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# FORMULATION DESIGN AND OPTIMIZATION OF PULSATILE RELEASE TABLET OF ACEBROPHYLLINE WITH SWELLING AND ERODIABLE LAYERS FOR TREATMENT OF NOCTURNAL BRONCHIAL ASTHMA

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## ABSTRACT

Acebrophylline is a bronchodilator with mucosecrytolytic and anti-inflammatory activity. It is used to treat the bronchial asthma, and chronic obstructive pulmonary diseases. This work is based on the formulation and optimization of time dependant pulsatile release tablets of Acebrophylline having adequate mechanical strength of tablet and proper drug release of tablet. Pulsatile drug delivery system has an advantage as delivers the drug at right place, right time and right quantity. The crucial aspect in the formulation of pulsatile drug delivery system is to release the drug as pulse after a lag time has to be designed in such a way that rapid and complete drug release follows after lag time. Present work conceptualizes a specific technology, based on pulsatile principles to develop drug delivery system, intended for chronotherapy in bronchial asthma. This approach will be achieved by using a programmed delivery of acebrophylline. In this work rapid pulse to pulsatile drug delivery system can be achieved through immediate release tablet with good mechanical strength and proper disintegration. Lag time in pulsatile drug delivery system can be maintained by using coating with time responsive polymer having good mechanical strength. In this study immediate release tablet can be prepared by using two super disintegrants as Cross carmellose sodium and Cross-povidone to give rapid pulse of drug. The lag time of pulsatile drug delivery system can be maintained by coating using extended release polymer as HPMC E 50 (Methocel E 50). The programmable pulsatile release of Acebrophylline was consistent with the demands of bronchial asthma.

**INTRODUCTION:** In the field of modified release, there has been a growing interest in time specific oral delivery, which generally refers to the pre-programmed release of drugs following administration to achieve improved therapeutic efficacy. These systems constitute a relatively new class of devices, the importance of which is especially connected with the recent advances in chronopharmacology [1] Particular rhythms in the onset and extent of symptoms were observed in diseases such as, bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, diabetes, attention deficit syndrome, hypercholesterolemia, and hypertension [2].

Numerous studies conducted in the last decade on animals as well as clinical trials have provided convincing evidence, that the pharmacokinetics and the drug's effects can be modified by the circadian timing of drug application within 24 h of a day [3-5].

All these acted as push for the development of pulsatile drug delivery which is based on the principle of rapid drug release matching the circadian pathophysiology after a predetermined off-release period, lag time [6]. Conventional pulsatile release dosage forms following oral administration are meant to release drug after a lag period of 5–6 h usually in the large intestine [7].

However, the viscous contents of lower part of GI tract cause hindrance to the drug diffusion and also enzymatic degradation of some drugs makes it an unfavorable site for drug release[8]. Further, highly variable nature of gastric emptying process may result in *in vivo* variability and bioavailability problems.

Nocturnal bronchial asthma, a condition prevalent in two-thirds of the asthmatics, is depends as a variable night time exacerbation of the underlying asthma condition associated with increase in symptoms and need for medication, increased airway responsiveness and worsening of lung function. Symptoms typically occur between midnight and 8 am, especially around 4.00 am [9-11].

It is inconvenient to take the medication at midnight. The maintenance of constant drug level is not always desirable for the optimal therapy. A drug should be delivered only when and/or where it is needed at the minimum required dose [12]. For the drugs to follow circadian rhythm, like in asthma, a reasonable and an acceptable rationale is a delivery system capable of releasing drugs in a pulsatile fashion rather than as a continuous delivery at the predetermined time/site following oral administration [13, 14].

Acebrophylline is a xanthine derivative with potent bronchodilator, mucosecretolytic and anti-inflammatory property. Ambroxol in Acebrophylline shows the mucosecretolytic activity and Theophylline-7-acetic acid shows specific bronchodilator activity. However drug shows site specific absorption in the intestine. Drug used to treat nocturnal bronchial asthma. Acebrophylline, thereby, favoring site specific pulsatile drug delivery [15].

Response surface methodology (RSM) is a collection of statistical and mathematical techniques, useful for developing, improving and optimizing processes [16, 17]. The basic components of the methodology include various types of experimental designs, regression analysis and optimization algorithms which are used to investigate the empirical relation. independent variables in the form of polynomial equations and mapping of the response over the experimental domain, with the ultimate goal of obtaining an optimal problem solution and establishing the robustness of the process.

The advantage of such methodology is in providing a rationale for simultaneous evaluation of several variables with minimum experimentation and time, thus proving to be far more efficient and cost effective than conventional methods of product development. Till date, application of RSM has not been reported in the development and optimization of time-lagged coating to achieve a pulsatile release profile.

