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Development and Evaluation of Fast-Dissolving Film of Salbutamol Sulphate

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ABSTRACT The objective of this work was to prepare and optimize the fast-dissolving film of salbutamol sulphate, which can be useful in an acute attack of asthma. The film was prepared using a solvent evaporation technique and is taken through the sublingual route. The film contains polyvinyl alcohol as a polymer, glycerol as a plasticizer, and mannitol as filler. A 3^3 full factorial design was utilized for the optimization of the effect of independent variables such as amount of polyvinyl alcohol, amount of glycerol, amount of mannitol on the mechanical properties, and % drug release of film. The multiple regression analysis of the results led to equations that adequately describe the influence of the independent variables on the selected responses. Polynomial regression equations and contour plots were used to relate the dependent and independent variables. The experimental results indicated that polymer concentration, plasticizer concentration, and filler concentration had complex effects on film mechanical behavior and % drug release. Furthermore, the desirability function was employed in order to determine the best batch out of all 27 batches of the factorial design. The % relative error was calculated, which showed that observed responses were in close agreement with the predicted values calculated from the generated regression equations. It was found that the optimum values of the responses for fast release film could be obtained at medium levels of polyvinyl alcohol and glycerol, and a high level of mannitol. The prepared film was clear, transparent, and had a smooth surface. The concept of similarity factors S_d was used to prove similarity of dissolution between distilled water and simulated saliva (pH 6.8) or simulated gastric fluid (pH 1.2).

KEYWORDS Fast-dissolving film, Factorial design, Desirability function, Similarity factor

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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 (Keiko et al., 2002; Khoda et al., 1997; Peh & Wong, 1999; Rossi et al., 2003; Shojaei, 1998). Recently, the use of polymeric films for buccal delivery has been investigated by Peh and Wong (1999). Here, an attempt was made to prepare the fast-dissolving film of salbutamol sulphate containing polyvinyl alcohol for the sublingual route.

The polluted environment and the raising levels of nitrogen dioxide, sulphur dioxide, particulates in the air, and fast life of the common human have increased diseases like asthma (Weinberger, 1987). Salbutamol sulphate, (RS)-1-(4-hydroxy-3-hydroxymethyl 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 the inhalation route but is also effective after oral administration (Morgan et al., 1986).

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 (David & Joseph, 1992; Hoogstraate et al., 1996; Keiko et al., 2002). As the fast-dissolving film is taken through the sublingual route, rapid absorption of drug is possible, which finally leads to quick onset of drug action.

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

Gohel and Panchal (2000) 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 of drug dissolved. Another advantage is that, unlike the similarity factor f_2, linear interpolation can be used to accurately express the results (Gohel & Panchal, 2002). 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 amounts of polyvinyl alcohol, glycerol, and mannitol on % drug release and mechanical properties of film were investigated.

MATERIALS AND METHODS

Materials

Salbutamol sulphate I. P. and strawberry flavor were a 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.

Preparation of Film

Fast-dissolving film of polyvinyl alcohol was prepared by the solvent-casting method (Weinberger, 1987). Aqueous solution I was prepared by dissolving the polymer and glycerol in specific proportion-in distilled water and 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 solutions I and II were mixed and stirred for 1 hour. Then the mixture solution was casted onto a plastic petri dish and it was dried in the oven at 50°C for 24 hour. The film was carefully removed from the petri dish, 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 a temperature of 30°±1°C and relative humidity 60±5% until further analysis. The thickness of each sample was measured using a thickness tester (Model 110, 0.01 mm capacity, Mitutoyo Manufacturing Corporation Ltd., Japan) at five locations (center and four corners) and the mean thickness was calculated. Samples with air bubbles, nicks, or tears and having mean thickness variations of greater than 5% were excluded from analysis.

Factorial Design and Desirability Function

To study all the possible combinations of all factors at all levels, a three-factor, three-level full factorial design was constructed and conducted in a fully randomized order (Derringer & Suich, 1980). 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 are 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 significantly affect response variables.

