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Research Article

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

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ABSTRACT

Doxofylline, a new generation xanthine analogue, is used for asthma and chronic obstructive pulmonary disease (COPD). The drug has less extra-respiratory effects than that of theophylline. A tablet system consisting of cores coated with two layers of swelling and erodiable coatings was prepared and evaluated as pulsatile drug delivery system. Cores containing Doxofylline were prepared by direct compression of lactose, microcrystalline cellulose and containing a superdisintegrants (croscarmellose sodium, crosspovidone) and an outer erodible layer of hydroxypropylmethylcellulose (Methocel E 50). The effect of core composition and magnesium stearate in erodible layer was investigated. Erodible and dissolution tests were performed using the paddle method at 50 rpm in Simulated Gastric Fluid and Simulated Intestinal Fluid. The lag time of the pulsatile release tablets decreased with increasing amount of microcrystalline cellulose in the cores and increased with increasing level of erodible hydroxypropylmethylcellulose (Methocel E 50) coating. Increasing levels of the hydroxypropylmethylcellulose (Methocel E 50) coating retarded the water uptake or erodes in presence of aqueous environment and thus prolonged the lag time. Addition of magnesium stearate to the hydroxypropylmethylcellulose coating lowered the mechanical strength of the film and improved the robustness of the system. A 32 full factorial design and statistical models were applied to optimize the effect of two factors, i.e., amount of erodible polymer (hydroxypropylmethylcellulose) and a Plasticizer concentration (Polyethylene glycol 4000: glycerol in 1:1 ratio). It was observed that the responses, i.e., tensile strength and elongation were affected by both the factors. These factors were responsible for maintaining desired lag time of pulsatile release tablet. The statistical models were validated and can be successfully used to prepare optimized pulsatile release tablets of doxofylline with swelling and erodible layers.

Keywords: Nocturnal asthma; Doxofylline; Erodible layer; lag Time; Optimization; Tensile strength; Elongation.

INTRODUCTION

Doxofylline is chemically designated as 7-(1,3-dioxolar-2-ylmethyl)-theophylline, a xanthine which has a dioxolone group in position 7. Doxofylline has greatly decreased affinity towards adenosine A1 and A2 receptors when compared with theophylline, which may contribute to the better safety profile, since in a number of studies, doxofylline has been shown to have better efficacy with fewer side effects than theophylline (see Table 1). Moreover, unlike theophylline, doxofylline does not interfere with calcium influx into cells nor antagonizes the action of calcium-channel blockers. As a consequence, the effective therapeutic dose of Doxofylline has less cardio-stimulant effects than Theophylline, such that doxofylline does not out significantly increase the cardiac frequency nor does it have arrhythmogenic effects[1].

Table 1: Comparisons of Theophylline and doxofylline[1]

Theophylline	Doxofylline
Adeosine receptor antagonism(A1 and A2), histone deacetylase activity stimulation, weak unspecific PDE inhibition	Some effect on adenosine receptors; mechanism not yet fully understood
Very narrow therapeutic index (5-15 µg ml^{-1})	
adeverse cardiac effects caused by adenosine antagonism	Cardiac safety improved, such as no increase in heart rate, and decresed arrhythmic effect
Adverse neurologic effects caused by adenosine antagonism (seizures)	Fewer CNS adverse effects, e.g. improved sleep quality, fewer nightly arousals, fewer cases of headache, insomnia, etc.
Interactions with many drugs, including cimatidine, phenytoin, erythromycin, ciprofloxacin, calcium-channel blockers, fluconazole, rifampin, phenobarbital and propranolol.	No known drug interactions
High protein diet has been demonstrated to increase thophylline clearance by 30%	No known food interactions
Monitoring of plasma levels obligatory	No monitoring of plasma levels necessary

The structural novelty in Doxofylline arises due to the unique methylene 1,3-dioxolone substitution at the N7 position of the Xanthine ring. Doxofylline has also been shown to have anti-inflammatory activity in a rat pleurisy model and to inhibit eosinophil activation by effecting calcium activated Kþ channels. Doxofylline is able to exert prophylactic effects against bronchoconstriction induced by PAF and methacholine.

