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Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILMS OF TERBUTALINE SULPHATE USING 3^2 FULL FACTORIAL DESIGN

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ABSTRACT

Fast dissolving films are playing an important role in the current pharmaceutical drug delivery systems. They have convenience and ease of use over solid and liquid dosage forms. In the present research, fast dissolving oral film of terbutaline sulphate were developed for treatment of asthma in pediatric and geriatrics using HPMC K15 LV as film forming polymer, SSG as superdisintegrant and PEG-400 as plasticizer. The films were prepared by solvent casting method. Optimization of HPMC E15 LV, SSG and PEG-400 was carried out using 3^2 full factorial designs. The formulated films of terbutaline sulphate were evaluated for their physic-mechanical parameters like disintegration time, tensile strength, percent elongation, folding endurance and In-vitro drug release. Estimation of drug content uniformity of terbutaline sulphate films was performed and the results were satisfactory. Optimized batch F_3 has thickness (0.188±0.001mm), disintegration time (13.40±1.81 sec.) tensile strength (1.35±0.183 Mpa), % Elongation (30.27±1.81), folding endurance (152±6.83), CPR_{1min} 66.214±1.27and CPR_{10min} 98.978±2.49.

Key words: *Fast dissolving oral film, terbutaline sulphate, 3^2 full factorial design, first pass effect.*

INTRODUCTION

Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration, but oral drug delivery systems still need some advancements to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking.

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Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets. The most common complaint was tablet size, followed by surface form and taste. The problem of swallowing tablets was more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water [1-4].

Fast-dissolving oral film is new drug delivery system for the oral delivery of the drugs. It was developed on the basis of technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly

hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal and intragastric absorption. Technology Catalysts forecasts the market for drug products in oral thin film formulations was valued of $500 million in 2007 and could reach $2 billion in 2012. Based on upward global growth trends of the past decade, the fast dissolving dosage market could produce revenues of $13 billion by 2017[5].

Terbutaline sulphate is chemically 2-*tert*-Butylamino-1-(3, 5-dihydroxyphenyl) ethanol sulphate. It is used as anti-asthmatic drug which is highly water soluble. The bioavailability of Terbutaline sulphate is very less due to extensive pre-systemic metabolism [6].
Terbutaline sulphate is a drug of choice for the treatment of asthma but it has several drawbacks such as short biological half-life of about 3.6 hours [7]. It is readily metabolized in the gut wall and liver when given orally. It has a short duration of action, low peak plasma level of 1.2 µg/ml and poor bioavailability of only 14.8%. These factors necessitated formulation of fast dissolving oral films of Terbutaline sulphate, as this route of drug administration reduces first pass hepatic metabolism of drug, as most of drug gets absorbed from oral mucosa that would reduce dose and related side effects, flexibility and convenience of administration leads to better patient compliance[6].

MATERIAL AND METHOD

Terbutaline sulphate was obtained as gift sample from Bioplus Life Science, Banglore, PEG-400, Tween-80, Tween-80, Citric acid, Methanol were purchased from Thomas baker, HPMC E15LV and aspartame purchased from Loba Chem, SSG was purchased from S.D. Fine, Mumbai. All the other chemicals and solvents used were of AR grade.

Experimental Design.

A 3^2 factorial design was employed where amount of film forming polymer(HPMC E15LV) and Superdisintegrant (sodium starch glycolate) were studied at three levels. Whereas amount of Plasticizer (polyethylene glycol-400) was kept constant. Table 1 summarizes the nine experimental runs, their factor combinations and translation of coded levels to the experimental units employed to study. Disintegration Time (Y_1), tensile strength(Y_2), folding endurance(Y_3) and Cumulative % drug release at 10 minutes(Y_4) were taken as response variable.

Table 1: Factors combinations as per the 3^2 factorial design

Formulation code	Trial No.	Coded Level	
		Factor 1	Factor 2
FDF1	1	-1	-1
FDF2	2	-1	0
FDF3	3	-1	+1
FDF4	4	0	-1
FDF5	5	0	0
FDF6	6	0	+1
FDF7	7	+1	-1
FDF8	8	+1	0
FDF9	9	+1	+1

*Table summarizes an account of the nine experiments runs studied. Amount of terbutaline sulphate, PEG-400, tween 80, citric acid, aspartame, menthol, flavour and colour were kept constant.