The current study illustrates the development of a simple pulsatile drug delivery system of Acebrophylline to provide relief from nocturnal bronchial asthma. It was aimed to modulate the pulsatile release profile from a time-lagged coating using an erodible (hydroxypropylmethylcellulose) polymer. Computer-aided optimization techniques using $3^2$ FFD were employed to investigate the effect of two factors viz., Hydroxypropylmethylcellulose addition and Plasticizer concentration, on Tensile strength and Elongation of Film which indirectly affect the lag time and cumulative release of pulsatile drug delivery system.

Hence, with the proposed delivery system, a *new therapeutic dimension* to an existing fallen-out-of-favor drug molecule can be achieved.

## MATERIALS AND METHODS:

**Materials:** Acebrophylline was generously gifted by Pretiwell, Mumbai, India. Microcrystalline cellulose (Avicel® PH102, Signet Chemical Corporation, Mumbai, India), Hydroxypropyl methyl cellulose (Methocel E50, Colorcon Asia Pvt. Ltd., Goa, India), croscarmellose sodium (Ac-Di-Sol®, FMC Biopolymer, Signet Chemical Corporation, Mumbai, India), magnesium stearate (Loba Chemie Pvt. Ltd., Mumbai, India), and colloidal silicon dioxide (Aerosil 200, Degussa, Frankfurt, Germany) were used as components of the core tablets.

The time-lagged coating was achieved with hydroxypropylmethylcellulose (Methocel E50, Colorcon Asia Pvt. Ltd., Goa, India), plasticized with Polyethylglycol-4000 and Glycerol (S.D. Fine Chem. Ltd., Mumbai, India). All other ingredients and reagents were of analytical grade and were used as received.

**Methods:**

**Formulation of Pulsatile Release Tablet:**

**Preparation of Immediate release core for burst release:** The core tablets containing acebrophylline (100 mg per tablet), croscarmellose sodium (Ac-Di-Sol®), crospovidone (Polyplasdone XL) and microcrystalline cellulose (Avicel® PH102) were prepared by direct compression. Initially, the core tablet excipients were dry blended for 10 min, followed by the addition of magnesium stearate (0.5%, w/w) and Aerosil® 200 (0.5%, w/w). The powder components were further blended for 5 min. The core tablets (biconvex; hardness, 4–5 kg/cm2; average tablet weight, 150 mg) were compressed using punch tableting machine.

**Optimization of Immediate Release Tablet:** A full factorial $3^2$ design was used for optimization procedure. It is suitable for investigating the quadratic response surfaces and for constructing a second-order polynomial model, thus enabling optimization of the time-lagged coating process. Mathematical modeling, evaluation of the ability to fit to the model and response surface modeling were performed with employing Design-Expert® software (Version 8.0.4, Stat-Ease Inc., Minneapolis, MN).

The studied factors (independent variables) were percentage weight ratios of crosscarmellose sodium (X1) and percentage weight ratios of crospovidone (X2). Preliminary studies provided a setting of the levels for each formulation variable. The responses (dependent variables) studied were disintegration time (Y1) and Friability (Y2) of immediate release tablet. **Table 1** summarizes the independent and dependent variables along with their levels

**TABLE 1: COMPOSITION OF EXPERIMENTAL FORMULATION**

| Test runs | Variable factors | |
|---|---|---|
| | X1 (% of crosscarmellose sodium added) | X2 (% of crospovidone added) |
| 1 | -1(2) | -1(5) |
| 2 | -1(2) | -1(5) |
| 3 | -1(2) | -1(5) |
| 4 | 0(4) | 0(10) |
| 5 | 0(4) | 0(10) |
| 6 | 0(4) | 0(10) |
| 7 | 1(6) | 1(15) |
| 8 | 1(6) | 1(15) |
| 9 | 1(6) | 1(15) |

**Time-lagged coating of Core Tablets for pulsatile release of acebrophylline:** 8% (w/v) coating solutions of hydroxypropyl methyl cellulose (erodible polymer) were prepared in pure water. The weight ratios of hydroxypropyl methyl cellulose (Methocel E50) were 4%, 6% and 8% (w/v) based on the experimental design. The solution was plasticized with Polyethylene glycol-4000 and glycerin with 0.5%, 1% and 1.5%. The polymer solution is kept at 4°C overnight to aid complete dissolution of hydroxypropylmethylcellulose. The homogeneous dispersion was gently stirred throughout the coating process. The polymer solution was sprayed onto the core tablets in a conventional pan coating apparatus till the desired weight gain (20% w/w). Coating conditions are listed in Table 2. At each stage the coated tablets were further dried in the coating pan for 15 min at 40°C. The tablets were then placed in the oven at 40°C for 2 h to remove the residual water content.

