values (mg per film of 4 cm^2 area)**
lamotrigine	5.00
Polyvinyl alcohol	- 25.00
Glycerol	4.0
Mannitol	6.00
Strawberry flavor	0.02

8.4.1.3 *Mechanical property*

Mechanical properties of the film such as tensile strength, elongation, elastic modulus were measured same as that of salbutamol sulphate film. Scanning electron microscopy and differential scanning calorimetry study of the film were carried out in same manner as that of sabutamol sulphate.

8.4.1.4 *In vitro dissolution study*

The dissolution study of the film was conducted similarly as that of salbutamol sulphate film with change in the analysis by measuring absorbance spectrophotometrically at 305 nm. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally ($r^2 > 0.99$). The dissolution test was performed in triplicate.

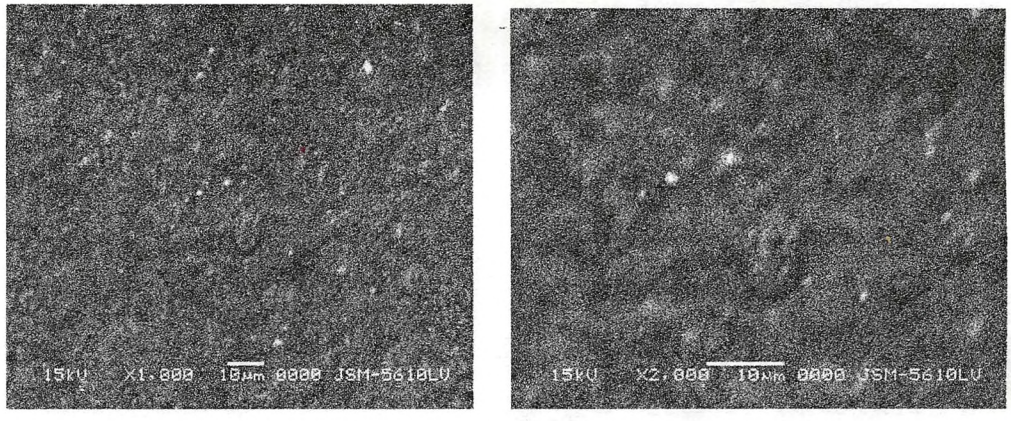
8.4.2 Results and Discussion

The mechanical properties of film of lamotrigine such as tensile strength, % elongation and elastic modulus is given in table 8.11.

Table 8.11. Mechanical properties of the film of lamotrigine.

Tensile strength (N/mm^2)	% Elongation	Elastic Modulus (N/mm^2)
7.36 ± 0.05	569.00 ± 2.04	0.86 ± 0.02

The prepared film containing lamotrigine was clear and colorless. The scanning electron photomicrograph of the film at 1000× magnifications and 2000× magnifications showed smooth surface with some little pores and with out any scratches or transverse striations (figure 8.13).



(A) **(B)**

Figure 8.13 SEM micrograph of lamotrigine film at (A)1000X and (B) 2000X magnification.

The DSC curves of pure drug, drug: polyvinyl alcohol: mannitol physical mixture and film containing lamotrigine is shown in figure 8.14. Lamotrigine showed an endothermic peak at 191.89 °C corresponding to its melting point. Drug: polyvinyl alcohol: mannitol (5:20:6) physical mixture showed two endothermic peaks, at 132.59°C corresponding excipients and another at 193.99 °C corresponding to drug. The film containing lamotrigine showed two peaks at 137.05°C corresponding to drug and another at 195.48 °C corresponding drug. The intact DSC peak of drug in the physical mixture and film indicated that the drug did not interact with the excipients used in the film.