Table 2: Translation of experimental levels into physical units

Coded Factor	*Level*	*Factor 1 (%w/v) HPMC E15LV*	*Factor 2 (%w/w) SSG*
-1	Low	3	2
0	Intermediate	4	5
+1	High	5	8

Preparation of Fast dissolving oral films of Terbutaline sulphate

The solvent casting method was used for the preparation of the fast dissolving oral films. From the preliminary physical observation of the films prepared during initial trials, the best compositions were used for the incorporation of drug. The required amount of film forming polymer was allowed to hydrate in 1/3 amount of water for about 6 hours and then it was uniformly dispersed to get clear solution of film forming polymer to this required amount of plasticizer was added. Drug and other ingredients such as superdisintegrant, sweetener, wetting agent, saliva stimulating agent and colour were dissolved one by one in other 1/3 amount of water with constant stirring to form clear aqueous solution. Menthol was dissolved in alcohol and then added to second portion of solution [8-10].

All the solutions were then mixed and remaining water is also added to the solution. The final prepared solution was sonicated to remove all the entrapped air bubbles. The final solution (10 ml) was poured in a glass mould having area of 75cm^2 kept on a leveled surface in hot air oven and dried at 30^0c temperature for 24 hours. The film thus formed was carefully removed from the moulds and were cut into size of 3*2 cm. Each containing ≈ 2.5 mg of terbutaline sulphate. The films were wrapped in aluminum foil and stored in airtight plastic bags till further use.

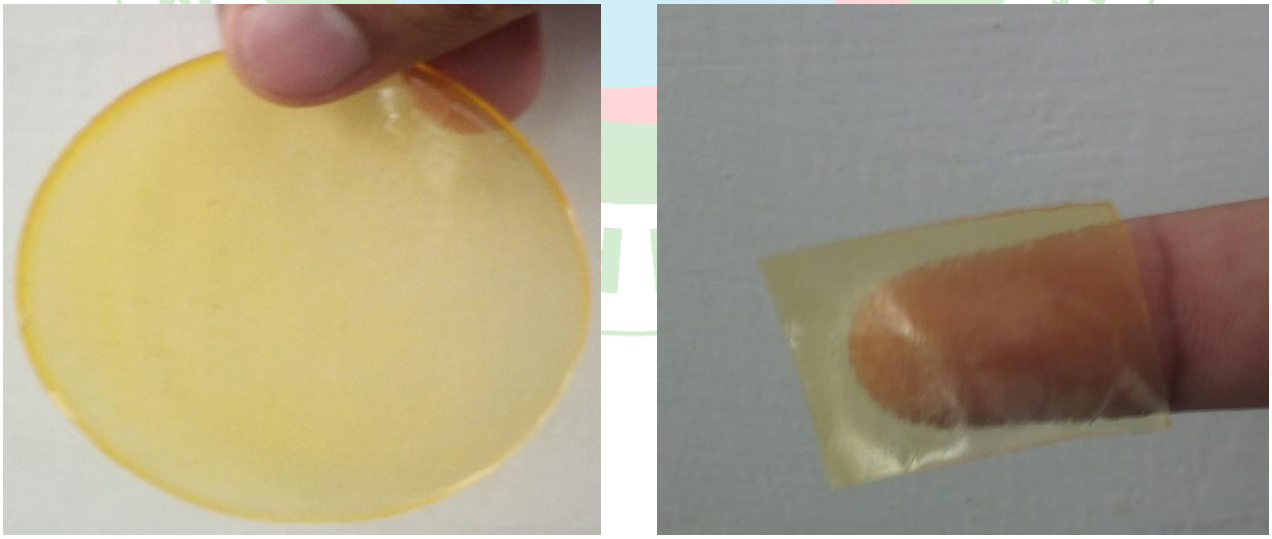

Fig: 1 Fast dissolving oral films of Terbutaline sulphate

Table 3: Response parameters for films prepared using 3^2 factorial design

Formulation	*Disintegration time (sec.)*	*Tensile strength (Mpa)*	*Folding endurance*	*CPR $_{10min}$*
FDF1	25.40±2.67	3.11±0.231	183±6.52	90.782±2.52
FDF2	21.20±2.32	2.86±0.217	175±5.71	92.626±1.85
FDF3	13.40±1.81	1.35±0.183	152±6.83	98.978±2.49
FDF4	22.80±1.93	2.57±0.147	155±7.35	89.479±1.97
FDF5	21.60±1.56	3.13±0.194	164±4.87	95.397±2.13
FDF6	17.20±2.11	2.52±0.205	142±6.93	96.317±2.48
FDF7	30.60±2.45	2.23±0.182	191±7.29	84.153±1.85
FDF8	28.20±2.19	3.64±0.136	198±5.45	86.568±2.36
FDF9	27.80±1.44	3.93±0.115	195±6.09	90.549±2.55

Evaluation of Fast dissolving oral films of terbutaline sulphate for critical factors

The fast dissolving oral films formed were removed carefully, placed in vacuum oven and vacuum was applied to remove traces of solvent if any. They were stored in desiccators for further evaluation tests. Formulated films were then subjected for critical factors of fast dissolving oral films such as disintegration time, tensile strength, percentage elongation, folding endurance, surface pH, and *in-vitro* release studies [8,9].

