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# Optimization of Formulations of Metoprolol Succinate Tablets Containing Ofada Rice Starch Acetate as Tablet Matrix for Sustained Release Using Response Surface Methodology

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

## Abstract

**Background**: Release-retarding polymers in matrix tablets play a vital role in controlling drug release from tablets.
**Objectives**: To prepare metoprolol succinate tablets by direct compression using Ofada rice (*Oryza glaberrima* Steud) starch acetate, degree of substitution (DS) 2.22, as a matrix for sustained release.
**Materials and methods**: The central composite design and response surface methodology were applied to evaluate the interactive effects of three variables: percent content of starch acetate ($X_1$), compression pressure ($X_2$) and compression time ($X_3$), on tablet crushing strength, friability and dissolution time ($t_{80}$).
**Results**: Crushing strength was 90.0 to 140.50 N; Friability 0.05 to 0.90 % and $t_{80}$ 5.75 to 11.50 h. $X_1$ and $X_2$ had significant effects on crushing strength and dissolution time ($p < 0.0001$). The interactions between $X_1$ and $X_2$ and those between $X_1$ and $X_3$ were significant on crushing strength and dissolution time, and on friability respectively ($p < 0.0001$). The correlation coefficients indicated that the regression model represented the experimental data well (**$R^2$ = 0.9971 and $R^2$ (Adj) = 0.9944 for crushing strength; $R^2$ = 0.9976 and $R^2$ (Adj) = 0.9954 for friability; $R^2$ = 0.9979 and $R^2$ (Adj) = 0.9961 for $t_{80}$). Optimized conditions for formulation of metoprolol succinate tablets were 60 %w/w Ofada starch acetate; 150 $MNm^{-2}$ compression pressure and 60 s compression time.
**Conclusion**: Optimized formulations of metoprolol tablets containing Ofada starch acetate with good mechanical strength and prolonged dissolution can be obtained when process conditions are adjusted within the reported values.
**Keywords**: Central composite design, Metoprolol succinate tablets, Ofada rice starch acetate, Response surface methodology

## INTRODUCTION

A matrix tablet is one of the most convenient approaches for the preparation of the sustained release dosage forms having the advantages of simple processing and low cost of fabrication (Reddy *et al*., 2003). Such sustained release matrix tablets can be prepared in two ways: direct compression of the powder blend containing the drug, polymer and other excipients, and granulation prior to compression. Selection of the proper method depends on the properties of the drug, polymer and other ingredients.
Modified starches such as carboxymethylated starches, pregelatinized starches, acid-hydrolyzed starches, cross-linked amylose starches and starch acetates have been investigated for their ability to modify drug release from matrix tablets (Pal *et al*, 2002; Nabais *et al*, 2007; Simi and Abraham, 2007). Starch acetates are novel starches produced by acetylation of native starches. Such chemically transformed starch acetates are less hydrophilic than most other modified starches owing to the hydrophobic nature of the acetoxy substituent. As the degree of substitution (DS) increases, the interparticulate bonding capacity of the starches increases and they form flexible, water insoluble films that are acid and heat-resistant and can substantially retard drug release (Korhonen *et al*, 2000; Tuovinen *et al*, 2003).
Metoprolol succinate (MS), a β-selective adrenoceptor blocker, is widely used in the treatment of hypertension, angina pectoris, and arrhythmias. The drug is freely soluble in water and is administered at a dose of 100 mg daily, the half-life of MS is about 3-4 h, and its oral bioavailability has been reported to be about 50 % (Parhi and Suresh, 2011). The maintenance of a constant plasma level of a cardiovascular drug is important in ensuring the desired therapeutic response. Since the half-life of MS is 3 to 4 hours, multiple doses are needed to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance. Conventional dosage form fails to maintain the drug plasma concentration over the extended period of time. These result in the frequent administration of a drug with higher dose, causing unwanted toxic effects. The therapeutic efficacy of MS can be improved by providing constant rate input and maintenance of steady-state blood levels. It has been

reported that MS shows good absorption in the entire GI tract, has rapid elimination and exhibits a well-defined relationship between the β-blocking effect and plasma drug concentration. Combination of the above properties make MS a suitable candidate for the development of a controlled-release formulation (Abrahamsson *et al*, 1996). For such drugs with high water solubility, hydrophobic polymers are suitable as matrix agents for developing sustained-release dosage forms (Abdelkader *et al*, 2008). Thus the focus of this research is to optimize the process of preparing the tablets of metoprolol succinate by direct compression using a novel polymer, Ofada starch acetate (DS 2.22), as matrix. The concentrations of the polymer as well as the compression pressures and compression times would be varied. Central composite design-response surface methodology (CCD-RSM), a statistical technique for analysing and optimizing the response of multivariate systems, was used to optimize the formulation by choosing crushing strength, friability and time taken for 50 % drug dissolution ($t_{50}$) as the evaluation indicators (Dutta and Jayanta, 2012; Jain *et al*, 2011). The adequacy of the proposed model would be revealed using the analysis of variance, ANOVA (Rosales *et al*, 2012).

## MATERIALS AND METHODS

### Methods

### Starch extraction and modification

Starch was extracted from Ofada rice grains according to the method described by Okunlola *et al*, 2015. Modification of starch by acetylation was done according to the method of Singh and Nath, 2012. Twenty five grams of dried powder of pregelatinized Ofada starch was dispersed in 200 g of pyridine in a 1 Litre round-bottom flask. One hundred grams of acetic anhydride was added to the dispersion. The round bottom flask was placed into an oil bath maintained at 100 ℃ and rotated at low speed inside a fume hood for 4 hours with continuous stirring. At the end of the reaction, the mixture was transferred to a beaker and cooled to room temperature and the product was precipitated from 1300 mL of ethanol under high shear homogenization. The precipitate was filtered, washed well with ethanol to remove the residual pyridine in the precipitate and then filtered again before drying in an oven at 40 °C. The percent of acetyl group and degree of substitution (DS) were calculated according to the method of Ogawa *et al.*, 1999.