**Optimization of Coating Solution:** In a full factorial design, all the factors are studied in all the possible combinations, as it is considered to be most efficient in estimating the influence of individual variables (main effects) and their interactions using minimum experimentation. In the present study, fitting a cubic model is considered to be better as the values of the response surfaces are not known. Hence, $3^2$ factorial designs were chosen for the current formulation optimization study. Amounts of HPMC added and Plasticizer were selected as independent factors, whereas Tensile strength and percent elongation (%E) were measured as responses. Based on initial trials, levels of HPMC added were selected as 4, 6, and 8 mg, whereas Plasticizer concentration levels were 0.5, 1, and 1.5 mg. 9 formulations were prepared according to $3^2$ factorial design and evaluated.

The responses were analyzed for analysis of variance (ANOVA) using Design Expert version 8.0.4 software. Statistical models were generated for each response parameter. The models were tested for significance.

**Validation of Statistical Model:** Levels of HPMC added and Plasticizer concentration were selected at six different points and responses predicted by the statistical models were calculated. Pulsatile release tablets were prepared using these levels and responses were measured practically. The predicted responses were compared against observed responses and closeness between them was checked.

**Response Surface Plots:** Response surface plots were generated for each response to study the effect of both factors on each response.

**TABLE 2: COMPOSITION OF CORE OF PULSATILE TABLET OF ACEBROPHYLLINE AS PER 32 FACTORIAL DESIGN**

| Ingredients (mg) | Formulation Code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cr1 | Cr2 | Cr3 | Cr4 | Cr5 | Cr6 | Cr7 | Cr8 | Cr9 |
| Acebrophylline | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Crospovidone | 7.5 | 7.5 | 7.5 | 15 | 15 | 15 | 22.5 | 22.5 | 22.5 |
| Cross carmellose sodium | 3 | 3 | 3 | 6 | 6 | 6 | 9 | 9 | 9 |
| MCC | 37.9 | 37.9 | 37.9 | 27.4 | 27.4 | 27.4 | 16.9 | 16.9 | 16.9 |
| Collidal sillicone dioxide | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 |
| Mg.sterate | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 |
| Total (mg) | 450 | 450 | 450 | 450 | 450 | 450 | 450 | 450 | 450 |

**TABLE 3 COMPOSITION OF TIME LAGGED COATING SOLUTION OF PULSATILE TABLET AS PER $3^2$ FACTORIAL DESIGN**

| Ingredients | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | CT1 | CT2 | CT3 | CT4 | CT5 | CT6 | CT7 | CT8 | CT9 |
| HPMC E50 | 4 | 4 | 4 | 6 | 6 | 6 | 8 | 8 | 8 |
| Plasticizer mixture (Glycerin: PEG 4000) | 0.5 | 0.5 | 0.5 | 1.0 | 1.0 | 1.0 | 1.5 | 1.5 | 1.5 |
| Opacifier (Titanium dioxide) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| FDC approved color | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

**Evaluation of Tablets:**

**General Parameters:** Tablets were evaluated for hardness (Monsanto hardness tester), friability (Roche friabilator), and weight variation [18, 19].

**Content Uniformity:** Twenty tablets were selected randomly, ground to fine powder and mixed thoroughly. A quantity of powder equivalent to 10 mg of acebrophylline was transferred to 100 ml volumetric flask and dissolve in 40 ml of distilled water by shaking on rotary flask shaker for 2 hr. The solution was filtered through Whatmann filter paper No. 41 and filtrate collected. Make up the volume of filtrate to 100 ml. After suitable dilutions, the absorbance of final sample corresponding to 20 µg/ml was recorded to 273 nm against water blank and content of Acebrophylline was estimated.

**Disintegration Time:** Disintegration test was carried out as described under procedure for plain coated tablets in USP. One tablet each was placed in each of six tubes of the basket of the assembly. Apparatus was operated for one hour using simulated gastric fluid, maintained at 37 ± 2°C as the immersion fluid. After 1 hrs we examined for disintegration, cracking and softening. Then the apparatus is operated for specified time. The remaining tests were carried out with simulated intestinal fluid maintained at 37 ± 2°C as the immersion fluid.

**Dissolution Studies:** Dissolution studies of the pulsatile tablet formulation of Acebrophylline were carried out using dissolution test apparatus USP-II paddle type. The dissolution medium consisted of 900 ml of standard buffer of pH 1.2 for the first 2 hours, followed by pH 7.4 for the remaining time period up to 8 to 10 hours. The temperature of the medium was maintained at 37±0.5$^0$C. The speed of rotation of the basket was kept at 100 rpm. Aliquots of 1 ml were withdrawn after every half an hours for a total of 10 hrs. These samples were diluted to make up the volume of 10ml with pH 1.2 buffer for first 2 hours and then by pH 7.4 buffer.