Thickness

The thickness of prepared films was measured using digital vernier caliper with a least count of 0.01 mm at five spots of the films. The thickness was measured at five different spots of the film, four at corners and one at center of film and average was taken. Data is represented as a mean± S.D. of five replicates [13].

Weight uniformity

For determination of film weight uniformity, three films each of 3*2 cm^2 of every formulation batch were taken and weighed individually on a digital balance. The average weights were calculated. Data is represented as a mean± S.D. of three replicates[14].

Disintegration time

Disintegration test was performed by placing the prepared film in the glass Petri dish containing 20 ml of 6.8 pH phosphate buffer. The time required for the film to complete disintegrate was recorded and results are expressed as mean of 3 determinations. Data is represented as a mean± S.D. of three replicates.[15]

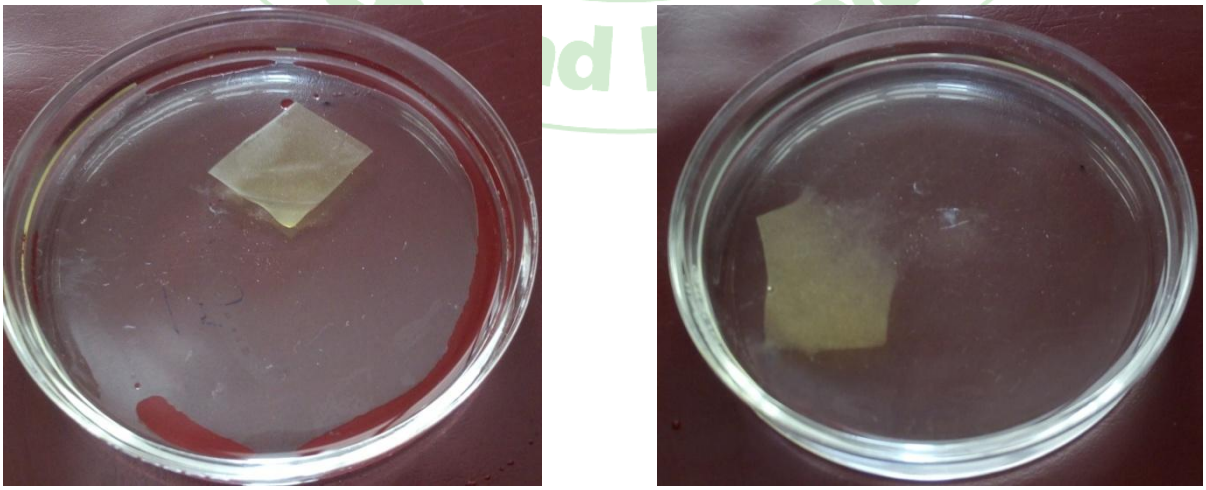

Fig:2 Disintegration of fast dissolving oral films of terbuutaline sulphate in 6.8 P^H buffer

Folding Endurance

Folding endurance of the films was determined manually by repeatedly folding each film at the same place till it broke. A film of (2 × 3 cm) was cut and repeatedly folded at the same place till it broke. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. Data is represented as a mean± S.D. of three replicates[14].

Drug content Determination The oral film of size 6 cm^2 was dissolved in 10 ml of phosphate buffer of P^H 6.8 and solution was filtered and drug content was estimated at 276 nm using double beam UV/Visible spectrophotometer .The experiments were carried out in triplicate for films of all formulations and average value was recorded as mean± S.D[14].

Surface pH

The films used for determination of their surface pH using universal digital pH meter. Film was wetted with deionized water and determines the surface pH with digital pH meter (Henna). The mean of three readings was recorded[13].

Tensile strength and % elongation

Mechanical properties of the film are important from packaging and patient handling point of view. Tensile test was performed to assess strength and elasticity of all film formulations. The elongation-to-break (also called ultimate elongation) is the strain on a material when it breaks and it gives an indication of toughness and stretch-ability prior to breakage. These parameters dictate the end-use handling properties and mechanical performance of the films. Casted films were cut into specimens of the specified size. Then 3 specimens were applied on tensile tester to determine the tensile properties. The tensile strength is expressed in terms of MPa and strain in terms of % elongation[16,17].

Tensile strength = (Load at failure×100) / (Strip thickness × Strip width)

and % Elongation = (Increase in length of strip × 100) /Initial length of strip.

