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Research Article

STATISTICAL OPTIMIZATION OF MATRIX TABLETS USING LINEAR REGRESSION ANALYSIS

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ABSTRACT

The objective of the current study was to formulate monolithic sustained release matrix tablets of Salbuatmol sulphate and to optimize its drug release profile using linear regression analysis. Tablets of seven batches (F 1 to F 7) were prepared by direct compression technique using two hydrophilic polymers Methocel ® K4M and K15M in different ratioand evaluated for various dissolution parameters. The concentration of each polymer was taken as independent variables. Fourier transform infrared (FTIR) spectroscopy, Differential scanning calorimetry(DSC) and X-ray powder diffractometry(XRD) studies were performed to observe the stability of the drug during compression and to check for drug polymer interactions. Various rheological and physicochemical parameters were studied and complied with the in-house specifications for tested parameters. Scanning Electron Microscopic study was performed to observe the morphological changes of tablets before and after dissolution process. The data obtained from *in-vitro*drug release study were fitted into different kinetic models to identify the pattern of drug release from the matrix systems. Various parameters obtained from the drug release studies were used to perform linear regression analysis using **Analyse-it + General 1.73** software demo version and found to be statistically significant ($p < 0.05$). On the basis of different regression equations obtained from the analysis, one new set of formulation (F 8) was prepared by taking any combinations of above mentioned polymers for the optimization of pharmaceutical formulations with desirable performance characteristics.

Keywords: Salbutamol sulphate, Differential Scanning Calorimetry, X-ray powder diffractometry.

INTRODUCTION

Salbutamol sulphate (SS), chemically (*RS*)-1-(4-hydroxy-3-hydroxy- methyl phenyl)-2-(*tert*-butylamino) ethanol sulphate a short acting highly selective beta 2 adrenoceptor agonist with bronchodilating property is widely used for the management of chronic obstructive pulmonary disease (COPD) which includes bronchial asthma, chronic bronchitis and emphysema[1]. SS is almost completely absorbed (about 71%) from the gastrointestinal tract after oral administration. The reported plasma half-lifeis 2.85±0.85 and the peak plasma concentration occurs about 30 minutes after an oral dose. The protein binding affinity of SS 7±1% and undergoes considerable first pass metabolism. The drug as sulphate is soluble in 1 to 4 of water, due to the hydrophilic nature it is readily excreted through urine[2 – 5]. These bio-pharmaceutical and physicochemical properties provide the rationality behind the fabrication of SS as a controlled release dosage form.

Pharmaceutical formulations are complex systems in which the properties and performance characteristics are influenced by numerous formulation and process factors that may not be easily understood. Pharmaceutical optimization has been defined as the implementation of systematic approaches to establish the best possible combination of materials and/or process variables under a

given set of conditions that will result in the production of a quality pharmaceutical product with predetermined and specified characteristics each time it is manufactured[6].

Hydrophilic monolithic matrix devices are a popular choice for the manufacture of sustained release solid oral dosage forms due to their ease of manufacture and the extensive amount of information available regarding this well understood technology. The use of hydrophilic matrix formulations to control the release of drugs from pharmaceutical tablets is well documented[7 – 10]. The rate and mechanism of drug release from monolithic devices can be adjusted by the levels and types of polymer combinations that are used to manufacture a formulation. When hydrophilic matrix tablets are immersed in aqueous media, the polymer hydrates, swells and increases in size after which the matrix dissolves and/or erodes with time. Early studies have shown that drug release from swellable hydrophilic matrices is dependent on the thickness of the hydrated gel layer that is formed during the swelling phase of polymer hydration[11, 12]. The degree of swelling determines the diffusional path length of a drug and the thicker the gel layer, slower the rate of drug release from a matrix[13]. Drug release from hydrophilic matrix formulations occurs by drug diffusion through the gel layer and/or erosion of the tablet matrix. Hydroxypropyl methylcellulose (HPMC) has been used extensively for the manufacturing of tablets[14 – 20].

The main objective of this work is to deliver the drug as much as possible in intact form into the intestine by modulating the suitable combinations of two hydrophilic polymers to hinder the entry of acid buffer as much as possible into the matrix bed keeping in view that SS is highly susceptible to first pass degradation. Present study concerns with the preparation of SS matrix tablet for prolong drug release leading to minimization of incidences of nocturnal and early morning asthmatic attacks, better patient convenience and a pharmaco-economic novel drug delivery system, for effective treatment for of COPD. Salbutamol sulphate conventional release tablets are administered 2 to 4 mg three to four times daily and their duration of action are last for 4 to 6 hours[5]. So the aim of this work was to design, formulate and develop a novel oral monolithic controlled release tablet dosage form that may be toiled to provide quasi steady state drug release over an extended period of time.

MATERIALS AND METHODS

MATERIALS

Salbutamol sulphate was obtained as a gift sample from Cipla Ltd., Mumbai, India, Hydroxypropyl methylcellulose K4M, K15M and Avicel PH 101 were purchased from Yarrow chem. Products Mumbai,India, Talc and Magnesium stearate were procured from LobaChemiePvt. Ltd. Mumbai,India. All the chemicals and reagents used were of analytical grade.

METHODS

Preparation of matrix tablets of Salbutamol sulphate

Different tablet formulations were prepared by direct compression technique. Thecompositions of each batch were shown in the following **Table - 1**.