The samples so withdrawn were replaced with the fresh dissolution medium equilibrated at the same temperature. The drug released at the different time intervals from the dosage form is measured by U.V. visible spectrophotometer, by measuring the absorbance for the samples solutions at 273 nm (for pH 1.2) Acebrophylline. The dissolution characteristics of each samples was studied, after accounting for loss in the initial concentration of the drug– acebrophylline while changing the buffer. The release studies for each formulation were conducted in triplicate, indicating the reproducibility of the results.

**Evaluation of Film [20]:** Film samples with air bubbles, nicks, or tears and having mean thickness variations of greater than 5% were excluded from analysis. Films were evaluated for following parameters:

**Mechanical Properties:** Mechanical properties of film were evaluated using Ubique tester. Film strips in dimensions of 15cm X 4cm and free from air bubbles or physical imperfections were held between two clamps to hold the sample straight. During measurement, the strips were pulled by the top clamp at a rate of 1cm/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. Two mechanical properties namely, tensile strength and % elongation were computed for the evaluation of the film.

**Tensile Strength:** 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:

Tensile strength = Force at break/Initial cross sectional area of the sample

Elongation % elongation = (increase in length/Original length) 100

**RESULTS AND DISCUSSIONS:**

**Precompression Blend Characterization:** The precompression blend of mixture containing different concentrations of two superdisintegrants was evaluated for Bulk Density, Tapped Density, Carr's Index and Hausner's Ration. There was no much difference in the precompression Blend Densities as shown in **Table 4** for different superdisintegrants.

**TABLE 4: PRE-COMPRESSION CHARACTERISTIC OF POWDER BLENDS**

| Formulation | Angle of Repose (Θ) | Bulk Density (g/cm$^2$) | Tap Density (g/cm$^2$) | % Compressibility |
|---|---|---|---|---|
| Cr 1 | 26.11±0.04 | 0.42±0.06 | 0.47±0.03 | 7.54±0.03 |
| Cr 2 | 26.88±0.03 | 0.48±0.06 | 0.51±0.05 | 6.12±0.04 |
| Cr 3 | 28.45±0.03 | 0.47±0.04 | 0.48±0.03 | 8.92±0.03 |
| Cr 4 | 28.67±0.02 | 0.51±0.05 | 0.58±0.06 | 7.94±0.05 |
| Cr 5 | 27.02±0.03 | 0.43±0.06 | 0.57±0.06 | 9.09±0.03 |
| Cr 6 | 27.78±0.03 | 0.52±0.04 | 0.54±0.05 | 11.11±0.05 |
| Cr 7 | 28.29±0.04 | 0.51±0.04 | 0.44±0.03 | 10.63±0.07 |
| Cr 8 | 30.89±0.05 | 0.48±0.05 | 0.58±0.06 | 7.54±0.03 |
| Cr 9 | 32.24±0.08 | 0.45±0.07 | 0.52±0.05 | 6.52±0.02 |

**Acebrophylline Tablets Characterization:** Tablets were evaluated for Weight variation, Friability, Hardness, Disintegration time, % drug content (% assay) and Dissolution as shown in **Table 5**.

**TABLE 5: POST-COMPRESSION CHARACTERISTICS OF COATED TABLETS**

| Formulation | Weight uniformity (mg) ± SD | Hardness | % Assay | Disintegration time (min) | Cumulative release (%) |
|---|---|---|---|---|---|
| CT 1 | 543±1.3 | 5.5±0.02 | 98.64±1.02 | 194 | 94.45 |
| CT 2 | 538±1.21 | 4.8±0.02 | 99.21±1.21 | 222 | 93.35 |
| CT 3 | 546±1.65 | 6.2±0.04 | 99.42±0.85 | 255 | 94.35 |
| CT 4 | 548±0.06 | 6.9±0.03 | 98.41±0.62 | 285 | 95.35 |
| CT 5 | 541±1.47 | 7.2±0.03 | 98.53±1.08 | 320 | 95.85 |
| CT 6 | 536±1.11 | 6.5.±0.05 | 98.02 ±0.96 | 340 | 96.24 |
| CT 7 | 545±1.53 | 5.0±0.03 | 97.93 ±1.21 | 360 | 96.68 |
| CT 8 | 541±0.97 | 4.7±0.05 | 99.78 ±1.05 | 380 | 97.12 |
| CT 9 | 535±1.05 | 5.2±0.02 | 97.23 ±0.85 | 400 | 97.284 |

