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Research Article

# Effects of Maltodextrin and Glycerin on Mechanical Properties of Oral Fast Dissolving Film of Salbutamol Sulphate

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**ABSTRACT**

In the present investigation experimental design techniques was used for the preparation and optimization of mouth dissolving film of salbutamol sulphate containing maltodextrin (MDX) and glycerine (Gly). A $3^2$ factorial design was used to study the effect of amount of MDX (X1) and Gly (X2) on the responses: tensile strength (TS), elastic modulus (EM) and elongation at break (EB). Analysis of variance (ANOVA) was performed for different variable. The numerical optimization technique based on the desirability approaches was used to optimize oral fast dissolving film (OFDF). The optimized OFDF 10, which contained 55.0 % MDX and 19.99 % Gly, showed 0.25 MPa TS, 0.131 MPa EM and 113.25 % EB. The observed values were more identical to predicated value.

**Key words:** Oral Fast Dissolving Film, Factorial Design, Tensile strength, Elongation at break, Elastic modulus.

## INTRODUCTION

Research and development in the oral drug delivery segment has led to great interest in the development of oral fast dissolving film (OFDF). Basically the OFDF can be described as an ultra thin film of postage stamp size with an active pharmaceutical ingredient (API) and other excipients. A fast dissolving film has been achieved a great role to deliver medicine to the patient, who have difficulty in swallowing (Okabea et al., 2008, Nishigaki et al., 2012). The advantages of convenience of dosing and portability of OFDF have resulted to acceptableness of this dosage form by paediatrics as well as the geriatric population equally (Dixit and Puthli, 2009, Arya et al., 2010, SURYADEVARA, 2010, Corniello, 2006, Reinera et al., 2010). The advantages of OFDF include larger surface area that leads to rapid disintegrating & dissolution, flexible in handling & transportation, accuracy in the administered dose and consumer-friendly due to its ease of swallowing property(Liew et al., March 2012).

Asthma is defined as a chronic inflammatory disease of the airways, which includes bronchial hyperactivity and bronchospasm characterized by tracheobrochial tree hyperresponsiveness to a variety of stimuli, resulting in the constricting of the airways, often went with by hypersecretion of mucus increased secretions resulting in dyspnea, wheezing cough, chest congestion and anxiety about being unable to breathe (Kim and Mazza, 2011). Asthma prevalence has raised very substantially in the late decades such that it is now one of the commonest chronic disorders in the world (Anandan C et al., 2010) . Asthma now affects an estimated 4 to 7% of the people worldwide (Pal et al., 2009). It smites approximately 53 million people across world mostly in United States, France, Germany, Italy,

Spain, United Kingdom, and Japan. Due to complications arising from serious asthma attack morbidity rate is more than 4000 people in India (S. Dineshmohan et al., 2010). Salbutamol sulphate, a selective $\beta_2$-adrenergic agonist and bronchodilator, is one of the widely used drugs for the treatment of the most respiratory diseases arising due to airway obstruction. Salbutamol sulphate is usually administered via inhaled route for direct effect on bronchial smooth muscle. This is normally achieved through metered dose inhalers (MDIs), with or without spacers, dry powder inhalers, and other aerosol systems. All these drug delivery systems have many drawbacks like inaccuracy of dosing (ten percent of administered dose deposited on the bronchi while rest of the drug is deposited in oropharynx), dry powder inhalers cause clogging of device, patient compliance due to the presence of chloro fluoro carbon (CFC), cost of the preparation and frequency of administration (Vasantha et al., 2011, Pandey et al., 2013). In order to overcome these disadvantages, in the present work, we developed fast dissolving film of salbutamol sulphate by using maltodextrin (MDX).
The objective of this study was to examine the essence of concentration of film forming polymer (maltodextrin) and plasticizer (glycerin) on the physicochemical, mechanical and disintegration properties of fast dissolving film of salbutamol sulphate s by using $3^2$ design.

## MATERIAL AND METHODS

### Material

### Preparation of fast dissolving film

The maltodextrin (MDX) and glycerine (Gly) were dispersed in distilled water at 80 $^0$Cand stir for 4 hr at 2000 rpm (Solution A). Saccharine sodium, Pineapple flavour and salbutamol sulphate were separately dissolved in 10 ml of distilled water (Solution B) and mixed to the solution A prepared and cooled earlier. The volume was making up to 50 ml with distilled water and stir for 1 hr at 2000 rpm. This final solution was kept for 1 hr to remove all the entrapped air bubble and 5 ml of this solution was cast in to polypropylene petri plate. The petri plates were dried in a tray dryer at 60$^0$C for 6 hr. The film was removed from petri plate and stored in a desiccator (Cilurzo et al., 2008, Cilurzo et al., 2010).

### Fourier Transform Infrared Spectroscopy

Compatibility among drug and excipients to be used for preparation of OFDF was evaluated by infrared spectroscopy. Furthermore, samples of salbutamol sulphate and physical mixture were characterized by Fourier transform infrared (FTIR) spectroscopy (840, Shimadzu, Japan) of pure drug and optimize formulation (OFDF 10).The pellets of sample and potassium bromide were prepared by compressing at 20 psi on hydraulic press and spectra range was 4000-600 cm$^{-1}$. Each spectrum was acquired by performing 32 scans (Pandey et al., 2013).