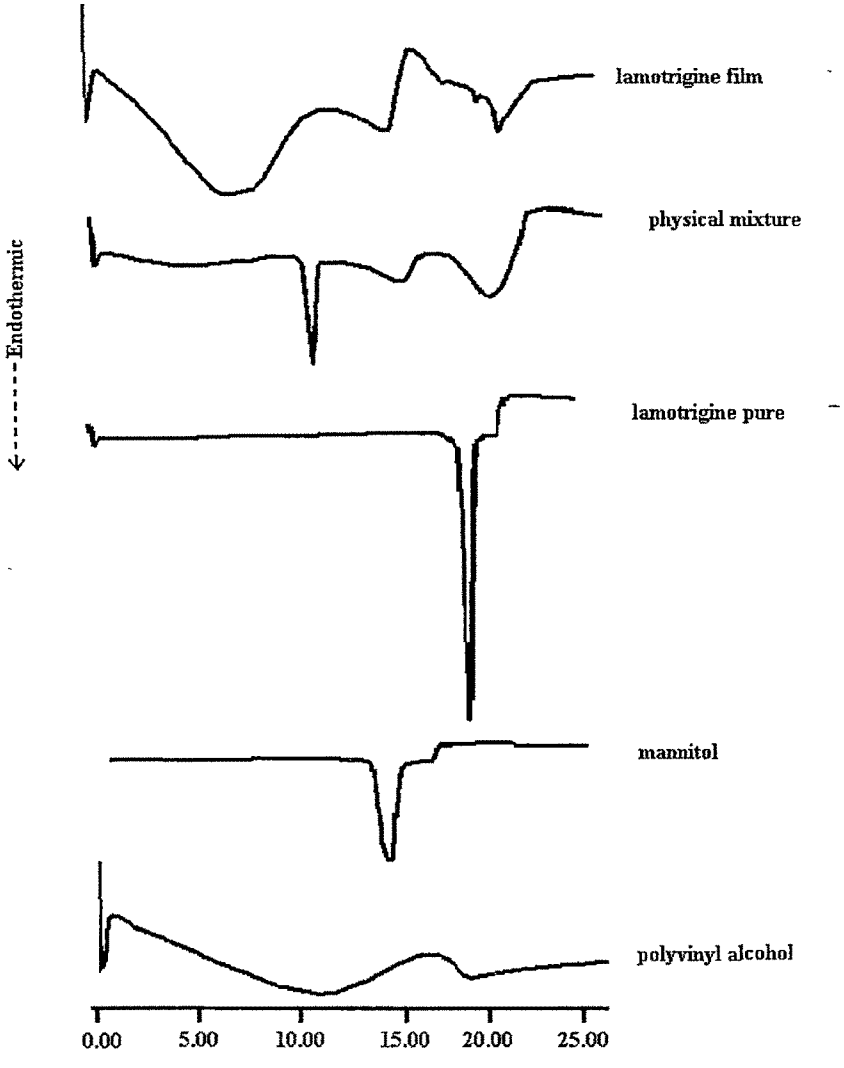


Figure 8.14. DSC of thermograms lamotrigine film.

Dissolution studies of film were carried out using distilled water, simulated saliva (pH 6.8) and simulated gastric fluid (pH 1.2) as absorption of drug from the film is through sublingual mucosa, esophagus and stomach. Table 8.12 shows the % drug release of the film in different dissolution media. Figure 8.15 depicts the dissolution profiles of the film of ondansetron hydrochloride in different media. The dissolution data of film in distilled water were compared with the dissolution data in simulated saliva and simulated gastric fluid using S_d statistics. An S_d value of 0.005627for simulated saliva and 0.01147 for simulated gastric fluid indicates that the release profile of film in distilled water and simulated saliva and simulated gastric fluid are comparable. In simulated gastric fluid, % drug release at 2 minute was 89.11% which revealed high efficacy of the film for rapid drug release.

Table 8.12. % Drug release of the film of lamotrigine in different dissolution media (n=5)

Time (minute)	% Drug release in distilled water ± S.D. (reference)	% Drug release in simulated saliva ± S.D. (test)	% Drug release in simulated gastric fluid ± S.D.
0	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00
0.5	33.63 ± 0.53	44.73 ± 0.74	36.84 ± 0.48
1	75.82 ± 0.31	64.83 ± 0.85	57.26 ± 0.63
2	87.29 ± 0.16	89.27 ± 0.94	92.15 ± 1.28
3	95.19 ± 1.09	95.83 ± 0.63	94.17 ± 0.93
5	98.23 ± 0.62	97.47 ± 0.68	96.34 ± 0.44
10	99.46 ± 0.67	98.49 ± 1.56	98.90 ± 0.35
20	99.34 ± 1.46	99.03 ± 1.64	99.38 ± 0.19