### Characterization of starches

### Morphology

The shape and size of starch granules were observed using a scanning electron microscope (Hitachi SU8030 FE-SEM Tokyo, Japan) at an accelerating potential of 5.0 kV. All samples were sputter-coated with Au/Pd prior to examination.

The starches were analyzed by FT-IR (FT-IR-Thermo Nicolet Nexus 870 Madison, WI, USA) in transmission mode. Starch powder (1% of the amount of KBr) was mixed with the KBr powder and trituration was done in an agate mortar for 5 minutes. The powder was pressed for1 minute (Thermo Qwik Handi-Press P/N 0016-125) to form a thin and transparent KBr disc. Transmission spectra were recorded using at least 64 scans with 8 $cm^{-1}$ resolution in the spectral range 4000–400 $cm^{-1}$.

### Formulation of metoprolol succinate tablets using Ofada starch acetate as matrix

Calculated amounts required to prepare a 200 g powder blend of drug (25 %w/w), Ofada rice starch acetate (30 to 50 % w/w), talc (1 %w/w), magnesium stearate (1 %w/w) and mannitol (to 100 %w/w) were mixed thoroughly. Magnesium stearate was added just before blending. The mixed dry blends of the formulations (200 mg) were compressed with predetermined loads (56.56 to 113.13 $MNm^{-2}$**)** on a tableting machine (Korsch XPI KOO10250, Berlin, Germany) using a 10 mm die and flat-faced punches for varied period of time (30 to 60 s). After ejection, the tablets were stored over silica gel for 24 hours to allow for elastic recovery and hardening. The weights (w) and dimensions of the tablets were then determined to within ± 1mg and 0.01 mm respectively.

### Evaluation of metoprolol succinate tablets

### Tablet weight and thickness

Twenty tablets were selected at random and their average weight was determined within ± 1mg (Mettler PC 440 Delta range®, CH-8606 Greifensee-Zurich, Switzerland). Using a micrometer screw gauge, the thickness of twenty tablets was measured within ± 0.01mm.

### Mechanical strength of tablets

The crushing strength of the tablets were determined at room temperature by diametral compression using a tablet hardness tester (DBK Instruments Mumbai, India). The results were taken only from tablets which split cleanly into two halves without any sign of lamination. The percent friability of the tablets was determined using a friabilator (DBK Instruments, England) operated at 25 rpm for 4 minutes. All measurements were made in triplicates and the results given are the mean values**.**

### Release properties of tablets

Ten tablets were crushed and dissolved in Phosphate buffer pH 6.8 and assayed for drug content using a UV/Visible Spectrophotometer (Beckman Coulter DU 730 Life Science UV/Vis Spectrophotometer USA) at wavelength 274nm to determine the amount of metoprolol succinate in the tablets.

Dissolution test was carried out on the tablets using the USPXX III paddle method at 100 rpm in 900ml of phosphate buffer pH 6.8 containing 2 % w/v of sodium lauryl sulphate maintained at a temperature of 37 ± 0.5 °C for 12 hours. Samples (5ml) were withdrawn and replaced with equal amounts of fresh medium. The sample was diluted and the amount of metoprolol released was determined at wavelength of 274 nm using a UV/Visible Spectrophotometer (Beckman Coulter DU 730 Life Science UV/Vis Spectrophotometer USA).

### Experimental design and optimization

In this study, Response Surface Methodology (RSM) was used for the optimization of process variables in

combination with the factorial experimental design of Composite Central Design (CCD). The statistical software Minitab 16 Software USA, (Minitab Inc., USA) was used for design of experiments, regression and graphical analyses of the data obtained, and statistical analysis of the model to evaluate the analysis of variance (ANOVA). Percent composition of starch acetate, compression pressure and compression time were chosen as three independent variables in the formulation process. Twenty experiments covering the full design of two factors were used for building quadratic models. The levels of the three parameters investigated in this study are presented in Table 1. Statistical combinations of variables in code and actual values along with the predicted and experimental responses are presented in Table 2 as a complete $2^3$ factorial design with four center points in cube, and six axial points and two center points in axial. The experimental data obtained from the CCD model experiments can be represented in the form of the following equation:

$$Y_i = f(y) = \beta_0 + \sum_{i=1}^{k} \beta_i X_i + \sum_{i=1}^{k} \beta_{ii} X_i^2 + \sum_{i=1}^{k} \sum_{i=1}^{k} \beta_{ij} X_i X_j + \varepsilon \quad (1)$$

Where $Y_i$ is the predicted response used to relate to the independent variable, $k$ is the number of independent variables (factors) $X_i$ (i = 1, 2, 3); while $\beta$ is a constant coefficient and $\beta_i$, $\beta_{ij}$ and $\beta_{ii}$ the coefficient of linear, interaction and square terms respectively and ε is the residual error (Moghaddam *et al*, 2010). Multivariate regression analysis with model equation (1) was carried out on the data to yield equation (2) which was used to optimize the product responses.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{11} X^2_1 + \beta_{22} X^2_2 + \beta_{33} X^2_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \varepsilon \quad (2)$$

The model developed for each determination was then examined for significance and lack-of-fit, while response surface plots were designed with the same software. The quality of the polynomial model was expressed by the coefficient of determination, namely, $R^2$ and Adj-$R^2$. The statistical significance was verified with adequate precision ratio and by the F test (Kayan and Gozmen, 2012).