In-vitro dissolution study

The release of drug from the prepared fast dissolving film into phosphate buffer pH 6.8 at 37 ± 0.5°C was performed using a six stage dissolution apparatus. Each fast dissolving film was keep to the vessel (900 ml capacity). Adequate sink conditions were provided by placing 200 ml of phosphate buffer pH 6.8 in each vessel. Dissolution paddle speed maintained at 50 rpm. After time intervals each of 1 minute from 1 minute to 10 minutes., 3 ml sample was withdrawn, filtered through a millipore filter of 0.45 µm pore size and assayed spectrophotometrically at λmax 276 nm. Immediately after each sample withdrawal, a similar volume of phosphate buffer pH 6.8 was added to the dissolution medium to maintain the sink condition. The absorbance of the polymeric additives was negligible and did not interfere with λmax of the drug[15].

INVESTIGATION OF DRUG-EXCIPIENT INTERACTIONS

FTIR

IR spectra of physical mixture of drug and excipients were recorded by KBr method using Fourier Transform Infrared Spectrophotometer. A base line correction was made using dried potassium bromide pellet. The potassium bromide-drug pellet of approximately 1 mm diameter was prepared by grinding 3-5 mg of physical mixture of drug-excipients with 100-150 mg of potassium bromide in pressure compression machine. The sample pellet was mounted in IR compartment and scanned at wavelengths 4000 cm^{-1} to 400 cm^{-1}.

Differential scanning calorimetry Thermograms were recorded using a differential scanning calorimeter (Netzsch DSC 200 F3). Drug, excipients and mixture (5-10mg) were weighed and hermetically sealed in flat bottomed aluminium pans. These samples were heated over a temperature range of 50-400°C in an atmosphere of nitrogen (200ml/min) at a constant rate of 10^0C per minute, with alumina being the reference standard.