### Experimental Design

In this work a $3^2$ randomized full factorial design was used for the optimization of OFDF. The effect of two factors, each at 3 levels on the mechanical property of OFDF was studied at 3 levels and experimental trials were performed at all 9 possible combinations. The amount of MDX and the amount of Gly were selected as the independent variables. The tensile strength (TS), elongation at break (EB) and Elastic Modulus (EM) were selected as dependent variables. The responses were analyzed using ANOVA and the individual response parameters were evaluated using F test and polynomial equation was generated for each response using multiple linear regression analysis (MLRA). The study design including investigated factors and responses is shown in Table 1.
A suitable OFDF should have a moderate tensile strength, high % elongation and low elastic modulus therefore the optimized formulation was prepared which have the TS in range, EB is maximize and EM is minimize(Mashru et al., 2005, Pandey et al., 2013). Constraints for responses and factors are shown in Table 2. By utilizing the software, we got one solution for optimized formulation. The optimized formulation is prepared and evaluated for TS, EB and EM. Observe response value of the optimized formulation is compared with predicted value.

### Film thickness

The film thickness was measured using a micrometer (Mitutoyo,model 102-309, Tokyo, Japan) with an accuracy of ±1 µm. Each film sample was measured at random five positions (centre and four other positions along the strip).An average value was reported. The average thickness was used to calculate mechanical properties of each film sample.

### Film Flexibility

The film flexibility was measured using ASTM bend mandrel test method (D 4338 – 97) as described in previous work(Pandey et al., 2013). A 2 X 3 cm film was bended over a mandrel and observed for cracks in a strong light. The acceptance criteria for flexible was, no cracks was shown at 5x magnification (Cilurzo et al., 2008, 2004).

### Flatness

Longitudinal strips of prepared patches were cut and length of each strip was measured. Constriction (%) was calculated using following formula

$$Constriction\% = \frac{(l_1 - l_2)}{l_2} X\ 100$$

Where: $l_1$ was initial length of each strip and $l_2$ was final length.

The value 100 – constriction (%) was considered as flatness of patch.

**Surface pH measurement**

The pH OFDF must be neutral, so that no irritation occurs after administration in oral mucosa. The surface pH of OFDF was determined according to method described by Bottenberg *et al*. OFDF were kept to swell on surface of agar plate (prepared by dissolving 2% agar in warmed isotonic phosphate buffer (pH 6.8) under stirring and then pouring the solution into a Petri dish till it gelled at room temperature).The pH of OFDD was assessed by getting the electrode in contact with surface of OFDF, letting it to equilibrate for 5 min. The measurement of pH was replicated three times (Vasantha et al., 2011, Bottenberg et al., 1991).

**Morphology Study**

Morphology of prepared film was observed under a scanning electron microscope (Model JSM 5610LV, Jeol, Japan). The samples were attached to slab surfaces with double-sided adhesive tapes, and scanning electron photomicrograph was taken at ×1,000 magnification.

**Uniformity of dosage units of OFDF**

Uniformity of dosage unit of OFDF was determined by assay of 20 units individually using UV spectrophotometric method. The acceptance value (AV) of the preparation is less than 15%, according to the JP15.The AV was calculated according to following equation

$$AV = |M - X| + ks$$

In USP30, the contents should be within a range between 85% and 115%, and the relative standard deviation should be less than or equal to 6.0% (Shimoda et al., 2009, Nishigaki et al., 2012, USP, 2007, Pandey et al., 2013).

**Mechanical properties**

The mechanical properties of OFDF were determined by method used previous (Pandey et al., 2013).Briefly, the film was cut in to 50 mm x10mm strip and equilibrated at $25^0$C for one week. Each OFDF strips were held in tensile grips of texture analyzer positioned at a distance of 30 mm . The crosshead speed was 500 mm/min. The test was considered over at the film break. The tensile strength (force/initial cross-sectional area) and elongation at break ($\Delta l/l_0$) were determined directly using the software Texture Expert V.1.15 (SMS) from the stress x strain curves, and the elastic modulus was calculated as the slope of the linear initial portion of this curve (Chatterjee et al., 2010, Cilurzo et al., 2008, Peh and Wong, 1999).

***In Vitro* disintegration study**

Disintegration of fast disintegrating preparation *in vivo* is attained by saliva, however amount of saliva in the mouth is limited and official disintegration test was not correlate with in vivo conditions. A modified method actually reported by Fu et al.(2006) for fast disintegrating tablet was used to determine disintegration time of the OFDF. A cylindrical vessel was used in which 10-mesh screen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve. To ascertain disintegration time, 3 ml of Sorenson's buffer (pH 6.8), was placed inside the vessel. The OFDD was kept on sieve and whole assembly was shook. The disintegration time is the time when all the particles pass through the sieve (Late et al., 2009, Fu et al., 2006).

***In vitro* dissolution study**

The *in vitro* drug dissolution study was carried out in 100 mL of Sorenson's buffer (pH 6.8) at 37.0±0.5°C, using USP 23 type 2 paddle method (Electrolab, EDT-08Lx) at a stirring speed of 50 rpm. The OFDF of 6 $cm^2$ was fixed on the glass disk with the help of a cyanoacrylate adhesive. The disk was put at the bottom of the dissolution vessel so that the OFDF remained on the upper side of the disk. 3 mL of samples were withdrawn at predetermined interval (1,2, 3,4, 5, 10, 20 and 30 min) and replaced with fresh medium. The samples were filtered through 0.45 µm filter and appropriately diluted with Sorenson's buffer (pH 6.8) and assayed spectrophotometrically at 278 nm **(Vasantha et al., 2011)**.

**RESULT AND DISCUSSION**

In the present study, solvent casting method was used because of its ease of manufacture and lower cost (Dixit and Puthli, 2009). The OFDF formulations were evaluated for important parameters like appearance, film thickness, flexibility, flatness and surface pH. The prepared OFDF formulations were transparent, flexible, flat and uniform in thickness. SEM of OFDF 10 shows that prepared formulation was homogenous with rough surface. The mean thicknesses of the OFDF formulations were 0.37 ± 0.06 – 0.42 ± 0.06 mm, there was no stastically significant difference (P > 0.05) in thickness among the OFDF formulation (Table 5). The result of the film flexibility study showed no cracks after bended over a mandrel at a 5 x magnification in a strong light. The flexibility of film is also indicated by result of mechanical property test. The flatness study showed no constriction in the transdermal patches. The pH of OFDF formulations (Table 5) were found to be within the range 6.8 ± 0.08 -7.2 ± 0.18, which is

within the limit. The almost neutral pH reflected, the OFDF will be non-irritant to oral mucosa.