**TABLE 6: MECHANICAL PROPERTIES OF FILM.**

| Formulation Code | Tensile strength ($N/mm^2$) | (%) Elongation |
|---|---|---|
| CT1 | 4.3±0.09 | 20±0.98 |
| CT2 | 3.8±0.08 | 27±1.06 |
| CT3 | 3.4±0.12 | 36±1.05 |
| CT4 | 6.0±0.13 | 45±1.08 |
| CT5 | 5.4±0.09 | 55±1.04 |
| CT6 | 4.9±0.11 | 63±0.86 |
| CT7 | 7.7±0.15 | 72±1.2 |
| CT8 | 7.1±0.14 | 76±0.87 |
| CT9 | 6.6±0.08 | 85±1.07 |
| Broad range | 3.4-7.7 | 20-85 |

**$3^2$ Factorial Design:** A statistical model, $Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$. Incorporating interactive and polynomial terms was used to evaluate the responses, where Y is the dependent variable, $b_0$ is the arithmetic mean response of the nine runs, and bi is the estimated coefficient for the factor Xi. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1X2) show how the response changes when two factors are simultaneously changed.

The polynomial terms ($X1^2$ and $X2^2$) are included to investigate nonlinearity. The D.T. and % F of the nine batches (Cr1 to Cr9) showed a wide variation (i.e., 13 to 54 Sec. and 0.35 to 1.02 %, respectively). The data clearly indicate that the disintegration time and % Friability values are strongly dependent on the selected independent variables. The fitted full equations relating the responses of disintegration time and % friability to the transformed factors are as:

$$D.T. = 33.11 - 14.83X_1 - 4.833X_2$$

$$\%F = 0.653 - 0.2417X_1 + 0.055X_1X_1 - 0.0767X_2$$

Similarly, $3^2$ factorial design also applied for the optimization of the coating solution as discussed above. The T.S. and % E of the nine batches (CT1 to CT9) showed a wide variation (i.e., 3.4 to 5.5 $N/mm^2$ and 25 to 92 %, respectively). The data clearly indicate that the disintegration time and % Friability values are strongly dependent on the selected independent variables. The fitted full equations relating the responses of disintegration time and % friability to the transformed factors are as:

$$\text{Tensile strength} = 6.67 + 1.65X_1 - 0.52X_2$$

$$\text{Elongation} = 58.33 + 25X_1 + 8X_2$$

**Response Surface Plots:** It was observed that D.T. and % F were dependent on both the factors. There was a linear decrease in the disintegration time with increase in the concentration of both factors. The same effect was observed with Friability. Similarly response surface plot for T.S. and % E shows linear decrease in the tensile strength with increase in the levels of both factors. The same effect was observed with Plasticizer concentration

**Fig. 1** shows linear synergistic relationship between the two independent variables (factors) on response *Y*1 (disintegration time) was also evident from the *p*-values listed in **Table 7**. This increase in disintegration time was due to decreased quantity of Crosscarmellose sodium as well as decreased in quantity of crospovidone.

However, the same effect has found on friability of tablet. This receives confirmation from the mathematical model generated for response *Y*1.

**Fig. 2** depicts a linear synergistic relationship for Y2 (% Friability) was also evident from the *p*-values listed in

Table 7. This decrease in friability was due to increased quantity of crosscarmellose sodium as well as increased in quantity of crospovidone. This receives confirmation from the mathematical model generated for response *Y*2.