TABLE 1 Composition and Responses for 3^3 Factorial Design

	Variables			Response values				
Batch	X_1	X_2	X_3	Tensile strength (N/mm^2)	% Elongation	Y_{2min}	Elastic modulus (N/mm^2)	Overall desirability
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

Finally, the desirability function was used for 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 of predicting optimum levels for the independent variables (Derringer & Suich, 1980).

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 (Derringer & Suich, 1980; Paterakis et al., 2002).

In this particular study, there were no specific requirements for tensile strength of the optimum formulation. Therefore, the range of 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 outside this range have a desirability of 0. These can be described by the following equations:

$$d_1 = 0 \text{ for } Y_i < Y_{max}$$

$$d_1 = 1 \text{ for } Y_{min} < Y_i < Y_{max}$$

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

where d_1 = 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:

$$d_2 \text{ or } d_3 = \frac{Y_i - Y_{min}}{Y_{target} - Y_{min}} \text{ for } Y_i < Y_{target}$$

$$d_2 \text{ or } d_3 = 1 \text{ for } Y_i > Y_{target} \quad (2)$$

where d_2 = the individual desirability of % elongation and d_3 = the individual desirability of % drug release at 2 minutes.

The values of Y_{target} and Y_{min} for % elongation are 590 and 210, 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:

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

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

where d_4 = 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:

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

Measurement of Mechanical Properties

Mechanical properties of film were evaluated using Instron Universal Testing Instrument (Model 1121, Instron Ltd., Japan) equipment with a 2-kilogram load cell. Film strips in dimensions 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 triplicate for each film.

Three mechanical properties, namely, tensile strength, elastic modulus, and % elongation 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: (Peh & Wong, 1999; Tao et al., 2000)

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

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 (Peh & Wong, 1999; Tao et al., 2000):

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

Percentage elongation can be obtained by the following equation:

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

Morphology Study

Morphology of the prepared film was observed under a scanning electron microscope (SEM) (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× magnification.

Differential Scanning Calorimetry (DSC)

The 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 a 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 (Nunthanid et al., 2001).

In Vitro Dissolution Studies

The dissolution studies were conducted using three media, distilled water, simulated saliva consisting 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 (Peh & Wong, 1999). 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 U.S. Pharmacopoeia (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, 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-minute time intervals and were filtered through 0.45 µm Whatman filter paper, diluted suitably and analyzed 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=0.9998). The dissolution test was performed in triplicate for each batch.

Similarity Factor S_d

The similarity factor S_d is defined as

$$S_d = \frac{\sum_{t=1}^{n-1} |\text{Log}((AUC_{R_t})/(AUC_{T_t}))|}{n-1} \quad (8)$$

where n = the number of data points collected during the in vitro dissolution test and AUC_{Rt} and AUC_{Tt} = 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 (Gohel & Panchal, 2000, 2002).

TABLE 2 ANOVA Results (P Value) of the Effect of the Variables on Mechanical Properties and % Drug Release of Film

	Tensile strength		% Elongation		Y_{2min}		Elastic modulus	
Factors	Coefficient	P	Coefficient	P	Coefficient	P	Coefficient	P
X_1	0.9756	<0.0001[a]	101.3330	<0.0001[a]	−7.5627	<0.0001[a]	−0.1583	0.0056[a]
X_2	0.1894	0.0587	61.3330	<0.0001[a]	−3.0172	0.0002[a]	−0.2394	0.0002[a]
X_3	−1.274	<0.0001[a]	−38.0000	0.0009[a]	5.8244	<0.0001[a]	−0.1922	0.0013[a]
X_1^2	−0.6278	0.0013[a]	26.222	0.1283	5.3083	0.0002[a]	−0.2694	0.0063[a]
X_2^2	0.1572	0.3439	−37.444	0.0359[a]	−0.4783	0.6724	0.2739	0.0057[a]
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[a]
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[a]	0.0908	0.1538
$X_1X_2X_3$	−0.2675	0.0734	27.270	0.0677	−0.7975	0.4191	−0.1962	0.0178[a]
Constant	6.7748	<0.0001[a]	420.9250	<0.0001[a]	78.8177	<0.0001[a]	1.6081	<0.0001[a]
r^2	0.9529		0.9212		0.9464		0.8436	

[a]Regression coefficients, statistically significant (P<0.05).