The OFDF formulations showed good drug content which varied between 95.23 ± 0.64 and 98.54 ± 0.46 %, with acceptance value (AV) ranged from 1.10 -6.98, within the limit (For L1, AV≤15) as per JP 15. Moreover relative standard deviation (RSD) varied from 0.44-0.93. Thus the OFDF formulations complies the USP 32 content uniformity specification.

*In vitro* disintegration time is very important for mouth dissolving formulation which is desired to be less than 60 s. The rapid disintegration may be due to the rapid uptake of water from the medium, swelling, burst effect and thus promoting bioavailability. The OFDF formulations had disintegrated within the 20.3 ± 0.24 - 43.12 ± 0.24 sec, which is met with acceptable limit. In addition disintegration time was reduced as the glycerine concentration increased and MDX concentration decreased (figure 2). Dissolution test was done in Sorenson's buffer (pH 6.8). Result (figure 3) shows that all OFDF formulations were shown rapid dissolution, in which approximately 60.23 – 94.36 % drug release with in 5 minute.

Strength and elasticity of the films were indicated by mechanical properties of film such as elastic modulus (EM) tensile strength (TS) and percentage elongation at break (%EB). It depends on the amount of film forming polymer and plasticizer. Film has to be strong enough and ductile to prevent rupture during processing and administration. Mechanical properties result showed that all the designed film formulations were flexible and soft, also supported by film flexibility study. Elastic modulus and tensile strength decreased as glycerine concentration increased, but elongation at break increased.

**Optimization of OFDF formulations by $3^2$ factorial designs**

To fabricate a oral fast dissolving film formulations, amount of film forming polymer (MDX) and plasticizer (Gly) amount are critical process parameters (CPPs), whereas mechanical properties (TS, EM and EB) are critical quality attributes (CQAs). A $3^2$ factorial design was employed to determine the optimum amount of film forming polymer (MDX) and plasticizer (Gly) to obtain a soft and elastic oral fast dissolving film with good mechanical strength. A total of 9 trial formulations were proposed by $3^2$ factorial design for two independent variables at three level (table 1). Overview of the experimental trial and observed responses are presented in Table 1.

The responses were analyzed using one way ANOVA and Polynomial models including interaction and quadratic terms were generated for each response variables using multiple linear regression analysis (MLRAs). The polynomial equation generated by this experimental design was as follows:

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where $y_i$ is the dependent variable,

$b_0$ is the arithmetic mean response of the 9 runs; and $b_1$ and $b_2$ are the estimated coefficients for the independent factors $X_1$ and $X_2$, respectively.

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 2 factors are simultaneously changed. The polynomial terms ($X_1^2$ and $X_2^2$) are including investigating nonlinearity.

The outcome of the analysis of variation (ANOVA) for responses TS (Y1), EM (Y2) and EB (Y3) ($P > 0.05$) were shown in table 3. The model F-value and high R square values indicated that these models were significant.

ANOVA results indicate that significant factors regarding the response TS (Y1) were main effects (X1 and X2), quadratic contribution (X12 & X22) along with interaction term (X1X2). The results of multiple linear regression analysis (MLRA) show that the coefficient $b_1$ have a positive sign for TS (Y1). Thus, an increase in MDX amount leads to increase in TS. Moreover the coefficient b2 bears a negative sign; indicate the antagonistic effect of X2. Hence, TS decreased as the amount of glycerine increased. MLRA result also shows that the effect of X2 (the amount glycerine) was greater than the effect of X1 (the amount of MDX). The polynomial equation for TS as response is as follows

$$TS = 0.78 + 0.21X_1 - 0.37X_2 - 0.044X_1X_2 - 0.058X_1^2 + 0.062X_2^2$$

For the response EM (*Y*2) ANOVA result revealed that EM was significantly affected by the main effects (*X*1 & *X*2). The polynomial equation (full model) for EM as response is as follows

$$EM = 0.286 + 0.0116X_1 - 0.0397X_2$$

The multiple linear regression analysis and equation (table 4) show that the effect of X2 (amount of glycerine) was more significant than the effect of X1 (concentration of MDX). Moreover the coefficient b2 bears a negative sign; indicate the counter effect of X2. Therefore, EM decreased as the amount of glycerine increased. But coefficient b2 have a positive sign, hence an increase in MDX amount leads to higher elastic modulus.

Mathematical relationship generated using multiple linear regression analysis for the response Y3 (EB) is expressed as follows

$$EB = 84.22 - 12.47X_1 + 28.70X_2 - 0.19X_1X_2 + 3.05X_1^2 - 14.18X_2^2$$

ANOVA result revealed that EB was significantly affected by the main effects (*X*1 & *X*2), quadratic contribution ($X_2^2$), while $X_1X_2$ and $X_1^2$ had no statistic significance ($p > 0.05$).
Model simplification was carried away by eliminating non-important terms ($p > 0.05$) and the equation for reduced model is as follows

$$EB = 86.22 - 12.47X_1 + 28.70\,X_2 - 14.18\,X_2^2$$

For response EM (Y3), the coefficient b1 bear a negative sign; indicate the counter effect of X1 (amount of MDX), thus, elongation at break decrease as an increase in MDX amount. But elongation at break increases with increase in glycerine amount as coefficient $b_1$ bear a positive sign. Moreover the effect of X2 (the amount glycerine) was more significant than the effect of X1 (the amount of MDX).
To optimize OFDF formulation a numerical optimization technique based on the desirability approach was taken. In this study optimization was performed with constraints for responses and factors as presented in Table 5 and figure 4. The optimal, calculated parameters were independent variable $X_1$ (amount of MDX) and $X_2$ (amount of glycerine) for formulation of optimize formulation were 55.0 % & 20.0 % respectively (Table 1&5). The observed value of Y1 (TS), Y2 (EM) and Y3 (EB) of check point batch/optimize formulation were in close agreement with the value predicted by the model.