## RESULTS AND DISCUSSION

### Characterization of acetylated starch

The Scanning Electron Microscope (SEM) image of acetylated Ofada rice starch is shown in Fig. 1(a). Native Ofada showed polygonal and angular-shaped granules with mean particle sizes of 2.20 ±0.05 µm which increased significantly with acetylation ($p < 0.05$), forming larger, fibrous, irregular aggregates with mean size 17.80 ± 0.75 µm (Okunlola and Owojori, 2016).

The FTIR spectrum of the acetylated starches is shown in Fig. 1(b). The spectrum indicate the formation of amorphous structure upon modification, resulting in decrease in the ordered structure of native starches which is characterized by new bands at 1700 $cm^{-1}$ (Stretching C=O), 1375 $cm^{-1}$ (Stretching C-CH3. FTIR bands at 3400 cm-1 (Stretching O–H) and 1083 cm-1 (C-O-C bond stretching) were weakened, confirming the replacement of the hydroxyl groups in the starch molecules with acetyl groups (Harvey *et al*, 2012; Okunlola and Ogunkoya, 2015).

### Characterization of metoprolol succinate tablets containing Ofada starch acetate

The average weight of the metoprolol succinate tablets was 201.50 ± 2.10 mg. The percentage weight variation was within the International Pharmacopeia limits of ±7.5% of the weight. The average thickness of all the formulations was 2.54 ± 0.10 mm and found to be within the limit of British Pharmacopeia specifications.

The most popular estimate of tablet strength has been crushing strength, which may be defined as the compressional force which, when applied diametrically to a tablet, just fractures it (Banker and Anderson, 2009). Furthermore, many reports relate crushing strength to other process and tablet parameters, among which include their linear proportionality to disintegration time and inverse proportionality with porosity over normal ranges of compression force (Rees and Hersey, 1972). Friability, a measure of tablet resistance to abrasion, is another relevant parameter that best measures the potential behavior of tablets during handling and packaging (Hiestand and Smith, 1984). It was observed that crushing strength increased but friability decreased with the Ofada starch acetate content, compression pressure and compression time.

The use of *in vivo* studies for direct assessment of a drug's release from various tablet properties is restricted for several reasons including the length of time required, the highly skilled personnel required for human studies, high cost of the studies and the low precision and high variability typical of the measurements. Consequently, *in vitro* dissolution tests have been extensively used as an indirect measurement of drug availability (Banker and Anderson, 2009). The times taken for 80 % dissolution of the drug ($t_{80}$) were observed to be within 5.75 – 11.50 h and $t_{80}$ values increased with Ofada starch content.

### Optimization of metoprolol tablet formulations using RSM-CCD

The levels of the three main parameters investigated were selected based on preliminary study results and RSM was used to optimize the process design factors (Myers *et al*. 1989). The number of experiments required (N) is given by the expression $2^k$ ($2^3 = 8$; star points) + 2 k (2 x 3 = 6; axial points) + 6 (center points; 6 replications) (Deriase *et al*, 2012). For the response surface method involving CCD, a total of 20 experiments was conducted for the three factors at five levels with the replicates at the center point.

Polynomial regression modelling was performed on the responses of the corresponding coded values of the three different process variables (Okunlola and Akindele, 2016) and the regression equation characterizing the influence of the three variables on crushing strength, friability and $t_{80}$ were obtained using equations 3, 4 and 5 respectively:

Crushing strength = $-54.431 + 2.892X_1 + 0.806X_2 + 2.052X_3 - 0.004X_1X_2 - 0.007X_1X_3 + 0.001X_2X_3 - 0.02X_1^2 - 0.002X_2^2 - 0.014X_3^2$ (3)

Friability = $0.594 - 0.113X_1 - 0.131X_2 - 0.130X_3 - 0.007X_1X_2 - 0.115X_1X_3 - 0.015X_2X_3 - 0.127X_1^2 - 0.003X_2^2 - 0.039X_3^2$ (4)

$t_{80} = 11.10 + 1.239X_1 + 0.302X_2 + 0.659X_3 + 1.213X_1X_2 + 0.725X_1X_3 - 1.088X_2X_3 - 0.661X_1^2 - 1.059X_2^2 - 0.0997X_3^2$ (5)

A positive sign indicate a synergistic effect whereas a negative sign indicate an antagonistic effect.