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 1.

The statistical evaluation of the results was carried out by analysis of variance (ANOVA) using Microsoft Excel Version 2000. The ANOVA results (p value) of the effect of the variables on mechanical properties and % drug release of film are shown in Table 2. 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 nonsignificant p value ($p>0.05$) have negligible contribution in obtaining dependent variables and thus are neglected (Gohel & Panchal, 2002).

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

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

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

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

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

Coefficients with one factor represent 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. A positive sign

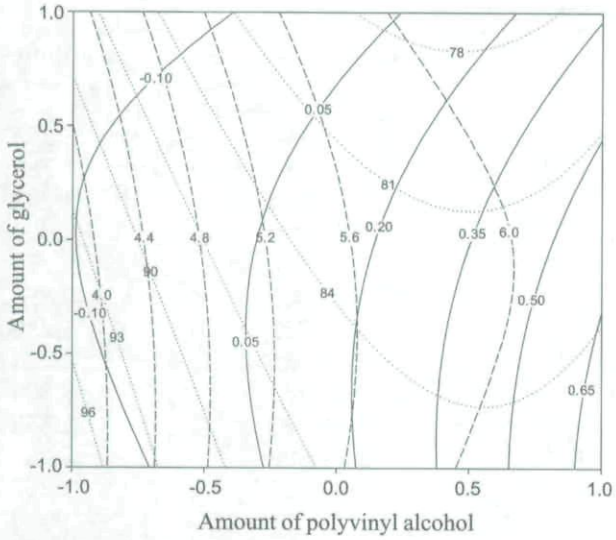

FIGURE 1 Contour Plot for Tensile Strength (- - - -), % Drug Release at 2 Minutes (·····) and Over All Desirability (——) Keeping Amount of Mannitol at 0 Level.

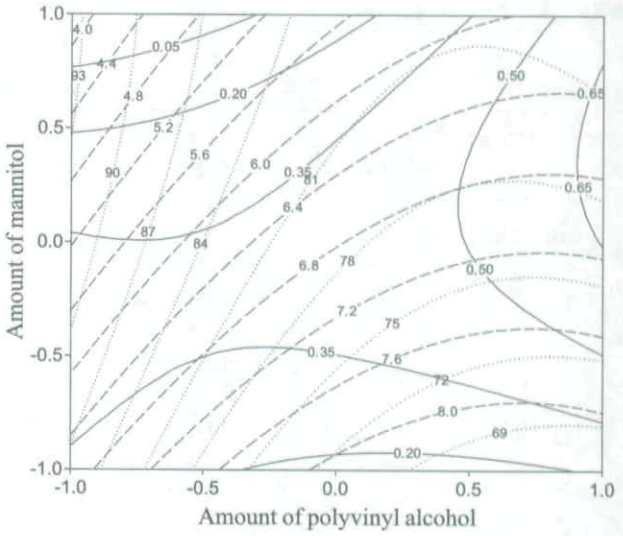

FIGURE 3 Contour Plot for Tensile Strength (- - - -), % Drug Release at 2 Minutes (·····) and Over All Desirability (——) Keeping Amount of Glycerol at 0 Level.