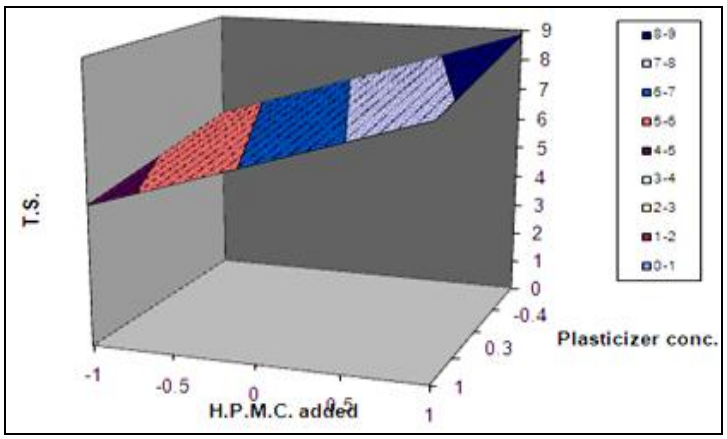


**FIG. 3: RESPONSE SURFACE PLOT FOR TENSILE STRENGTH**

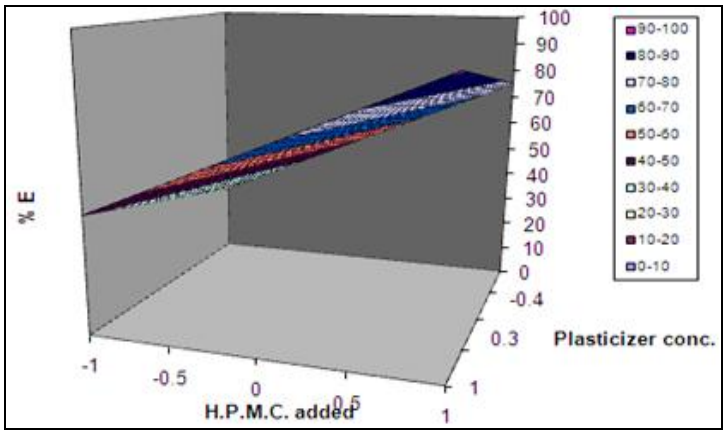


**FIG. 4: RESPONSE SURFACE PLOT FOR ELONGATION**

**Fig. 3** A linear synergistic relationship between the two independent variables (factors) on response *Y*1 (Tensile strength) was also evident from the *p*-values listed in **Table 8**. This increase in tensile strength was due to increased quantity of hydroxypropyl-methylcellulose polymer as well as increased coating thickness.

However, the effect of plasticizer concentration on tensile strength was opposite. This receives confirmation from the mathematical model generated for response *Y*1.

**Fig. 4** depicts a linear synergistic relationship for Y2 (% Elongation) was also evident from the *p*-values listed in Table 8. This increase in elongation was due to increased quantity of hydroxypropylmethylcellulose polymer as well as increased coating thickness.

However, the effect of plasticizer concentration on elongation was same. This receives confirmation from the mathematical model generated for response *Y*2.

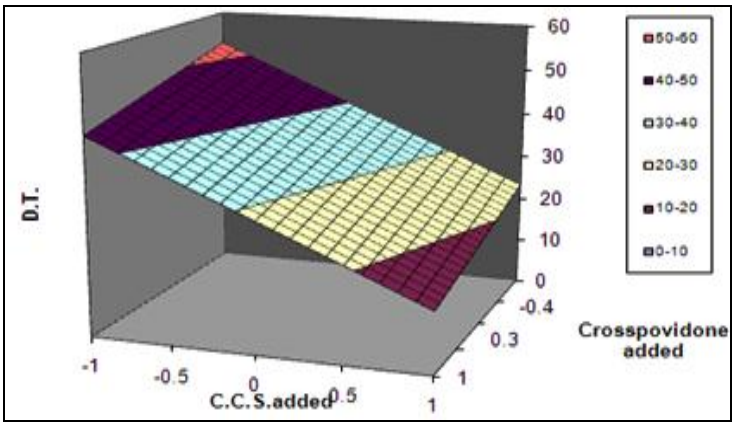


**FIG. 1: RESPONSE SURFACE PLOT FOR DISINTEGRATION TIME**

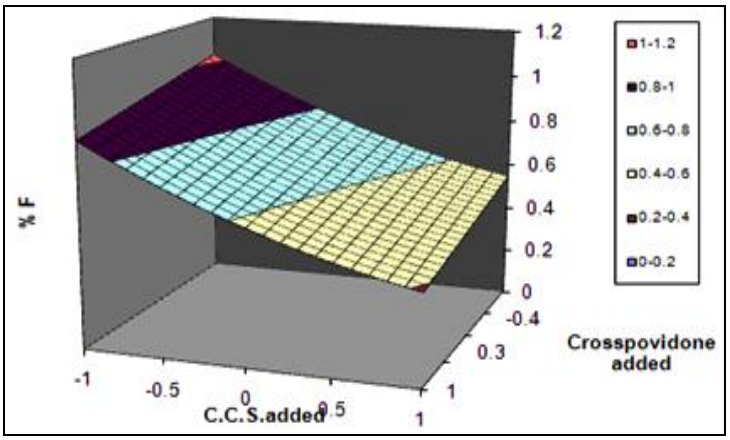


**FIG. 2: RESPONSE SURFACE PLOT FOR FRIABILITY**

**TABLE 7: ANOVA USED TO GENERATE STATISTICAL MODELS**

| Response model | Sum of squares | df | Mean square | F value | P value | $R^2$ | Adequate Precision |
|---|---|---|---|---|---|---|---|
| D.T. | 1605.31 | 4 | 401.33 | 1751.24 | <0.0001 | 0.9994 | 115.841 |
| % F | 0.37 | 4 | 0.12 | 365.26 | <0.0001 | 0.9955 | 52.791 |