## CONCLUSION

In closing, the formulation of oral fast dissolving film of Salbutamol sulphate using solvent casting method is viable. Moreover we may prepare mouth dissolving film with excellent mechanical properties by employing design of experiment based on $3^2$ factorial designs. The optimized mouth dissolving film was made with 55.0 % w/w MDX and 19.99 % w/w Gly. This developed optimized oral fast dissolving film showed rapid disintegration and dissolution of OFDF with good flexibility and tensile strength, thus the oral fast dissolving film as one of the promising tool for delivery of salbutamol in order to achieve rapid disintegration, improved patient compliance and bioavailability.

**Table 1: $3^2$ Factorial design layout**

| Formulation | Variables in coded Form | | TS | EB | EM |
|---|---|---|---|---|---|
| | X1(%) | X2(%) | | | |
| **OFDF 1** | -1 | -1 | 0.879 | 0.334 | 57.8 |
| **OFDF 2** | 0 | -1 | 1.23 | 0.38 | 40.77 |
| **OFDF 3** | 1 | -1 | 1.39 | 0.45 | 31.57 |
| **OFDF 4** | -1 | 0 | 0.528 | 0.229 | 96.96 |
| **OFDF 5** | 0 | 0 | 0.761 | 0.262 | 86.44 |
| **OFDF 6** | 1 | 0 | 0.923 | 0.372 | 75.37 |
| **OFDF 7** | -1 | 1 | 0.25 | 0.141 | 116.12 |
| **OFDF 8** | 0 | 1 | 0.46 | 0.196 | 97.1 |
| **OFDF 9** | 1 | 1 | 0.585 | 0.231 | 89.12 |
| **OFDF 10** | **55.00** | **19.99** | **0.25** | **0.131** | **113.24** |
| **Coded Value** | **Actual Value (%)** | | | | |
| | **X1** | **X2** | | | |
| -1.000 | **55** | **15.0** | | | |
| 0.000 | **60** | **17.5** | | | |
| 1.000 | **65** | **20.0** | | | |

X1 indicates amount of MDX (%w/w); X2, amount of Gly (%w/w of MDX); TS,Tensile strength (Mpa);EB, Elongation at break(%) and EM (MPa) Elastic modulus. OFDF 10 used as checks point and optimized batch.

**Table 2: Optimization of oral fast dissolving film formulation**

| Constraints | | | | | |
|---|---|---|---|---|---|
| **Name** | **Goal** | **Lower limit** | **Upper Limit** | | |
| Amount of MDX | In range | 55 | 65 | | |
| Amount of Gly | In range | 15 | 20 | | |
| TS (Mpa) | In range | 0.25 | 1.39 | | |
| EM (Mpa) | minimize | 0.141 | 0.45 | | |
| EB (%) | maximize | 31.57 | 116.12 | | |
| **SOLUTION (OFDF 10)** | | | | | |
| **Amount of MDX** | **Amount of PEG 1000** | **TS** | **EM** | **EB** | **Desirability** |
| **55.00** | **19.99** | **0.25** | **0.131** | **113.24** | **0.983** |

TS, Tensile strength (Mpa);EB, Elongation at break(%) and EM (MPa) Elastic modulus. OFDF 10 used as checks point and optimized batch.

**Table 3: Physicochemical properties, Disintegration time and uniformity of dosage form for OFDF formulations**

| Formulation | Thickness | pH | Flatness | Disintegration time | Uniformity | | |
|---|---|---|---|---|---|---|---|
| | | | | | Drug Content | RSD | AV |
| OFDF1 | 0.39 ± 0.08 | 6.9 ± 0.21 | 100 | 32.6 ± 0.21 | 95.23 ± 0.64 | 0.67 | 4.80 |
| OFDF2 | 0.42 ± 0.06 | 6.8 ± 0.16 | 100 | 39.26 ± 0.41 | 98.28 ± 0.56 | 0.57 | 1.56 |
| OFDF3 | 0.38 ± 0.09 | 7.1 ± 0.19 | 100 | 43.12 ± 0.24 | 95.82 ± 0.61 | 0.64 | 4.14 |
| OFDF4 | 0.40 ± 0.01 | 6.9 ± 0.21 | 100 | 25.3 ± 0.23 | 98.54 ± 0.46 | 0.47 | 1.10 |
| OFDF5 | 0.37 ± 0.05 | 7.1 ± 0.18 | 100 | 35.2 ± 0.84 | 97.62 ± 0.43 | 0.44 | 1.91 |
| OFDF6 | 0.38 ± 0.06 | 6.9 ± 0.12 | 100 | 40.2 ± 0.63 | 93.61 ± 0.87 | 0.93 | 6.98 |
| OFDF7 | 0.39 ± 0.03 | 7.2 ± 0.18 | 100 | 20.3 ± 0.24 | 93.60 ± 0.64 | 0.68 | 6.43 |
| OFDF8 | 0.38 ± 0.05 | 6.9 ± 0.13 | 100 | 39.6 ± 0.41 | 97.31 ± 0.48 | 0.49 | 2.34 |
| OFDF9 | 0.37 ± 0.06 | 7.1 ± 0.12 | 100 | 37.82 ± 0.56 | 98.51 ± 0.67 | 0.68 | 1.60 |
| OFDF10 | 0.40 ± 0.08 | 6.8 ± 0.08 | 100 | 38.12 ± 0.23 | 96.81 ± 0.58 | 0.60 | 1.40 |

RSD indicates: relative standard deviation; AV, Acceptance value.