Pulsatile drug delivery systems are gaining a lot of interest in the field of modified release drug delivery systems. These systems constitute a relatively new class of devices, the importance of which is especially connected with the recent advances in chronopharmacology. 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. 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. 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. 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. 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. Further, highly variable nature of gastric emptying process may result in *in vivo* variability and bioavailability problems.

Nocturnal asthma, a condition prevalent in two-thirds of the asthmatics, is depend 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 am2-4. 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 dose5. 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 administration6,7.

Thus, this study attempts to design and evaluate a chronomodulated drug delivery system of doxofylline, a methylxanthines derivatives used for treatment of nocturnal asthma. It was aimed to have lag time of six hours i.e., the system is taken at the bed time and expected to release the drug after a period of 6 h i.e., at 4.00 am when the asthma attacks are more prevalent. Such time-controlled pulsatile delivery can be achieved mainly with drug containing cores, which are covered with release controlling layers. The core serves as reservoir, and the release controlling layers protect the core from the environment e.g., water, acidic pH and enzymes until the drug is released after a predetermined lag phase. The coatings can erode/dissolve, rupture or alter their permeability at the required time. Single unit rupturable pulsatile drug delivery system was chosen as the model system over erodible pulsatile drug delivery system or Pulsincap® and PORT® systems8 because of ease of manufacturing, better reproducibility of the lag time and rapid drug release after a lag time. The proposed system consisted of core tablet coated with an erodible layer (HPMC E50) aimed to release the drug after a lag time of 6 h.

Response surface methodology (RSM) is a collection of statistical and mathematical techniques, useful for developing, improving and optimizing processes. 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[9].

The current study illustrates the development of a simple pulsatile drug delivery system of Doxofylline to provide relief from nocturnal asthma. It was aimed to modulate the pulsatile release pro file 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

Doxofylline was generously gifted by Olcare laboratories, Surendranagar, 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 doxofylline (400 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, 450 mg) were compressed using punch tableting machine.

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 4^0c overnight to aid complete dissolution of hydroxypropyl methyl cellulose. 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 3.** 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[10-13]

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 from the previous findings. Hence, 3^2 factorial design was 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. Nine 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.

3^2 factorial design model validation.

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 tablet of Pulsatile tablet

Ingredients	Formulation Code								
	Cr1	Cr2	Cr3	Cr4	Cr5	Cr6	Cr7	Cr8	Cr9
Doxofylline	400	400	400	400	400	400	400	400	400
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

All quantities in milligram

Table 3: Composition of time lagged coating solution of Pulsatile tablet as per 3^2 factorial design.

Ingredients	Formulation code								
	CT	CT	CT	CT	CT	CT	CT	CT	CT
	1	2	3	4	5	6	7	8	9
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

All quantities in milligram

Evaluation of Tablets

General parameter

Tablets were evaluated for hardness (Monsanto hardness tester), friability (Roche friabilator), and weight variation[14,15].

Uniformity of content

Twenty tablets were selected randomly, ground to fine powder and mixed thoroughly. A quantity of powder equivalent to 10 mg of doxofylline 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 Whatmans 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 272 nm against water blank and content of Doxofylline was estimated[16].

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 ± 2^0 c as the immersion fluid. After 1 hrs 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 ± 2^0 c as the immersion fluid.

Dissolution studies

Dissolution studies of the pulsatile tablet formulation of Doxofylline 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 hrs 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 272 nm (for pH 1.2) Doxofylline. The dissolution characteristics of each samples was studied, after accounting for loss in the initial concentration of the drug– doxofylline while changing the buffer. The release studies for each formulation were conducted in triplicate, indicating the reproducibility of the results.