**TABLE 8: ANOVA USED TO GENERATE STATISTICAL MODELS**

| Response model | Sum of squares | df | Mean square | F value | P value | $R^2$ | Adequate precision |
|---|---|---|---|---|---|---|---|
| T.S. | 17.94 | 4 | 8.97 | 2306.14 | <0.0001 | 0.9987 | 120.357 |
| % E | 4134 | 4 | 2064 | 563.73 | <0.0001 | 0.9947 | 59.69 |

**Validation of Statistical Model:** The predicted responses of the six formulations and corresponding actual experimentally observed values were found to be in close agreement as indicated in **Table 9.** Thus, the models developed to predict the responses were not only significant statistically but also were found to be valid to predict values that were very close to the practical observations.

Similarly, validation of statistical model for optimization of coating solution shows predicted responses of the six formulations and corresponding actual experimentally observed values were found to be in close agreement as indicated in **Table 10.** Thus, the models developed to predict the responses were not only significant statistically but also were found to be valid to predict values that were very close to the practical observations.

**TABLE 9: TABLE SHOWS COMPARISONS OF PREDICTED VALUES AND OBSERVED VALUES**

| Formulation Code | Predicted value | Observed value | Residuals |
|---|---|---|---|
| Cr1 | D.T. 13.45 | D.T. 12 | -1.45 |
| | % F 0.389 | % F 0.40 | 0.01 |
| Cr2 | D.T. 14.99 | D.T. 15 | 0.01 |
| | % F 0.403 | % F 0.42 | 0.017 |
| Cr3 | D.T. 16.416 | D.T. 17 | 0.584 |
| | % F 0.418 | % F 0.43 | -0.012 |
| Cr4 | D.T. 17.31 | D.T. 18 | 0.73 |
| | % F 0.45 | % F 0.47 | 0.012 |
| Cr5 | D.T. 18.79 | D.T. 19 | 0.21 |
| | % F 0.464 | % F 0.48 | 0.016 |
| Cr6 | D.T. 18.68 | D.T. 20 | 1.32 |
| | % F 0.479 | % F 0.49 | 0.011 |

**TABLE 10: TABLE SHOWS COMPARISONS OF PREDICTED VALUES AND OBSERVED VALUES**

| Formulation code | Predicted values | Observed values | Residuals |
|---|---|---|---|
| CT1 | T.S. 8.216 | T.S. 8.0 | 0.216 |
| | % E 84.93 | % E 82.5 | 2.43 |
| CT2 | T.S. 8.117 | T.S. 7.9 | 0.217 |
| | % E 83.43 | % E 81.25 | 2.18 |
| CT3 | T.S. 7.886 | T.S. 7.55 | 0.336 |
| | % E 79.93 | % E 78.52 | 1.41 |
| CT4 | T.S. 8.84 | T.S. 9 | 0.16 |
| | % E 75.31 | % E 76.0 | 0.69 |
| CT5 | T.S. 8.741 | T.S. 8.5 | 0.241 |
| | % E 73.83 | % E 71.5 | 2.33 |
| CT6 | T.S. 8.51 | T.S. 4.8 | 0.0269 |
| | % E 70.33 | % E 71.25 | 0.92 |

**Fig. 5 and 6** shows linear correlation plots between the observed and predicted response variables. The graphs demonstrate high values of correlation coefficient, *r*2 (>0.9) indicating excellent goodness of fit. Thus, the lower magnitude of residuals (-1.45 to 1.32 for *Y*1 and -0.012 to 0.21 for *Y*2) as well as significant values of *r*2 in the current study indicates the robustness of the mathematical model and high prognostic ability of RSM.

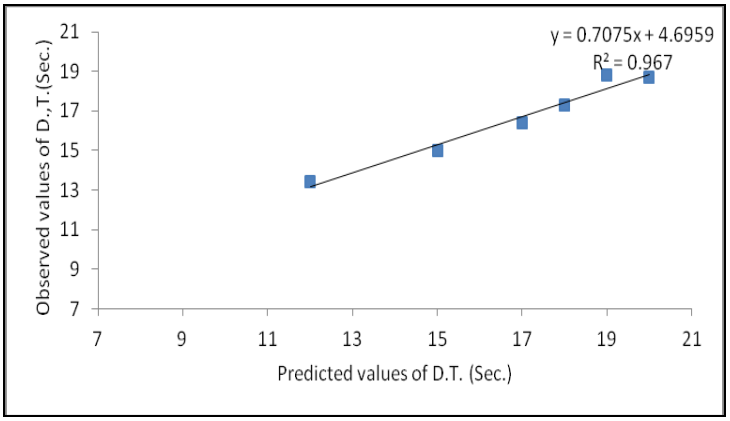


**FIG. 5: SHOWS LINEAR CORRELATION PLOTS BETWEEN OBSERVED AND PREDICTED VALUES FOR RESPONSE *Y*1 (DISINTEGRATION TIME, SEC.)**