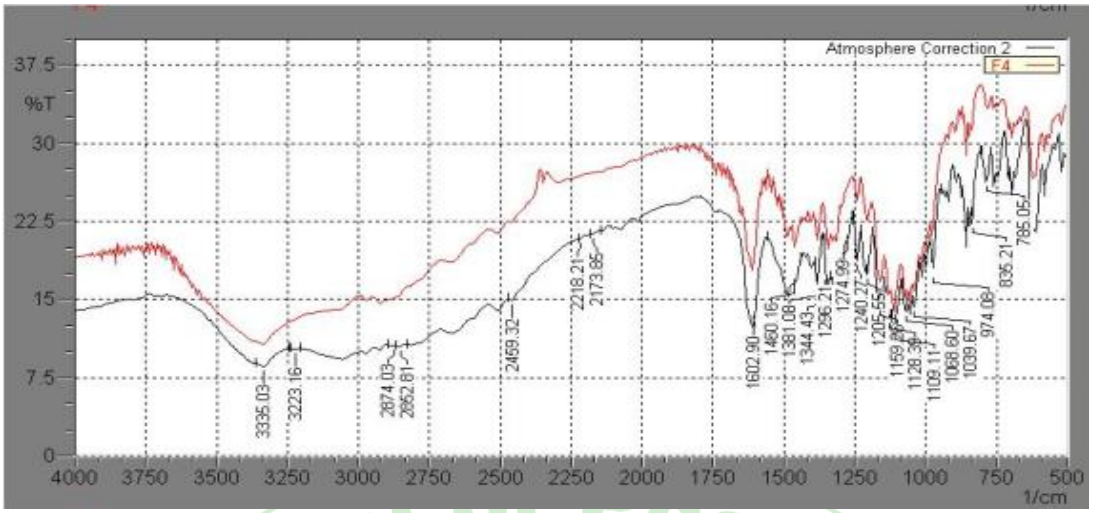

Figure 3 FT-IR overlay spectra of Drug + excipients

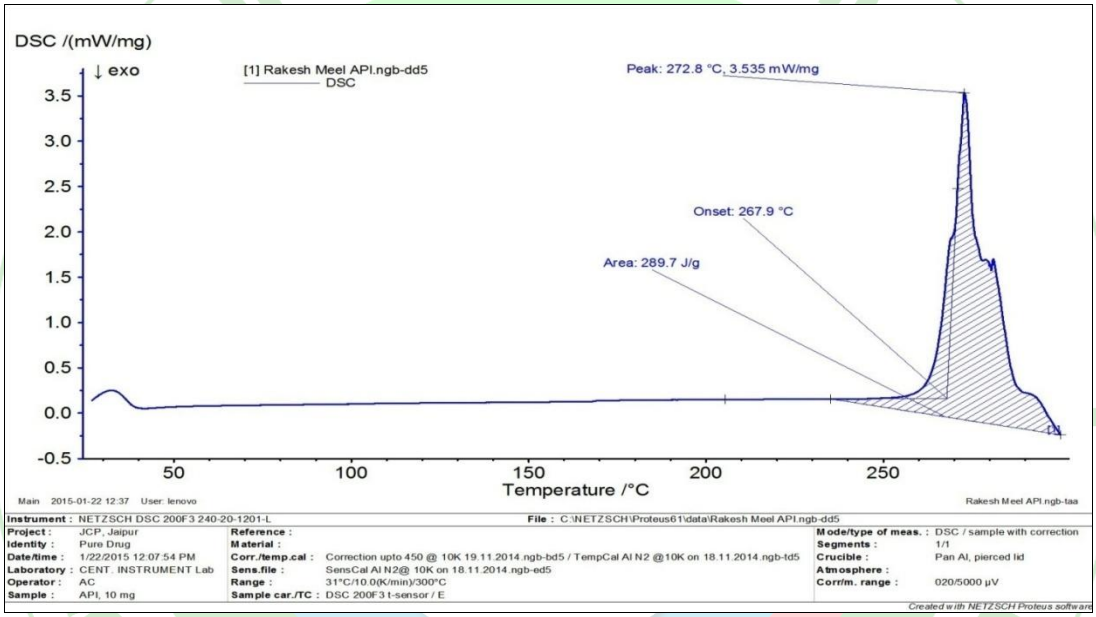

Fig 4 DSC thermogram of pure drug

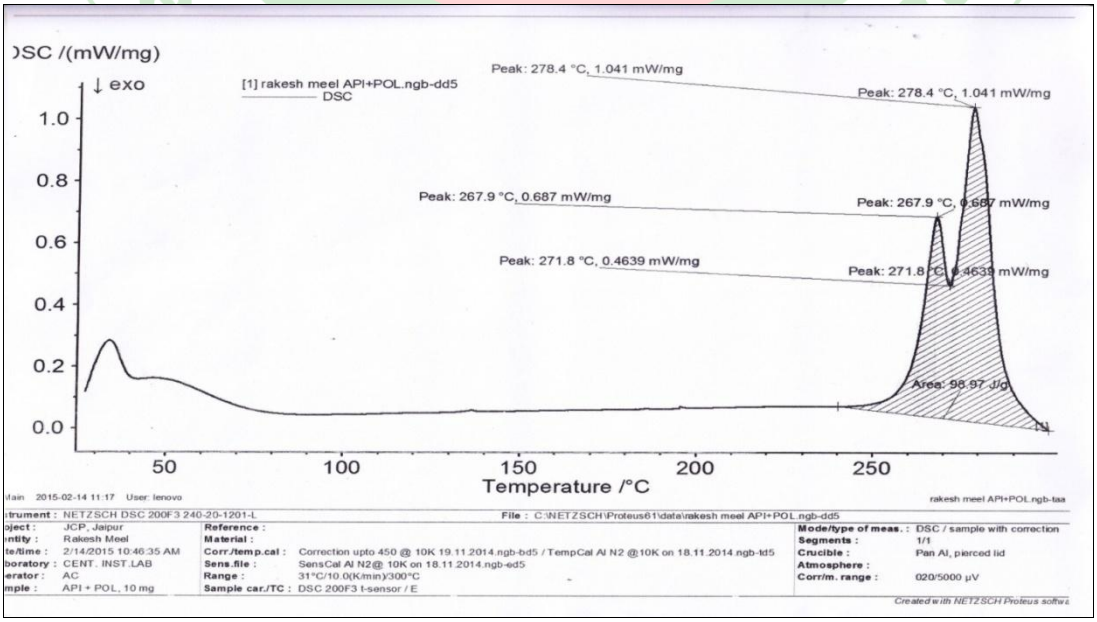

Figure 5 DSC thermogram of physical mixture (Drug + excipients)

Optimization using multiple linear regression and surface methodology

Various RSM computation for the optimization study were performed employing Design Expert® software 10 trial version Statistical second order model was generated for multiple linear regression for all the response variables. First order model equation shows as in below

$$Y = bo + b_1X_1 + b_2X_2 + b_1X_1^2 + b_2X_2^2 + b_{12}X_1X_2 \ldots\ldots\ldots\ldots\ldots$$

Where Y is the independent variable, Y indicates the quantitative effect of the independent variables X_1 and X_2,b_0 the intercept for all the nine runs, b_1-b_5 are the coefficients of the term X. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factor are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. The simplified models were then used to produce 3-D response surface plots and contour plots to study the influence of independent variables. The polynomial equation was used to draw results after considering the intensity of coefficient and mathematical sign it carries, i.e. positive or negative. A positive sign signifies synergistic effect and negative sign signifies antagonistic effect. Statistical validity of the regression analysis was established on the basis of ANOVA provided in the Design Expert® software. Level of significance was considered at $p<0.05$. Also, 3-D response surface plots and contour plots were generated with the help of software for better elucidation.

RESULT AND DISCUSSION

Physicochemical analysis.