in front of the terms indicates a positive effect, while a negative sign indicates a negative effect of the factors. It can be concluded from the equations that only polyvinyl alcohol showed a positive effect on tensile strength, while only mannitol showed a positive effect on % drug release. But polyvinyl alcohol and mannitol had negative effects 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. Figures 1, 2, and 3 show the contour plots for tensile strength, % drug release at 2 minutes, and overall 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 the other factor is kept constant. The contour lines indicate that the addition of a higher amount of polyvinyl alcohol resulted a higher tensile strength, lower % drug release, and higher overall desirability, while the addition of amount of glycerol resulted 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 (Tao et al., 2000). The addition of a higher amount of mannitol resulted in lower tensile strength, higher % drug release, and higher overall desirability. The optimum level of mannitol was desired because greater amounts of mannitol made film more brittle.

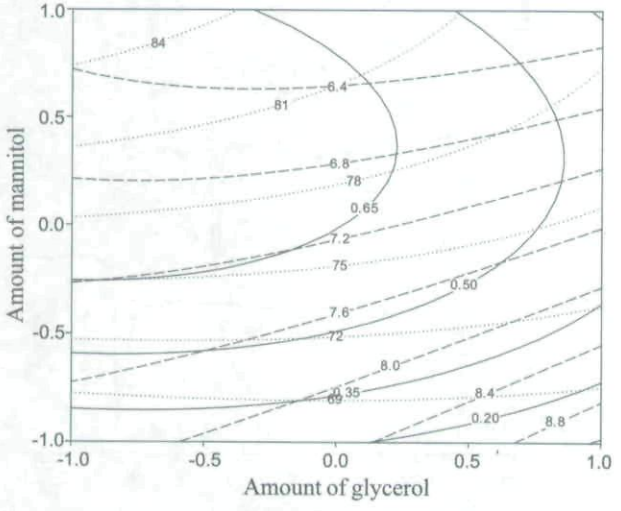

FIGURE 2 Contour Plot for Tensile Strength (- - - -), % Drug Release at 2 Minutes (·····) and Over All Desirability (——) Keeping Amount of Polyvinyl Alcohol at 0 Level.

TABLE 3 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

TABLE 4 Comparison Between Observed and Predicted Results of Checkpoint 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

Desirability function was utilized to find out the best batch out of 27 batches. Batch V_{24} showed the highest overall desirability of 0.785. Therefore, this batch was considered to be the best batch and the values of independent variables of this batch were considered to be optimum values for the preparation of film. The final formulation of film containing salbutamol sulphate is given in Table 3.

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 checkpoint 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 (Paterakis et al., 2002). The experimental values and predicted values of each response are shown in Table 4. The % relative error between predicted values and experimental values of each response was calculated using the following equation:

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

The % relative error obtained from checkpoint batch was in the range of 0.89–8.95. It can be seen that in all cases there was a reasonable agreement of

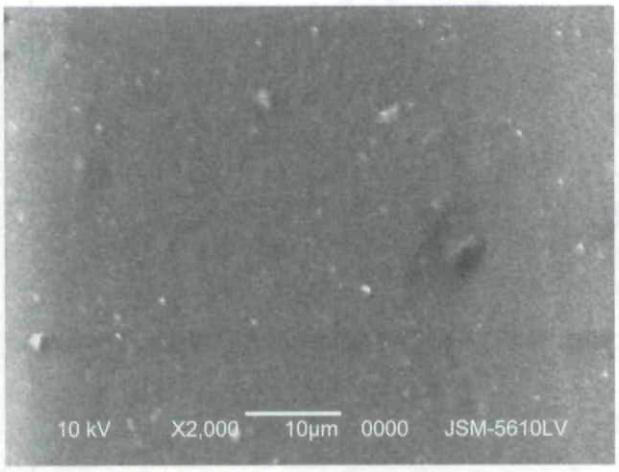

FIGURE 4 Scanning Electron Photomicrograph of Salbutamol Sulphate Film at 2000× Magnification.