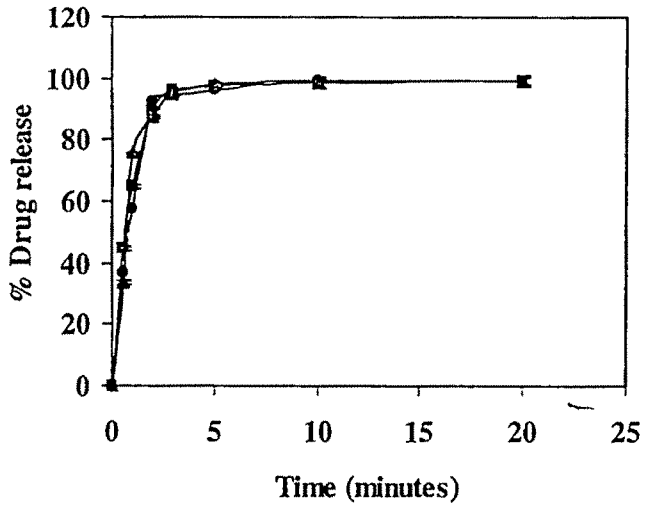


Figure 8.15. Comparative dissolution profiles of batch V_{24} in distilled water (▲), simulated saliva (pH 6.8) (■) and simulated gastric fluid (pH 1.2) (●)

8.4.3 Conclusions

The fast dissolving film of lamotrigine obtained by solvent casting method showed acceptable mechanical characteristics and satisfactory % drug release. The prepared film was transparent with smooth surface without any interactions between drug and polymer. The film showed fast drug release and suitable mechanical properties. The high % drug release of the film in simulated saliva and simulated gastric fluid indicated that it could be helpful for the treatment of epileptic attack where quick bioavailability of the drug is desired.

8.5 STABILITY STUDIES OF THE FAST DISSOLVING FILMS

The stability studies of the prepared films were done at the conditions as stated in the ICH guideline. The intermediate stability studies of the films were carried out at temperature of 30°C and at humidity of RH 65% RH. The accelerated stability studies were carried out at the temperature of 40°C and at humidity of RH 75% and To maintain the RH of 60% and 75 % saturated solutions of $MgCl_2$ and Mg $(NO_3)_2$ respectively were

prepared. These solutions were filled in separate glass desiccators. Twenty film of 4 cm^2 area placed in a petridish were kept in each desiccator for six months. The films were tested at 0, 1, 2, 3, 4, 5, 6 months time intervals for tensile strength, % elongation, elastic modulus and in vitro dissolution study in triplicate. The results of the stability study of salbutamol sulphate film is shown in table 8.13.

Test	Time (month)												
	0	1		2		3		4		5		6	
		I	A	I	A	I	A	I	A	I	A	I	A
Tensile strength ± S.D. (N/mm^2)	6.41± 0.04	6.32± 0.03	6.13± 0.11	6.08± 0.06	5.92± 0.23	5.73± 0.12	4.73± 0.06	4.28± 0.02	4.24± 0.21	4.11± 0.26	4.02± 0.12	3.93± 0.11	3.82± 0.10
% Elongation ± S.D.	474± 2.17	468± 1.46	456± 3.06	442± 2.21	413± 1.19	420± 1.52	401± 2.03	409± 1.83	382± 1.92	394± 3.73	368± 1.62	373± 1.72	351± 2.73
Elastic modulus (N/mm^2) ± S.D.	2.52± 0.03	2.47± 0.16	2.73± 0.07	2.84± 0.09	2.36± 0.10	2.18± 0.08	1.83± 0.06	1.78± 0.12	1.72± 0.04	1.68± 0.12	1.36± 0.08	1.46± 0.06	÷.29± 0.04
Y_{2min} ± S.D.	92.31 ± 0.33	91.02 ± 2.14	92.84 ± 1.12	93.27 ± 1.06	93.26 ± 2.62	93.86 ± 0.71	94.78 ± 2.62	94.38 ± 1.25	95.27 ± 0.52	95.81 ± 1.54	95.28 ± 2.62	96.92 ± 1.25	96.93 ± 1.52

Table 8.13. Results of the stability studies of salbutamol sulphate film.