The physicochemical parameters of the prepared films are summarized in Table 3 the thickness of fast dissolving films was in the range of 0.171±0.001 to 0.208±0.001 mm. The PH and drug content of films was within acceptable range. The weight of films was in the range of 38.054±0.35 to 48.038±0.55. Tensile strength and percent elongation was in the range of 1.35±0.183 to 3.93±0.115 and 30.27±1.81 to 40.35±1.57 respectively. Folding endurance was in the range of 142±6.9 to 198±5.45.

Drug –excipient interactions.

FTIR-

shows appearance or disappearance of peaks and/or the shift of their positions are often indications of interactions such as hydrogen bonding. Terbutaline sulphate presented characteristic peak at 3373.61 cm^{-1} due to NH, did not deviate from its position in presence of excipients can be concluded as no interaction between drug and excipients.

DSC analysis-

DSC thermogram of Terbutaline sulphate exhibited melting point at 272-274^{0}C. The mixture of drug, HPMC K15 LV and SSG, and Physical mixture (without drug) which was kept in accelerated condition of 40^{0}C/ 75% RH for 30 days and subjected to DSC analysis. The characteristic melting point of terbutaline sulphate does not deviated from 272-274^{0}C that predicts that there is no interaction between drug and excipients

Effect of formulation variable on Disintegration time

The constant and regression coefficient for Disintegration time were as follows:

$$Y = 21.067 + 4.434X_1 - 3.4X_2 + 3.9X_1^2 - 0.8X_2^2 + 2.3X_1X_2 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots$$

Final regression equation in terms of Coded factors was X_1 is Amount of HPMCK15LV and X_2 is Amount of Sodium Starch Glycolate.

The multiple linear regression equation and ANOVA for disintegration time (Y_1) was found significant with an F value of 33.25 ($p=0.0078$).The value of correlation coefficient (r^2) was found to be 0.9822. Equation indicates that X_1, X_2, X_1^2 and X_1X_2 are significant terms. From the both Contour plot and 3D Response surface plot it was observed that Disintegration time increases with increase in HPMC concentration where as Disintegration time decreases with increase in concentration of Sodium starch glycolate.

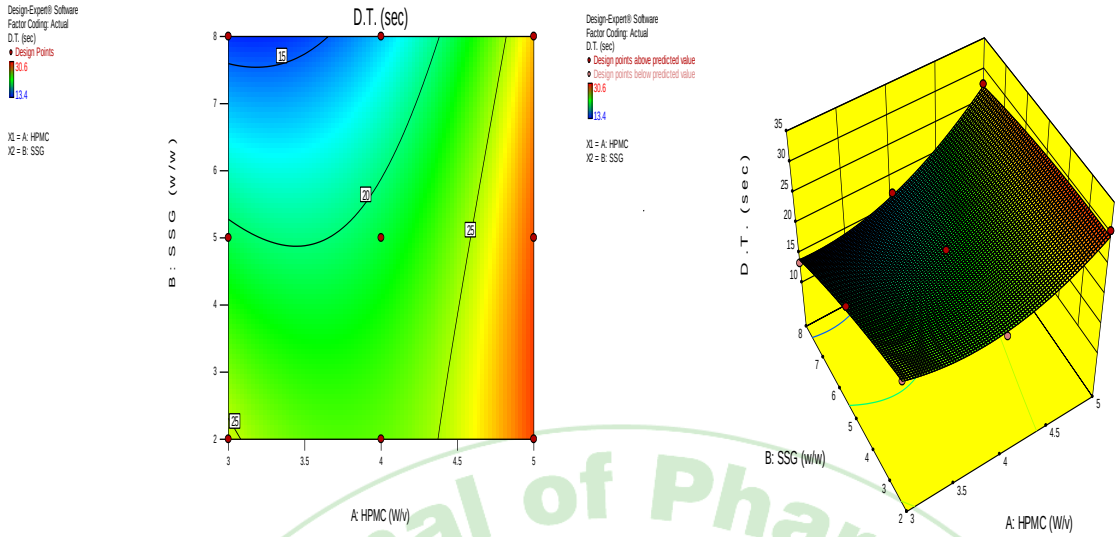

Fig 6 Contour plot and 3D response plot for disintegration time

Effect of formulation variable on Tensile Strength

$$\text{Tensile Strength} = 3.1344 + 0.4133\,X_1 - 0.01833\,X_2 + 0.1134X_1^2 - 0.592X_2^2 + 0.865X_1X_2 \ldots$$

When the model terms for Y Tensile strength were fitted in the polynomial quadratic model, they were found to be significant with an F value of 1572.23 ($p<0.0001$). The value of correlation coefficient (r^2) was found to be 0.9996. In this equation the effect of factors X_1, X_1^2, $X_2^2$and X_1X_2 are significant. HPMC have most prominent effect on Tensile strength where as Sodium starch glycolate has negative effect on tensile strength.