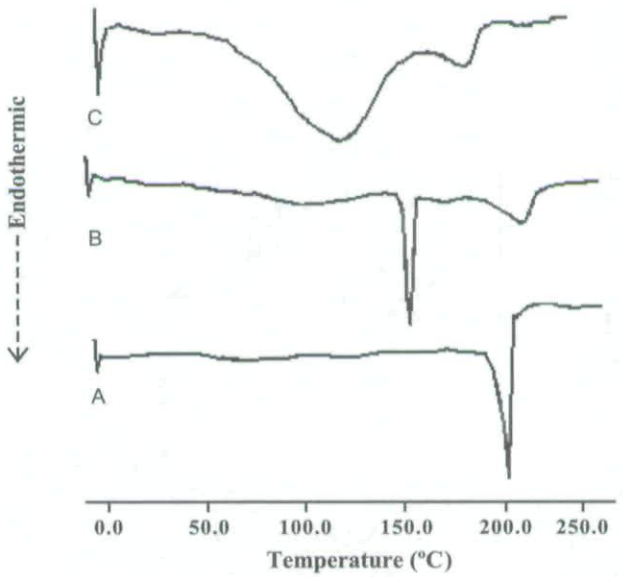

FIGURE 5 DSC of Thermograms: (A) Pure Drug, (B) Drug: Polyvinyl Alcohol: Mannitol (4:20:6) Physical Mixture and (C) Optimized Film.

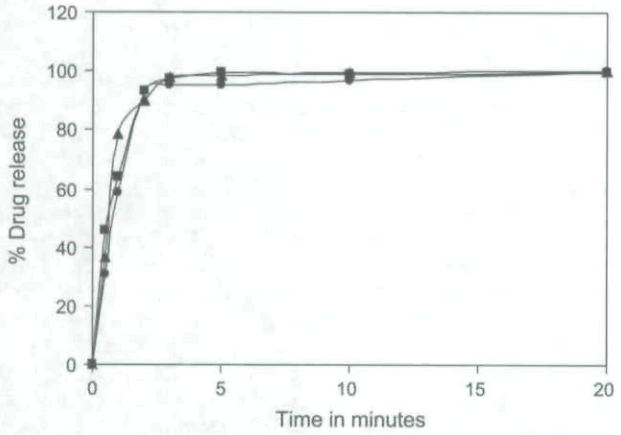

FIGURE 6 **Comparative Dissolution Profiles of Batch V_{24} in Distilled Water (▲), Simulated Saliva (pH 6.8) (■) and Simulated Gastric Fluid (pH 1.2) (●).**

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 the model, and ascertained the effects of polyvinyl alcohol, glycerol, and mannitol on % drug release and mechanical properties of the film.

Morphology of Film

The prepared film containing salbutamol sulphate was clear and colorless. The scanning electron photomicrograph of the film at 2000× magnification showed smooth surface with some little pores and without any scratches or transverse striations (Fig. 4).

Differential Scanning Calorimeter

The DSC curves of pure drug, drug:polyvinyl alcohol:mannitol physical mixture and film containing salbutamol sulphate is shown in Fig. 5. Salbutamol sulphate showed an endothermic peak at 205.09°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 the 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 indicates that the drug did not interact with the excipients used in the film.

In Vitro Release Study

Dissolution studies of all batches were carried out using distilled water as a dissolution medium. Dissolution study of optimized batches 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. Figure 6 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 (Gohel & Panchal, 2002; Moore & Flanne, 1996; Nunthanid et al., 2001; Pillay & Fassihi, 1998). An S_d value of 0.006323 for simulated saliva and 0.01421 for simulated gastric fluid indicates that the release profiles of batch V_{24} in distilled water and simulated saliva and simulated gastric fluid are comparable. In simulated gastric fluid, % drug release at 2 minutes was 92.11%, which revealed high efficacy of the film for rapid drug release.

CONCLUSION

The fast-dissolving film of salbutamol sulphate obtained by the 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 led 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.

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