Evaluation of Film[17]

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 characteristics of powder blends

Formulation	Angle of Repose (Θ)	Bulk Density (g/cm²)	Tap Density (g/cm²)	% 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

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

Doxofylline Tablets Characterization

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

3² Factorial Designs

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 T.S. and %E for the nine batches (CT1 to CT9) showed a wide variation (i.e., 3.4 to 5.5N/mm² and 25% to 90% respectively). The data clearly indicate that the T.S. and %E values are strongly dependent on the selected independent variables. The fitted full equations relating the responses T.S. and %E to the transformed factors are as:

Tensile strength = $6.67+1.65X_1-0.52X_2$

Elongation = $58.33+25X_1+8X_2$

Response Surface Plots

It was observed that T.S. and %E were dependent on both the factors. There was a linear decrease in the tensile strength with increase in the levels of both factors. The same effect was observed with Plasticizer concentration (Fig.1, 2).

This increase in tensile strength was due to increased quantity of hydroxylpropylmethylcellulose polymer as well as increased coating thickness. However, the effect of plasticizer concenteration on tensile strength was opposite. This receives confirmation from the mathematical model generated for response *Y*1.

Fig. 2 depicts a linear synergistic relationship for Y2 (% Elongation) was also evident from the *p*-values listed in **Table 7.** This increase in elongation was due to increased quantity of hydroxylpropylmethylcellulose polymer as well as increased coating thickness. However, the effect of plasticizer concenteration on elongation was same. This receives confirmation from the mathematical model generated for response *Y*2.

Table 7: Table shows the results of the ANOVA which was used to generate statistical models

Response model	Sum of squares	df	Mean square	F value	P value	R^2	Adeq. 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