**Table 4 Result of Analysis of variance (ANOVA)**

| **For TS** | | | | | | |
|---|---|---|---|---|---|---|
| **Model** | **Df** | **SS** | **MS** | **F** | **P value** | **$R^2$** |
| FM | 5 | 1.09 | 0.22 | 384.92 | 0.0002 | 0.9984 |
| **Residual** | | | | | | |
| FM | 3 | $1.69 \times 10^{-3}$ | $5.65 \times 10^{-4}$ | | | |
| **For EM** | | | | | | |
| FM | 2 | 0.080 | 0.040 | 128.56 | < 0.0001 | 0.9772 |
| **Residual** | | | | | | |
| FM | 6 | $185.3 \times 10^{-3}$ | $3.09 \times 10^{-4}$ | | | |
| **For EB** | | | | | | |
| FM | 5 | 6295.90 | 1259.18 | 185.60 | 0.0006 | 0.9938 |
| RM | 3 | 6277.10 | 2092.37 | 267.24 | < 0.0001 | 0.9968 |
| **Residual** | | | | | | |
| FM | 3 | 20.35 | 6.78 | | | |
| RM | 5 | 39.15 | 7.18 | | | |

*DF indicates: degrees of freedom; SS, sum of squares; MS, mean of squares; F, ischer's ratio; $R^2$ , regression coefficient.*

**Table 5: Summary of multiple linear regression analysis**

| For TS | | | | | | |
|---|---|---|---|---|---|---|
| Response | $b_0$ | $b_1$ | $b_2$ | $b_{12}$ | $b_{11}$ | $b_{22}$ |
| **FM** | 0.78 | 0.21 | -0.37 | -0.044 | -0.058 | 0.062 |
| **p value** | | 0.0002 | < 0.0001 | 0.0343 | 0.0413 | 0.0351 |
| **For EM** | | | | | | |
| Response | $b_0$ | $b_1$ | $b_2$ | $b_{12}$ | $b_{11}$ | $b_{22}$ |
| **FM** | 0.29 | 0.058 | -0.099 | | | |
| **p value** | | 0.0002 | < 0.0001 | | | |
| **For EB** | | | | | | |
| Response | $b_0$ | $b_1$ | $b_2$ | $b_{12}$ | $b_{11}$ | $b_{22}$ |
| **FM** | 84.22 | -12.47 | 28.70 | -0.19 | 3.05 | -14.18 |
| **p value** | | 0.0013 | 0.0001 | 0.8919 | 0.1959 | 0.0046 |
| **RM** | 86.26 | -12.47 | 28.70 | - | - | -14.18 |
| **p value** | | 0.0001 | < 0.0001 | - | - | 0.0008 |