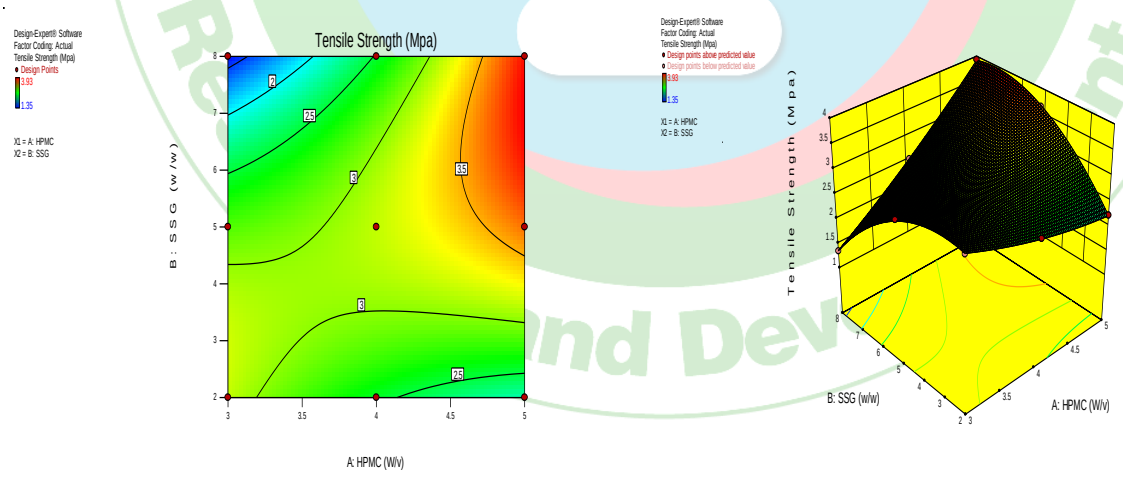

Fig 7 Contour plot and 3D response plot for Tensile strength

Effect of formulation variable on Folding Endurance

$$\text{Folding Endurance} = 159.889 + 12.334\,X_1 - 6.667X_2 + 28.667X_1^2 - 9.334X_2^2 + 8.75X_1X_2 \ldots$$

When the model terms for Y (Folding Endurance) were fitted in the polynomial quadratic model, they were found to be significant with an F value of 49.31 ($p<0.0004$). The value of correlation coefficient (r^2) was found to be 0.987.

Both contour plot and response surface plot shows that Folding endurance of films increases at higher level of polymer and at low level of

polymer slight increase in folding endurance observed. Effect of HPMC is more than twice prominent then SSG. Folding endurance of film increase at low level of SSG it will slightly increase at intermediate level and at higher level it get slight decrease due to its negative impact.

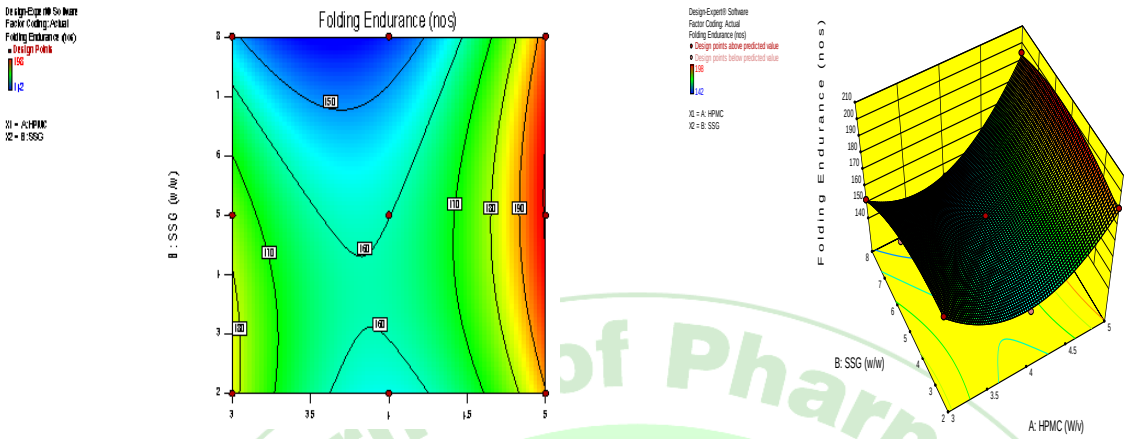

Fig 8 Contour plot and 3D response plot for folding endurance

Effect of formulation variable on Cumulative Percent Drug Release in 10min

$$CPR\ 10min = 93.611 - 3.519X_1 + 3.572X_2 - 3.112X_1^2 + 0.1794X_2^2 - 0.45X_1X_2 \ldots\ldots\ldots$$

When the model terms for Y (CPR_{10min}) were fitted in the polynomial quadratic model, they were found to be significant with an F value of 12.90 (p=0.0306). The value of correlation coefficient (r^2) was found to be 0.955.