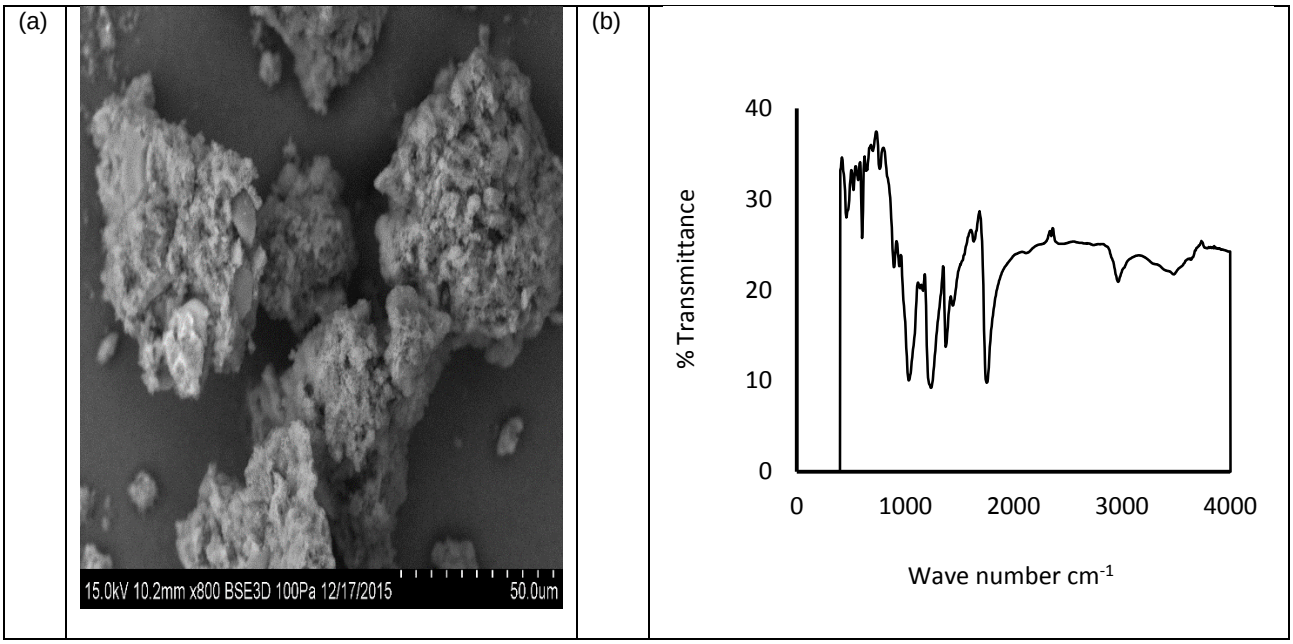


**Figure 1: (a) SEM and (b) FTIR spectra of acetylated Ofada rice starch**

**Table 1: Experimental range and levels of the independent variables**

| Variables | Factor | Range and level | | | | |
|---|---|---|---|---|---|---|
| | | -α | -1 | 0 | +1 | +α |
| Ofada starch acetate (% w/w) | $X_1$ | 23.18 | 30.00 | 40.00 | 50.00 | 56.82 |
| Compression pressure ($MNm^{-2}$) | $X_2$ | 18.05 | 56.60 | 113.15 | 169.70 | 208.26 |
| Compression time (s) | $X_3$ | 19.77 | 30.00 | 45.00 | 60.00 | 70.23 |

**Statistical Analysis and Validation of Model**

The analysis of variance (ANOVA) values for the quadratic regression model obtained from CCD are presented in Table 3. Statistical test was carried out using the Fisher's test for ANOVA which indicated statistically significance at 95% confidence level, with *F*-value of 376.61, 454.53 and 537.26 for crushing strength, friability and $t_{80}$ respectively, and very low probability *P* value of < 0.0001**.** The values of the determination coefficients, $R^2$ and $R^2$(Adj), measurement of the model fitting reliability for the models were calculated to be $R^2$ = 0.9971 and $R^2$(Adj) = 0.9944 for crushing strength; $R^2$ = 0.9976 and $R^2$ (Adj) = 0.9954 for friability and ; $R^2$ = 0.9979 and $R^2$ (Adj) = 0.9961 for $t_{80}$. These suggests that approximately 99.71 %, 99.76 % and 96.77 % of the respective variance is attributed to the variables and indicates high significance of the models. Agreement between experimental and predicted values of response variables confirm the adequacy of the regression models. A high correlation, $R^2$ = 0.997, 0.998 and 0.998 for crushing strength, friability and $t_{80}$ respectively**,** was observed between the predicted and experimental values indicating that the data fitted well with the models and showed good estimate of responses for the system in the experimental range studied (Rauf *et al*, 2008). The normal probability plots indicate good validity for the approximation of the quadratic regression model. In the plots of residual versus predicted values for the responses, points of observed runs were scattered randomly within the constant range of residuals across the graph, revealing no obvious pattern and unusual structure and further indicating the adequacy of the model (Singh and Ahuja, 2004).

**Table 2: Central composite design experiments and experimental results**

| Design point | Independent variables coded | | | Real values of independent variables | | | Observed crushing strength (N) | Predicted crushing strength (N) | Observed Friability % | Predicted Friability % | Observed $t_{80}$ (h) | Predicted $t_{80}$ (h) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $X_1$ | $X_2$ | $X_3$ | $X_1$ (%w/w) | $X_2$ ($MNm^{-2}$) | $X_3$ (s) | | | | | | |
| 1 | +1 | -1 | +1 | 50.00 | 56.60 | 60.00 | 125.00 | 125.89 | 0.45 | 0.45 | 10.50 | 10.60 |
| 2 | -1 | +1 | +1 | 30.00 | 169.70 | 60.00 | 110.10 | 132.63 | 0.69 | 0.16 | 7.50 | 5.08 |
| 3 | +1 | +1 | -1 | 50.00 | 169.70 | 30.00 | 120.20 | 120.07 | 0.20 | 0.20 | 10.95 | 10.84 |
| 4 | -1 | -1 | -1 | 30.00 | 56.60 | 30.00 | 90.00 | 91.31 | 0.90 | 0.89 | 7.00 | 7.03 |
| 5 | +1 | +1 | +1 | 50.00 | 169.70 | 60.00 | 140.50 | 139.21 | 0.15 | 0.14 | 11.50 | 11.43 |
| 6 | -1 | -1 | +1 | 30.00 | 56.60 | 60.00 | 110.20 | 110.35 | 0.45 | 0.43 | 9.00 | 9.07 |
| 7 | +1 | -1 | -1 | 50.00 | 56.60 | 30.00 | 112.12 | 111.11 | 0.45 | 0.45 | 5.75 | 5.63 |
| 8 | -1 | +1 | -1 | 30.00 | 169.70 | 30.00 | 110.10 | 109.23 | 0.69 | 0.67 | 7.50 | 7.38 |
| 9 | 0 | 0 | -1.682 | 40.00 | 113.15 | 19.77 | 105.00 | 105.43 | 0.70 | 0.70 | 7.00 | 7.20 |
| 10 | -1.682 | 0 | 0 | 23.18 | 113.15 | 45.00 | 115.20 | 114.25 | 0.40 | 0.43 | 7.20 | 7.14 |
| 11 | 0 | +1.682 | 0 | 40.00 | 208.26 | 45.00 | 120.20 | 120.97 | 0.35 | 0.37 | 8.50 | 8.62 |
| 12 | 0 | -1.682 | 0 | 40.00 | 18.05 | 45.00 | 95.50 | 94.71 | 0.80 | 0.81 | 7.65 | 7.59 |
| 13 | +1.682 | 0 | 0 | 56.82 | 113.15 | 45.00 | 135.50 | 136.43 | 0.05 | 0.04 | 11.20 | 11.31 |
| 14 | 0 | 0 | +1.682 | 40.00 | 113.15 | 70.25 | 138.00 | 137.54 | 0.25 | 0.27 | 9.50 | 9.39 |
| 15 | 0 | 0 | 0 | 40.00 | 113.15 | 45.00 | 130.00 | 130.52 | 0.60 | 0.59 | 11.00 | 11.10 |
| 16 | 0 | 0 | 0 | 40.00 | 113.15 | 45.00 | 130.50 | 130.52 | 0.59 | 0.59 | 11.00 | 11.10 |
| 17 | 0 | 0 | 0 | 40.00 | 113.15 | 45.00 | 130.50 | 130.52 | 0.58 | 0.59 | 11.10 | 11.10 |
| 18 | 0 | 0 | 0 | 40.00 | 113.15 | 45.00 | 130.50 | 130.52 | 0.60 | 0.59 | 11.20 | 11.10 |
| 19 | 0 | 0 | 0 | 40.00 | 113.15 | 45.00 | 131.10 | 130.52 | 0.60 | 0.59 | 11.10 | 11.10 |
| 20 | 0 | 0 | 0 | 40.00 | 113.15 | 45.00 | 130.50 | 130.52 | 0.60 | 0.59 | 11.20 | 11.10 |