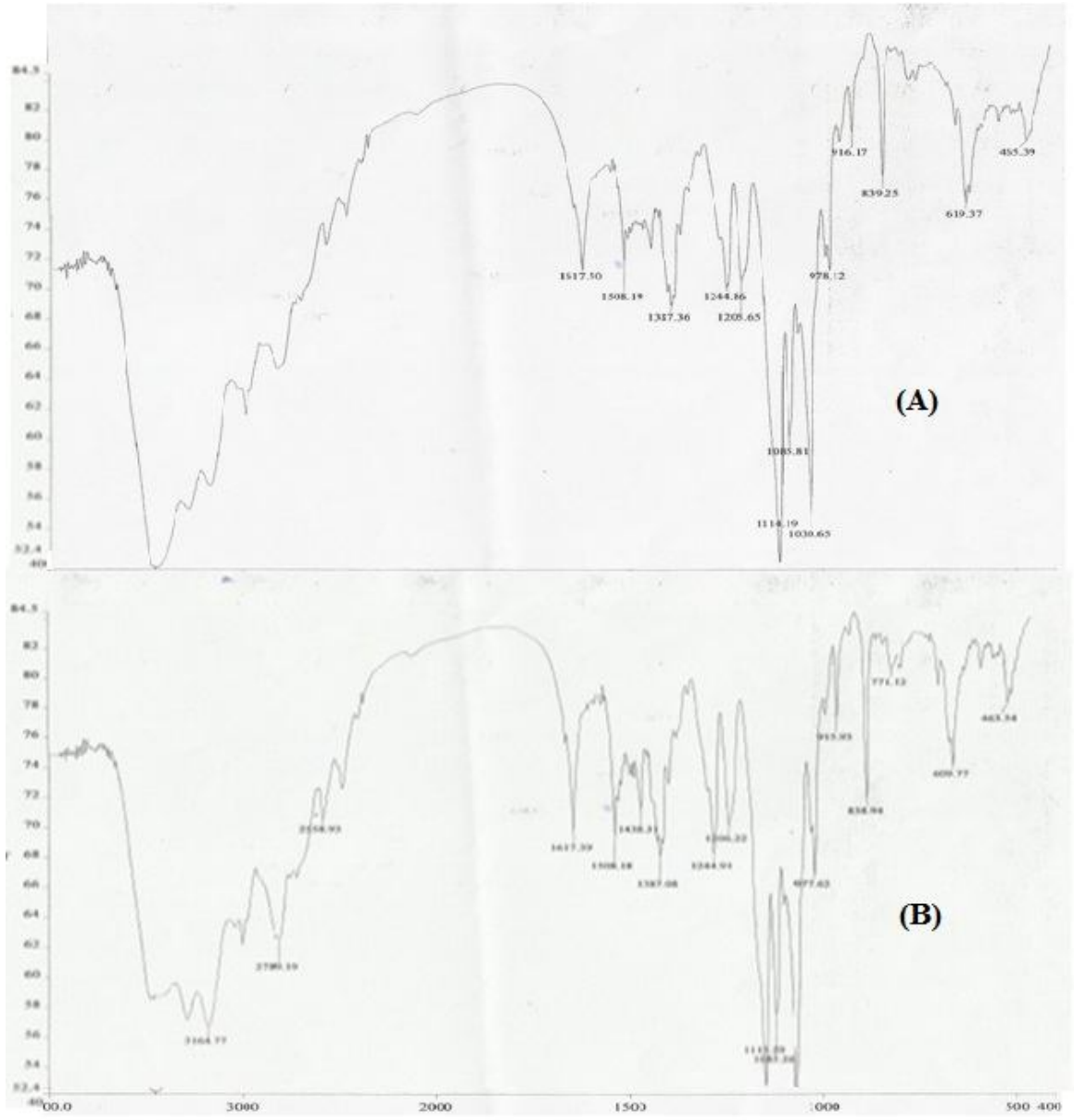


**Figure 1: Drug excipients compatibility study: FTIR spectrum of salbutamol sulphate (A) and physical mixture (B)**

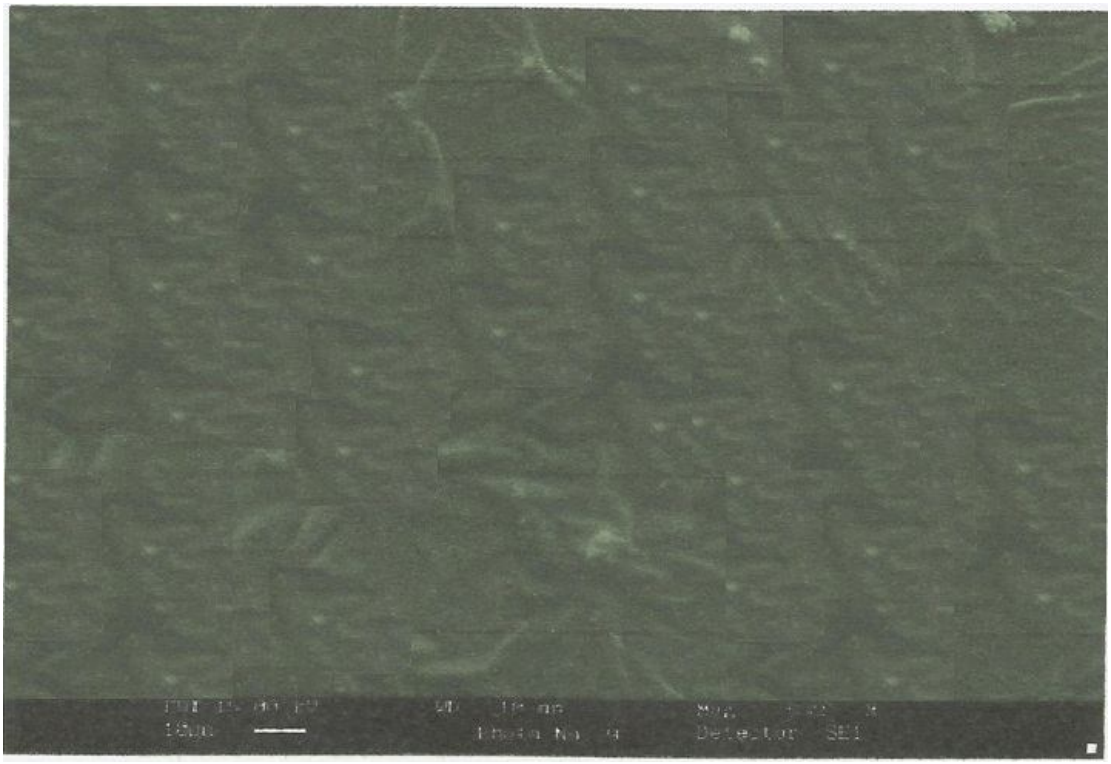

**Figure 2: SEM photograph of oral fast dissolving film (OFDF 10), showing homogenous and smooth surface**

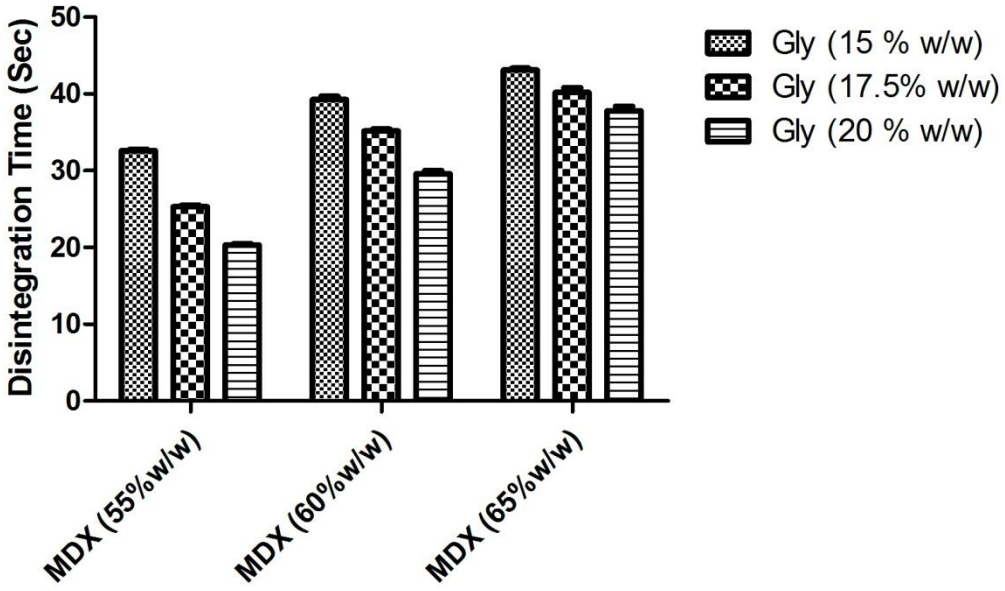


**Figure 3: Effect of maltodextrin and glycerine amount on disintegration time of oral fast dissolving film**

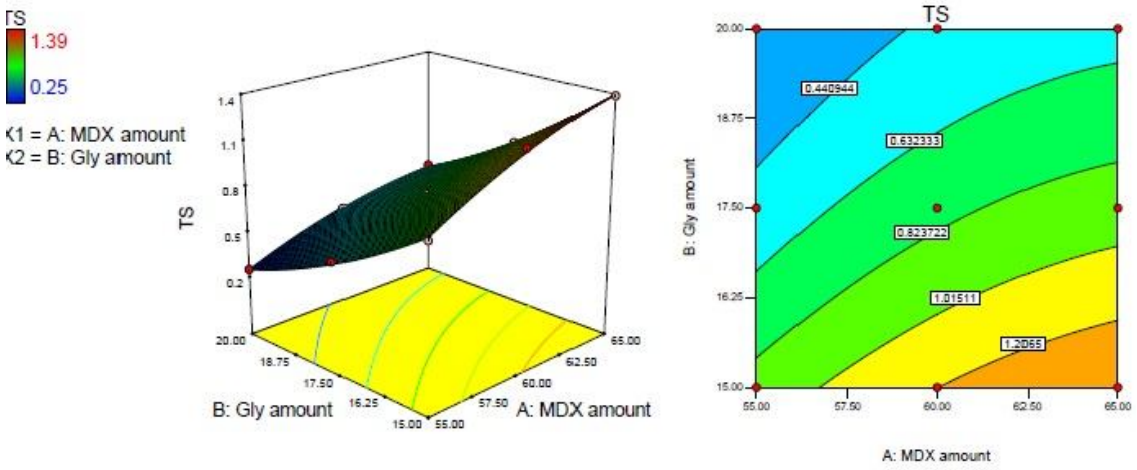


**Figure 4: Three dimensional plot showing the influence of MDX amount and Gly amount on TS (Mpa) and