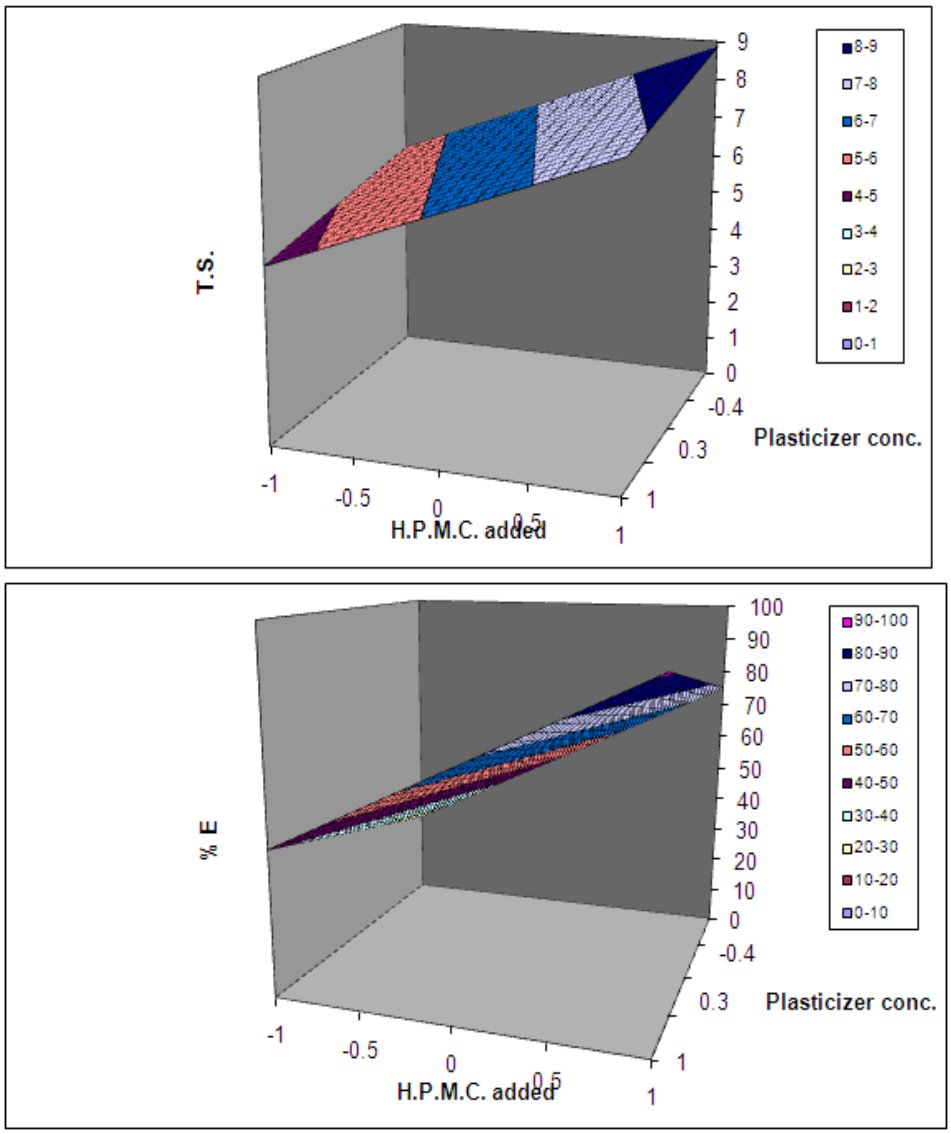

Fig. 1, 2: It shows a linear synergistic relationship between the two independent variables (factors) on response *Y*1 (Tensile strength) was also evident from the *p*-values listed in Table 7

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 8. 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.

Fig. 3 and 4 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 offit. 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.

Table 8: Table shows comparisons of Predicted values and Observed values

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

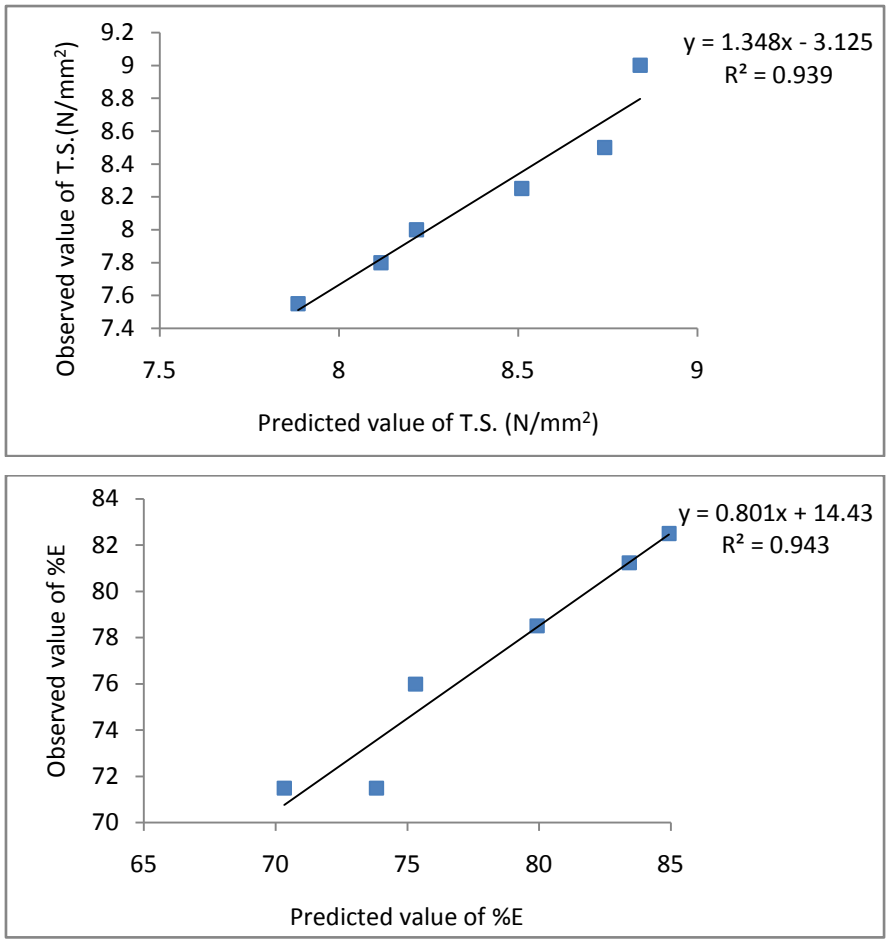

Fig. 3, 4: It shows linear correlation plots between observed and predicted values for response *Y*1 (Tensile strength, N/mm²) and response *Y*2 (% Elongation)

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