**Table 3: ANOVA regression model for crushing strength, friability and dissolution time ($t_{80}$)**

| Source | Degrees of freedom | Sum of squares | Mean square | F value | P value |
|---|---|---|---|---|---|
| Crushing strength | | | | | |
| Mode | 9 | 3749.81 | 416.65 | 376.61 | 0.000 |
| $X_1$ | 1 | 593.91 | 593.91 | 536.83 | 0.000 |
| $X_2$ | 1 | 832.39 | 832.39 | 752.40 | 0.000 |
| $X_3$ | 1 | 1244.70 | 1244.70 | 1125.08 | 0.000 |
| $X_1^2$ | 1 | 9.84 | 48.35 | 43.70 | 0.000 |
| $X_2^2$ | 1 | 863.35 | 926.66 | 837.90 | 0.000 |
| $X_3^2$ | 1 | 146.91 | 146.91 | 132.79 | 0.000 |
| $X_1 X_2$ | 1 | 40.14 | 40.14 | 36.28 | 0.000 |
| $X_1 X_3$ | 1 | 9.07 | 9.07 | 8.20 | 0.017 |
| $X_2 X_3$ | 1 | 9.50 | 9.50 | 8.59 | 0.015 |
| Residual | 10 | 11.06 | 1.11 | | |
| Lack of fits | 5 | 10.45 | 2.09 | 17.19 | 0.004 |
| Pure error | 5 | 0.61 | 0.12 | | |
| Friability | | | | | |
| Mode | 9 | 0.9957 | 0.1106 | 454.53 | 0.000 |
| $X_1$ | 1 | 0.1756 | 0.1756 | 721.44 | 0.000 |
| $X_2$ | 1 | 0.2364 | 0.2364 | 971.20 | 0.000 |
| $X_3$ | 1 | 0.2311 | 0.2311 | 949.70 | 0.000 |
| $X_1^2$ | 1 | 0.2230 | 0.2327 | 955.76 | 0.000 |
| $X_2^2$ | 1 | 0.0000 | 0.0002 | 0.65 | 0.439 |
| $X_3^2$ | 1 | 0.0216 | 0.0216 | 88.52 | 0.000 |
| $X_1 X_2$ | 1 | 0.0005 | 0.0005 | 1.85 | 0.204 |
| $X_1 X_3$ | 1 | 0.1058 | 0.1058 | 434.65 | 0.000 |
| $X_2 X_3$ | 1 | 0.0018 | 0.0018 | 7.39 | 0.022 |
| Residual | 10 | 0.0024 | 0.0024 | | |
| Lack of fits | 5 | 0.0021 | 0.0004 | 5.95 | 0.036 |
| Pure error | 5 | | | | |
| $t_{80}$ | | | | | |
| Mode | 9 | 84.66 | 9.41 | 537.26 | 0.000 |
| $X_1$ | 1 | 20.98 | 20.98 | 1198.21 | 0.000 |
| $X_2$ | 1 | 1.25 | 1.25 | 71.31 | 0.000 |
| $X_3$ | 1 | 5.94 | 5.94 | 339.07 | 0.000 |
| $X_1^2$ | 1 | 3.32 | 6.31 | 360.08 | 0.000 |
| $X_2^2$ | 1 | 13.42 | 16.17 | 923.34 | 0.000 |
| $X_3^2$ | 1 | 14.33 | 14.33 | 818.62 | 0.000 |
| $X_1 X_2$ | 1 | 11.76 | 11.76 | 671.69 | 0.000 |
| $X_1 X_3$ | 1 | 4.21 | 4.21 | 240.15 | 0.000 |
| $X_2 X_3$ | 1 | 9.46 | 9.46 | 5403.4 | 0.000 |
| Residual | 10 | 0.18 | 0.18 | | |
| Lack of fits | 5 | 0.14 | 0.03 | 3.38 | 0.10 |
| Pure error | 5 | 0.04 | 0.008 | | |