corresponding contour plot showing the relationship between various levels of 2 independent variables.**

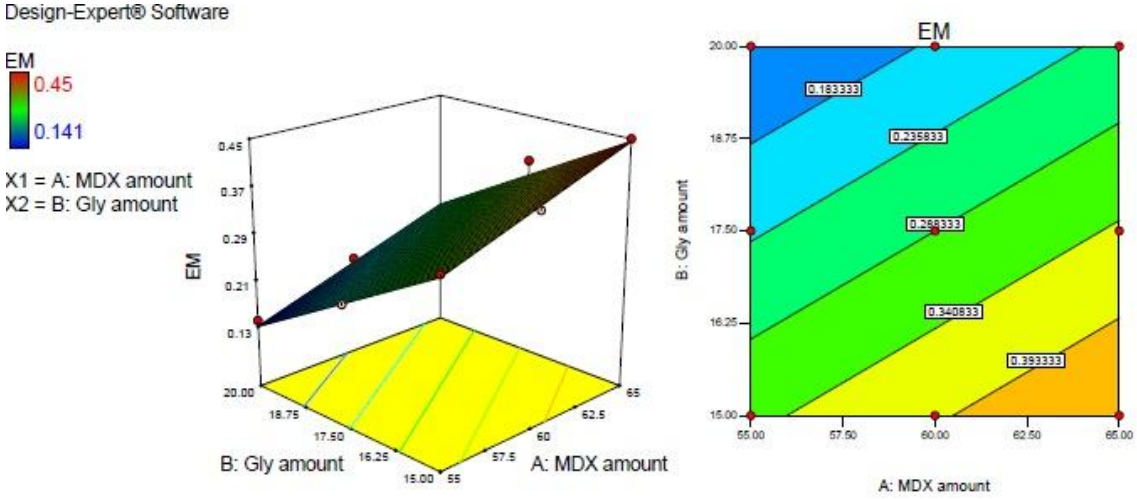


**Figure 5: Three dimensional plot showing the influence of MDX amount and Gly amount on EM (Mpa) and corresponding contour plot showing the relationship between various levels of 2 independent variables.**

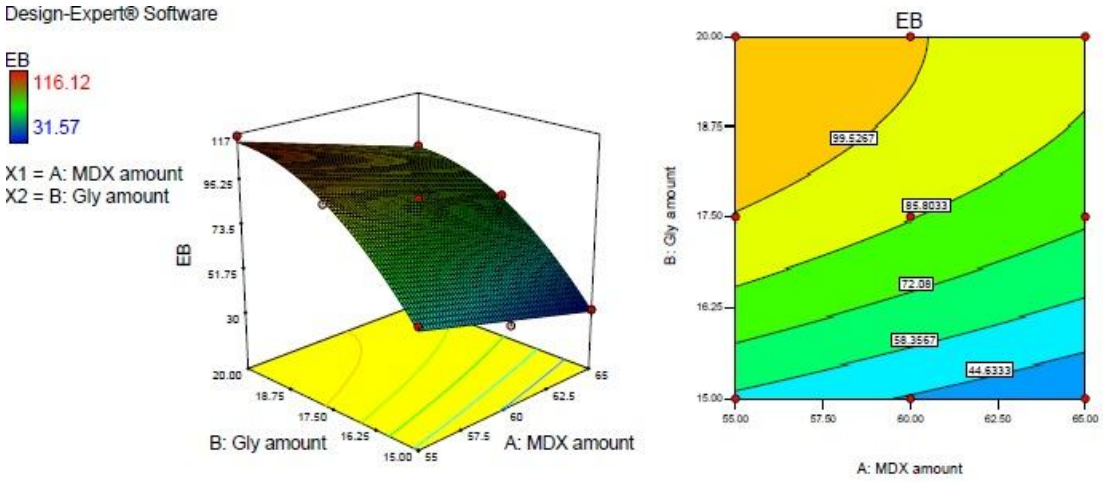


**Figure 6: Three dimensional plot showing the influence of MDX amount and Gly amount on EB (%) and corresponding contour plot showing the relationship between various levels of 2 independent variables.**