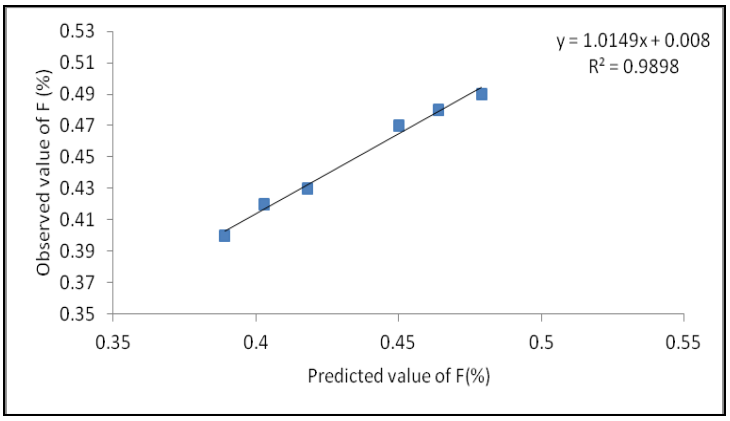


**FIG. 6: SHOWS LINEAR CORRELATION PLOTS BETWEEN OBSERVED AND PREDICTED VALUES FOR RESPONSE *Y*2 (% FRIABILITY)**

**Fig. 7 and 8** shows linear correlation plots between the observed and predicted response variables. The graphs demonstrate high values of correlation coefficient, *r*2 (>0.9) indicating excellent goodness of fit. Thus, the lower magnitude of residuals (0.026 to 0.336 for *Y*1 and 0.69 to 2.43 for *Y*2) as well as significant values of *r*2 in the current study indicates the robustness of the mathematical model and high prognostic ability of RSM.

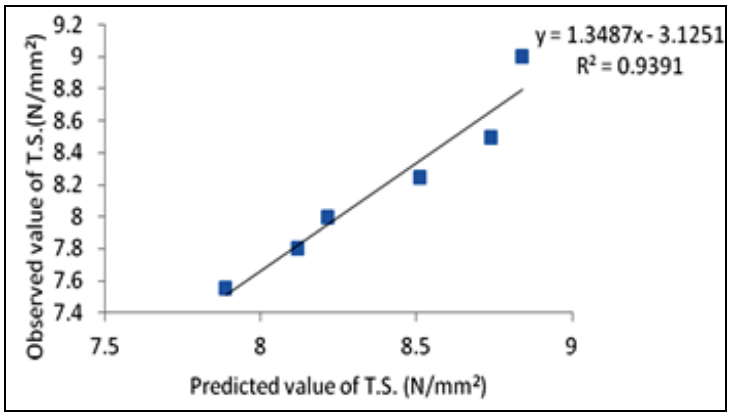


**FIG.7: FIGURE SHOWS LINEAR CORRELATION PLOTS BETWEEN OBSERVED AND PREDICTED VALUES FOR RESPONSE *Y*1 (TENSILE STRENGTH, N/mm$^2$)**

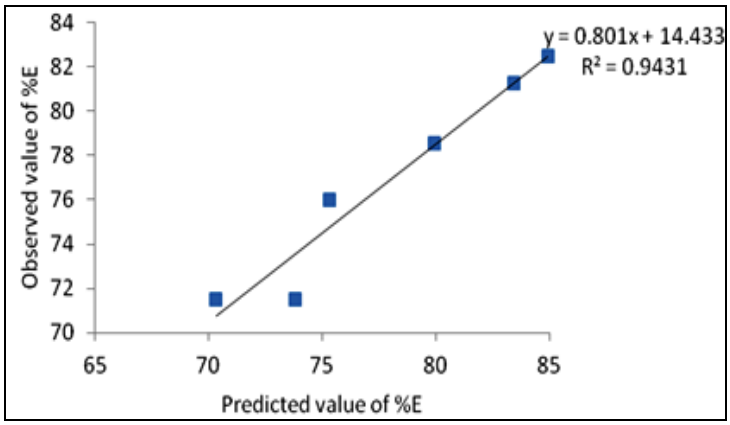


**FIG. 8: SHOWS LINEAR CORRELATION PLOTS BETWEEN OBSERVED AND PREDICTED VALUES FOR RESPONSE *Y*2 (% ELONGATION)**

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