**Interactive effects of factors influencing crushing strength, friability and $t_{80}$**

To understand the impact of each variable, three dimensional (3D) plots were made for the estimated responses to investigate the interactive effects of two factors and these plots are presented in Figs. 2 - 4. Fig. 2 (i) represents the effects of varying percent content of Ofada starch acetate (% w/w) and compression pressure ($MNm^{-2}$) in the formulation of metoprolol succinate tablets, $X_1X_2$, on crushing strength at constant compression time, 45 s. From the plots it can be concluded that crushing strength was augmented by both variables. However, it can be observed that the percent Ofada starch acetate had greater effect on crushing strength than compression pressure as the values increased with increase in starch content of the tablet formulation. Crushing strength increased with

compression pressure up to a maximum at 100 $MNm^{-2}$ followed by a slight reduction in crushing strength which was maintained at a steady value as compression pressure increased from 100 to 150 $MNm^{-2}$. Maximum crushing strength was 140.50 N at 60 % w/w Ofada starch acetate content and compression pressure 100 $MNm^{-2}$. Fig. 2 (ii)

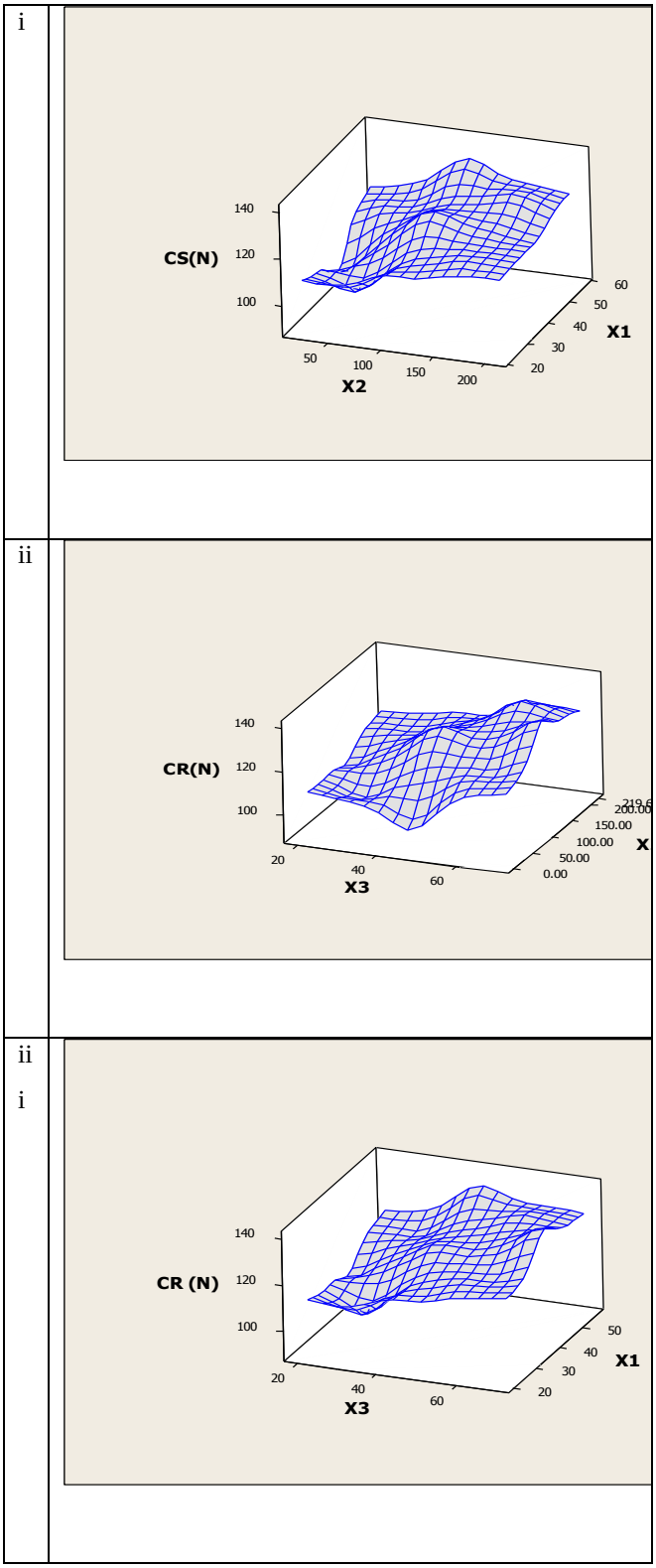


**Fig. 2: 3D plots of crushing strength (N)**

shows the effect of both compression pressure ($MNm^{-2}$) and compression time (s), $X_2X_3$, on crushing strength, keeping Ofada starch content constant at 40 %w/w. Crushing strength was observed to increase with increase in compression pressure from 50 to 150 $MNm^{-2}$. Crushing strength remained almost constant as compression pressure was increased beyond 150 $MNm^{-2}$. On the other hand, crushing strength initially reduced slightly as compression time was increased from 20 to 30 s followed by a great increase as compression time increased from 30 to 60 seconds. Maximum crushing strength of 140.50 N occurred at compression pressure of 219.67 $MNm^{-2}$ and compression time of 60 s. Fig. 2(iii) shows the interactive effects of percent Ofada starch acetate content and compression time, $X_1X_3$, on crushing strength, keeping compression pressure constant at 113.15 $MNm^{-2}$. Crushing strength was also observed to increase with increase in Ofada starch content. There was an increase in crushing strength as compression time increased from 20 to 40 s but remained almost constant as compression time was increased to 60s. Maximum crushing strength of 140.50 N occurred at percent Ofada starch acetate 60 %w/w and 60 s of compression time.