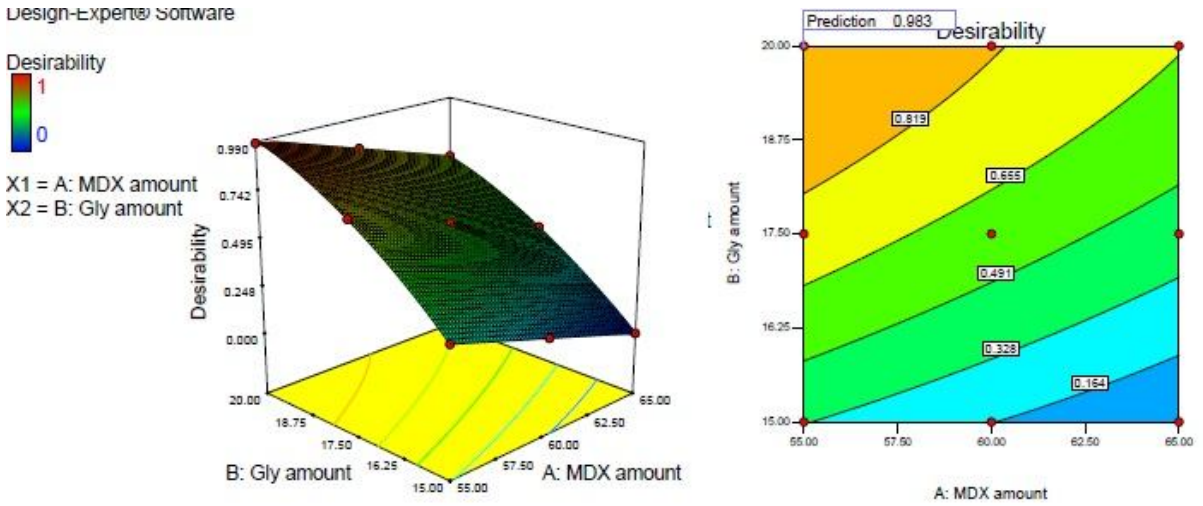


**Figure 7: Three dimensional plot and corresponding contour plot showing the desirability approach**

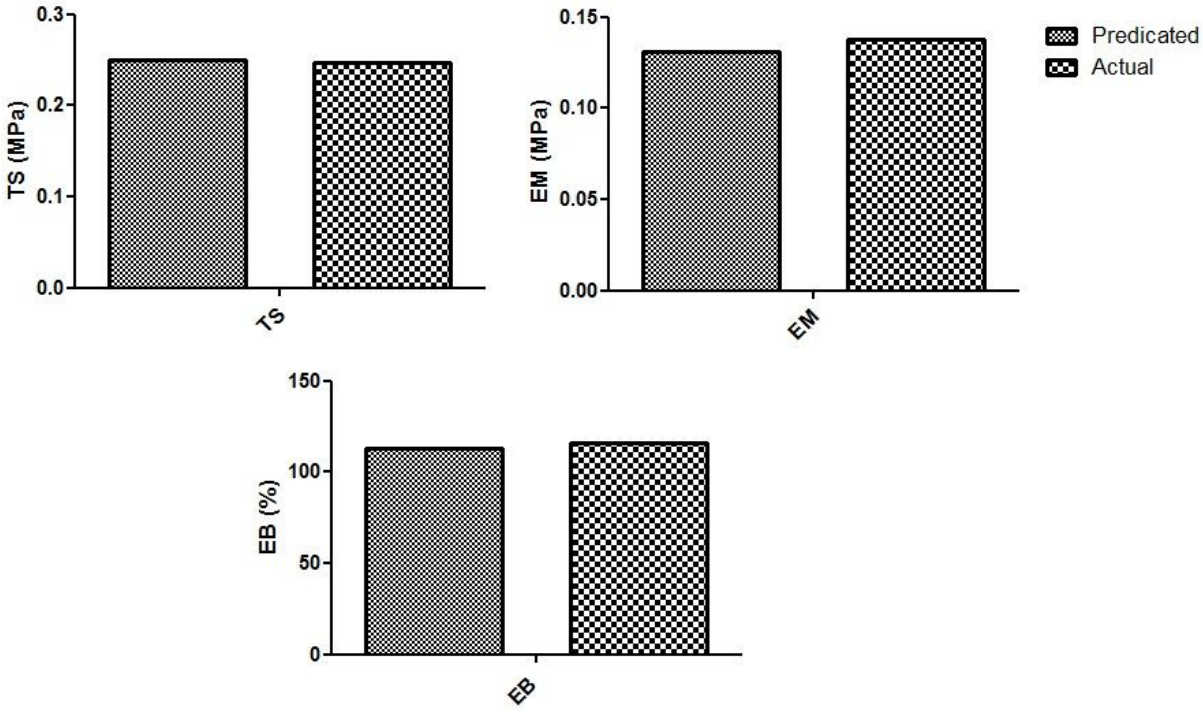


**Figure 8: Comparison between actual and predicated value of dependent variables (TS, EM and EB)**

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