I = Intermediate condition (30 °C/60%)

A= Accelerated condition (45°C/75 %)

The results of the stability study of ondansetron tablets is shown in table 8.14.

Table 8.14. Results of the stability studies of ondansetron hydrochloride film.

Test	Time (month)												
	0	1		2		3		4		5		6	
		I	A	I	A	I	A	I	A	I	A	I	A
Tensile strength ± S.D. (N/mm^2)	8.49± 0.12	7.92± 0.07	7.62± 0.21	7.37± 0.07	6.97± 0.14	6.82± 0.20	5.82± 0.13	6.03± 0.11	5.84± 0.03	5.36± 0.05	5.72± 0.14	5.81± 0.15	5.36± 0.08
% Elongation ± S.D.	584± 1.17	538± 0.92	547± 1.26	525± 1.62	512± 1.73	504± 0.85	498± 1.05	486± 0.92	475± 0.82	479± 2.06	458± 0.92	462± 0.82	462± 1.62
Elastic modulus (N/mm^2) ± S.D.	1.93± 0.08	1.62± 0.26	1.63± 0.08	1.73± 0.16	1.85± 0.25	1.62± 0.12	1.74± 0.03	1.66± 0.61	1.72± 0.11	1.39± 0.05	1.36± 0.13	1.52± 0.11	1.36± 0.13
Y_{2min} ± S.D.	89.95 ± 1.94	90.34 ± 1.57	92.62 ± 1.61	92.83 ± 2.16	93.88 ± 0.73	93.72 ± 1 78	94.37 ± 0.82	94.26 ± 0.91	95.63 ± 1.31	95.63 ± 0.41	95.82 ± 1.22	95.94 ± 0.73	96.15 ± 0.51

I = Intermediate condition (30 °C/60%)

A= Accelerated condition (45°C/75 %)

The results of the stability study of lamotrigine film is shown in table 8.15.

Table 8.15. Results of the stability studies of lamotrigine film.

Test	Time (month)												
	0	1		2		3		4		5		6	
		I	A	I	A	I	A	I	A	I	A	I	A
Tensile strength ± S.D. (N/mm^2)	7.78± 0.07	7.82± 0.15	7.03± 0.06	7.11± 0.17	6.77± 0.09	6.95± 0.08	6.54± 0.05	6.72± 0.21	6.44± 0.18	6.62± 0.32	5.93± 0.13	6.07± 0.18	5.48± 0.14
% Elongation ± S.D.	588± 1.78	573± 1.53	559± 1.22	562± 0.64	538± 2.53	542± 1.08	561± 2.36	568± 0.99	511± 0.65	538± 2.58	484± 0.73	502± 0.83	476± 0.89
Elastic modulus (N/mm^2) ± S.D.	1.73± 0.06	1.63± 0.22	1.52± 0.08	1.48± 0.23	1.36± 0.09	1.22± 0.12	1.16± 0.05	0.99± 0.13	0.96± 0.07	0.86± 0.15	0.81± 0.11	0.79± 0.10	0.74± 0.08
Y_{2min} ± S.D.	88.31 ± 1.75	89.14 ± 0.96	90.31 ± 1.07	90.26 ± 1.97	92.53 ± 1.06	91.26 ± 2.93	93.93 ± 1.06	92.63 ± 0.85	94.96 ± 1.46	94.74 ± 1.07	95.41 ± 2.06	95.73 ± 1.07	96.07 ± 1.06

I = Intermediate condition (30 °C/60%)

A= Accelerated condition (45°C/75 %)

From the results of the stability studies it can be observed that at 60 % RH and 75 % RH after six months, the films of all the drugs showed a decrease in tensile strength, elongation and elastic modulus while increase in the % drug release (Y_{2min}). The films showed more decrease in tensile strength at 75 % RH than 60 % RH. The moisture

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