Fig. 3(i) represents the effects of varying percent content of Ofada starch acetate (% w/w) in metoprolol succinate tablet formulations and compression pressure ($MNm^{-2}$), $X_1X_2$, on friability (%), at compression time, 45 s. From the contour plot it was evident that a declining trend was initially obtained with ascending order of starch content up from 40%w/w followed by a slight increase and then reduction again from 50 to 60% w/w. Friability reduced with increase in compression pressure from 50 to 150 $MNm^{-2}$, then remained almost constant above 150$MNm^{-2}$. The lowest friability value was 0.35 % and was obtained at percent starch content of 50 % w/w and compression pressure of 150 $MNm^{-2}$. Fig. 3 (ii) shows the effect of both compression pressure ($MNm^{-2}$) and compression time (s), $X_2X_3$, on friability, keeping Ofada starch content constant at 40 %w/w. Compression pressure exhibited a more significant effect than compression time as friability was observed to increase with increase in compression pressure up to 150 $MNm^{-2}$. Friability values reduced slightly as compression time was increased from 30 to 40 s, followed by an increase and then a decrease at 60 s. The lowest value for friability was 0.35 % and was observed at compression pressure of 150 $MNm^{-2}$ and compression time 60 s. Fig. 3 (iii) shows the interactive effects of percent Ofada starch acetate content and compression time, $X_1X_3$, on friability, keeping compression pressure constant at 113.15 $MNm^{-2}$. With increase in starch acetate content friability reduced with the lowest value observed at 40 %w/w. Similarly, friability was observed to reduce with increase in compression time with the lowest friability value observed at 60 s.

Fig. 4 (i) represents the effects of varying percent content of Ofada starch acetate (% w/w) in metoprolol succinate tablet formulations and compression pressure ($MNm^{-2}$), $X_1X_2$, on dissolution time, $t_{80}$ (h), at compression time, 45 s. A significant positive impact was observed on the effect of percent starch content on dissolution time, i.e. $t_{80}$ increased with increase in amount of Ofada starch acetate

with a maximum value of 11.43 h observed at 60 %w/w content. Dissolution time was initially reduced followed by an increase in time as compression pressure increased from 100 to above 150 $MNm^{-2}$, Maximum dissolution time (11.43 h) was observed at compression pressure of 150 $MNm^{-2}$. Fig. 4 (ii) shows the effect of both compression pressure ($MNm^{-2}$) and compression time (s), $X_2X_3$, on $t_{80}$, keeping Ofada starch content constant at 40 %w/w.

The interactive effect of compression pressure and compression time was observed to be in an ascending order i.e. increasing the amount of both increased the response.

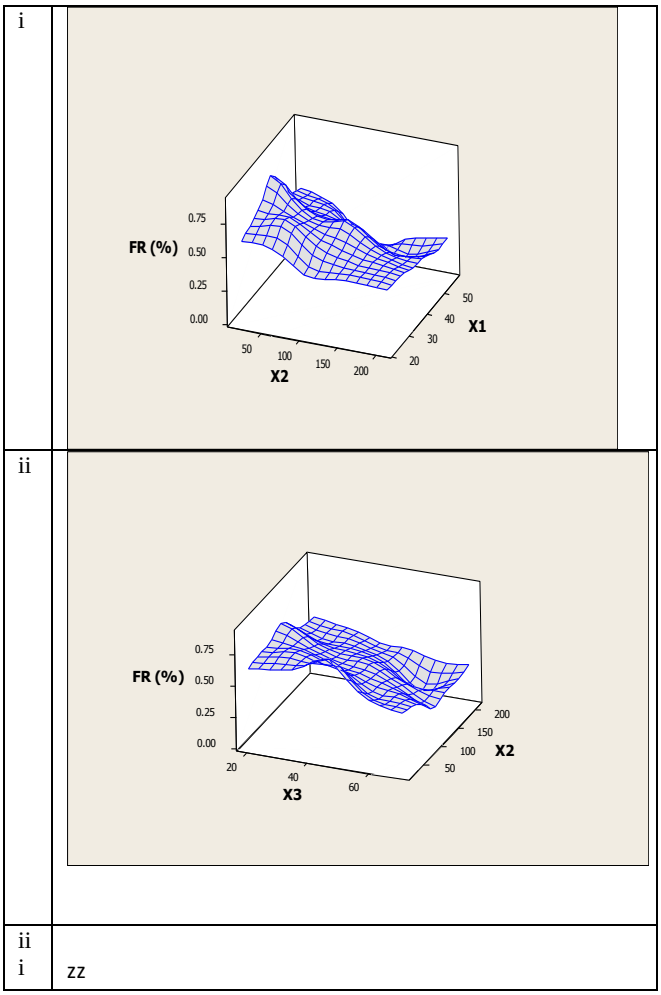


**Fig. 3. 3D plots of Friability (%)**

The effect of compression pressure was found to be linear at all pressures up to 150 $MNm^{-2}$. The dissolution time appeared to increase slightly as compression time was increased from 20 to 40 s, followed by a sharp increase. Maximum dissolution time was observed at compression pressure of 200 $MNm^{-2}$ and compression time 40s. From the plots it is quite evident that compression pressure had a comparatively greater influence on dissolution time than compression time on dissolution time. Fig. 4 (iii) shows the interactive effect of percent Ofada starch acetate content and compression time, $X_1X_3$, on $t_{80}$, keeping compression pressure constant at 113.15 $MNm^{-2}$. With increase in starch acetate content $t_{80}$ increased with the maximum time of dissolution at 60 %w/w starch acetate content. On the other hand, $t_{80}$ was observed to initially reduce with increase in compression time from 20 to 40s followed by a sharp increase with a maximum dissolution time observed at compression time of 60 s.