In this equation the effect of both factors A and B are significant.

HPMC shows negative effect on CPR so, as the concentration of HPMC increases the CPR decreases significantly, where as SSG has significant positive impact on CPR, at higher level of SSG higher Drug release was observed.

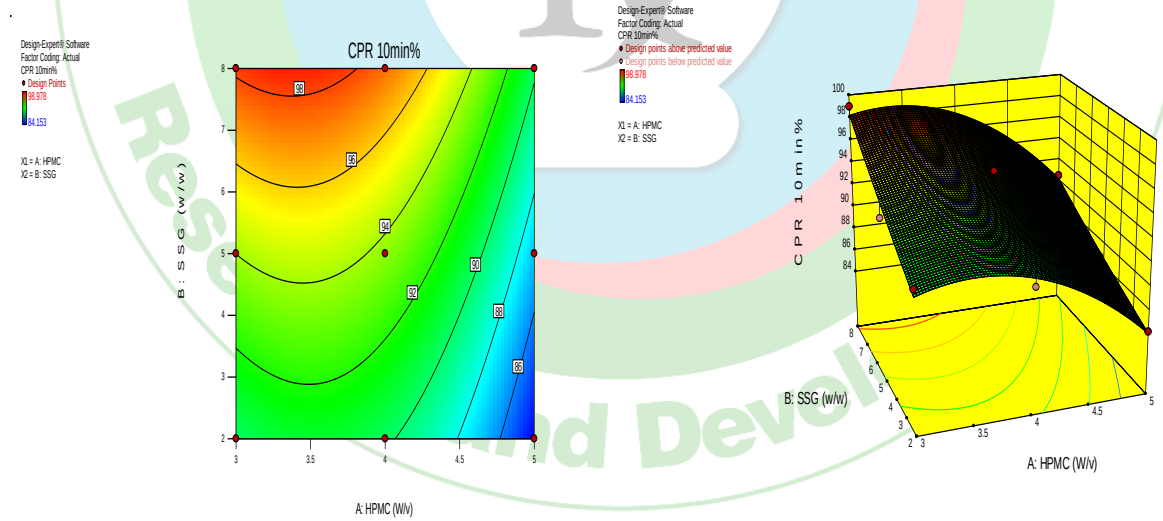

Fig 9 Contour plot and 3D response plot for disintegration time

The results of ANOVA for the dependent variables (Table) for the dependent variables shows the model was significant for all the response variables

CONCLUSION

The formulation of fast dissolving oral films of terbutaline sulphate from design of experiment and optimization with the help of response surface methodology involving the factors as amount of film forming polymer(HPMC

E15LV) and superdisintegrant (sod. Starch glycolate) and responses taken as disintegration time, tensile strength, folding endurance and cumulative percent drug release at 10 minutes($CPR_{10\ min}$).The formulation FDF3 was found to be optimized formulation with desirable disintegration time, tensile strength, folding endurance and maximum cumulative percent drug release at 10 minutes($CPR_{10\ min}$) in the oral cavity . One major advantage of the fast dissolving oral films is that they dissolve in oral cavity within seconds without leaving any residue. Terbutaline sulphate fast dissolving oral films will be potentially useful to patients for pediatric and geriatric or patients with dysphagia or who are travelling that require an immediate relief from asthmatic attacks.

Table 4: Results of analysis of variance (ANOVA) of measured responses

Disintegration time (Sec.)								
Parameter	**df**	**SS**	**MS**	**F**	**Significance F**	**R**	**R2**	**Adj. R^2**
Regression	5	240.146	48.029	33.251	0.007	0.991	0.982	0.952
Regression	4	238.866	59.716	42.553	0.001	0.988	0.9770	0.954
Residual	3	4.333	1.444					
Residual	4	5.613	1.403					
F calculated	0.886							
F tab	10.127							
Tensile strength (Mpa)								
Regression	5	4.745	0.949	1572.23	2.53	0.999	0.999	0.998
Residual	3	0.001	0.0006					
Total	8	4.747						
Folding endurance								
Regression	5	3303.361	660.6722	49.31071	0.004427	0.993	0.987	0.967
Residual	3	40.19444	13.39815					
Total	8	3343.556						
CPR 10_{min}								
Regression	5	171.3675	34.27349	12.89662	0.030562	0.977	0.955	0.881
Regression	2	151.0259	75.51297	16.00178	0.003935			
Residual	3	7.972667	2.657556					
Residual	6	28.31421	4.719034					
F calculated	28.31							
F tab	9.276628							

CONFLICT OF INTERESTS

The authors report no conflict of interests.

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