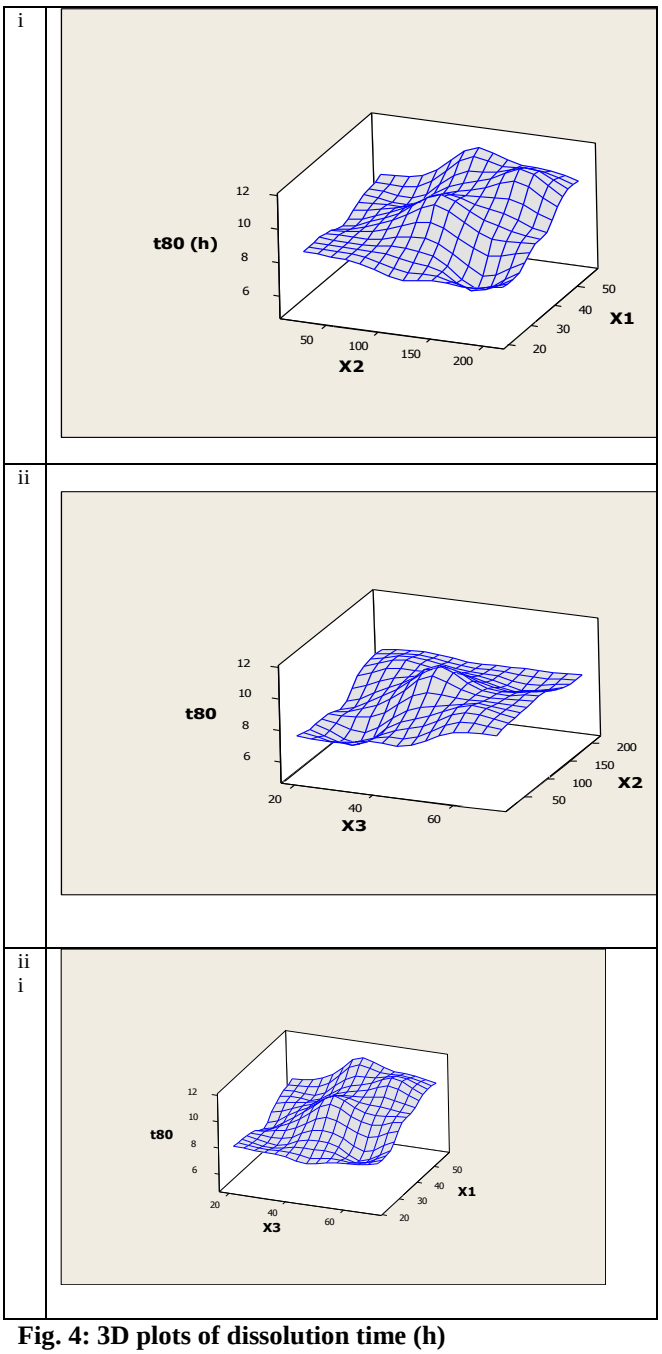


**Fig. 4: 3D plots of dissolution time (h)**

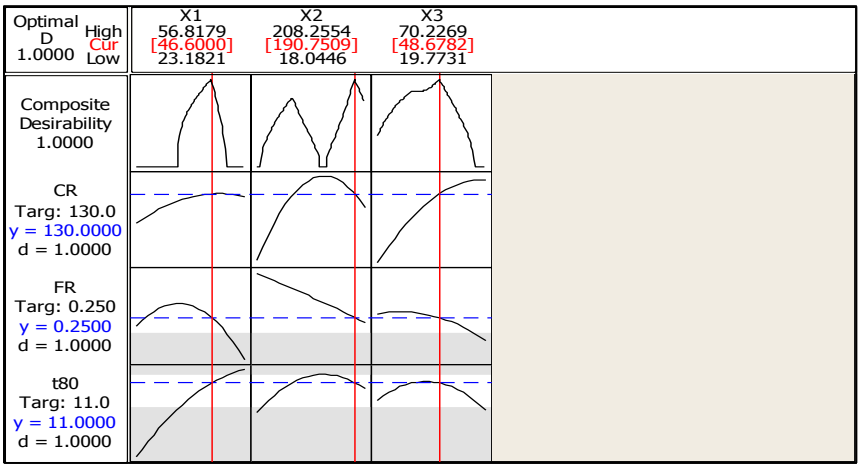


**Figure 5: Optimization plots for input variable combinations**

**Optimization of Formulation process and Model Verification**

The optimization process was carried out to determine the optimum value of crushing strength, friability and dissolution time $t_{80}$, using the Minitab 16 Software USA, (Minitab Inc., USA). The desired goal for each operational condition: percent content of Ofada starch acetate (% w/w), compression pressure (MNm-2) and compression time (s) was chosen within the studied range. The Response Optimizer in Minitab was used to identify the combination of input variable settings that jointly optimize a set of responses (Chi *et al*, 2012) and the optimization plots are shown in Fig. 5. Using the Response Optimizer, the maximum response (arcsin) for crushing strength (N); friability (%) and $t_{80}$ (h) respectively were 130 N, 0.25 % and 11.00 h respectively, with a desirability of 1. In order to verify the suggested optimizer values, confirmation runs were conducted. The values of the input parameters from the response optimizer suggestion were used to conduct tests under the optimized conditions. The maximum crushing strength, friability and $t_{80}$ were 127.5 N, 0.27 % and 10.85 h, respectively. Hence the predicted and experimental values under optimized conditions are in agreement.

**CONCLUSION**

Combination of the input variables namely**:** percent content of Ofada starch acetate, compression pressure and compression time enhanced crushing strength, reduced friability and prolonged dissolution time of metoprolol succinate tablets containing acetylated Ofada starch as tablet matrix. An important contributor to high mechanical strength and prolonged dissolution time was the percent content of Ofada starch acetate in the formulations. A highly significant regression quadratic model equation was obtained and the predicted values were found to be in agreement with the experimental values, defining the propriety of the model in the optimization of the process for the formulation of metoprolol succinate tablets. Ofada starch acetate is therefore suitable as a matrix for the sustained release of formulations of tablets and can serve as a cheaper substitute to synthetic polymers in drug delivery.

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