All the powders were passed through USP 100 mesh sieve. Total polymer amount was kept 50 % w/w of total tablet weight. Required quantity of two polymers were poured in geometric dilution into preheated water and stirred continuously until they form viscous gel. To it required amount of drug (i.e. maintenance dose) was added and stirred vigorously for a time period of 4 hrs. Then the gel was kept into a dryer at a temperature of 60^0 C until it formed dried film. The film was then triturated in a mortar to form powder and again passed through USP 35 mesh sieve. This polymer coated drug was then mixed thoroughly with diluent and remaining portion of drug (i.e. loading dose). To it required quantity of talc and magnesium stearate was added and compressed the mixture using 6 mm round concave punchesto get the tablets having the hardness between 5 to 7 kg/ cm^2[21 – 23].

Evaluation of rheological parameters of powder mixture[24 - 25]

Angle of Repose

The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following formula:

$$\theta = \tan^{-1} h/r$$

Where, h = Height of power cone and
r = Radius of the power cone

This was done thrice, from that average angle of repose and standard deviation was calculated.

Poured Density

Poured density or apparent bulk density (ρ_b) was measured by pouring the pre-weighed (M) blend into a graduated cylinder. The bulk volume (V_b) of the blend was determined. Then the bulk density was calculated by using the formula:

$$\rho_b = M / V_b$$

This was done thrice, from that average poured density and standard deviation was calculated.

Tapped Density

The measuring cylinder containing a known mass (M) of blend was tapped for a fixed time, and the minimum volume (V_t) occupied in the cylinder was measured. The tapped density ρ_t was calculatedby using the following formula:

$$\rho_t = M / V_t$$

This was done thrice, from that average tapped density and standard deviation was calculated.

Compressibility Index or Carr's Index

Compressibility index or Carr's index is the simple, fast, and popular methods of predicting powder flow characteristics.The compressibility index was determined by measuring both the poured density and the tapped density of a powder and calculated as follows:

$$C = 100 X (1 - \rho_b / \rho_t)$$

Where, C = Compressibility index or Carr's index

ρ_b and ρ_t are poured and tapped density respectively

Hausner's Ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula:

$$H = \rho_t / \rho_b$$

Where, H = Hausner's Ratio

ρ_t and ρ_b are tapped and poured density respectively

Drug excipient compatibility study

Fourier Transform Infra-red Spectroscopy (FT-IR)[26]

An infrared spectrum of pure drug and optimized formulation was recorded on Fourier transform infrared instrument (Shimadzu, Japan) equipped with temperature-controlled high-sensitivity deuterated L-alanine doped triglycinesulfate detector. Sample was prepared and compressed with KBr on Minipress (Jasco, Japan) to form a disk. The compressed disks were scanned over 4,000 to 400 cm^{-1}, and characteristic peaks were recorded.

Differential Scanning Calorimetry(DSC)[27]

The Differential Scanning Calorimetry studies of pure drug and optimized formulation were carried out using Pyris Diamond TG/DTA. Accurately weighed samples were placed on aluminium plate, sealed with aluminium lids and heated at a constant rate of 5^0 C/ min over a temperature range of 0 to 300^0 C to better integrate the information and the flow of argon was kept at 80 ml/min.

X-ray Powder Diffractometry (XRD)

X-ray powder diffraction spectra were obtained with a Bragg – Brentano geometry using a Cu Kα radiation over the 20 – 40 2θ range. The powder was packed into the rotating sample holder of X-ray diffractometer (Rigaku, Japan) and analyse the spectra of pure drug, 1:1 physical mixture of drug and polymer before compression and formulation to observe the interaction.

Physicochemical characteristics of formulations[24, 25, 28]

The tablets were evaluated for following parameters to meet the Pharmacopoeial standards.

Determination of weight variation

Twenty tablets were selected at random from each batch and were weighed accurately using an electronic balance (Sartorius GC 103) and average weights and the standard deviation were calculated.

Determination of thickness and diameter

Thickness and diameter of twenty randomly selected tablets from each batch were measured with a verniercaliper. Then the average diameter and thickness and standard deviation were calculated.

Determination of hardness

Ten tablets were sampled randomly from each batch and the hardness was determined by using Monsanto Hardness Tester (Campbell Electronics, India). Then average hardness and standard deviation was calculated.

Determination of friability

Twenty tablets were sampled randomly from each batch and the friability was determined using Roche friabilator (Campbell Electronics, India). A pre-weighed tablet sample was placed in friabilator which was then operated

for 100 revolutions (25 rpm). The tablets were then dusted and reweighed. Then percentage friability was calculated using the following formula:

%Friability= (Loss in weight/ Initial weight) x 100

Determination of tensile strength[29]

Tensile strength of the tablet depends on the development of a correct state of stress within the compact, but is less dependent on the compact geometry than the crushing strength measurements. The radial tensile strength, which measures the tablet failure as a result of the application of tensile strength only, is given by the following relationship:

$$\sigma_x = 2F/ \pi DT$$

Where, σ_x= Tensile strength
F = Force require to break the tablet
D = Diameter of the tablet
T = Thickness of the tablet

Determination of content uniformity

The content uniformity was assessed according to USP requirements. The test is used to ensure that every tablet contains the amount of drug substance intended with a negligible variation among tablets within a batch. Ten tablets from each formulation were tested. Each tablet was weighed individually and crushed to a powder. An accurately weighed sample (100 mg) was placed in a 50 ml volumetric flask and the drug was extracted by distilled water. The content of the flask was sonicated for 20 minutes at room temperature. 5 ml of aliquot was filtered through 0.45 µm membrane filter and analysed spectrophotometrically (UV 1800, Lab India, Mumbai, India) at 276 nm.

***In-vitro* swelling study**

The swelling of polymers were determined by water uptake study. It was observed that the swelling indices were varied with the nature as well as the proportion of individual polymer present in the matrix systems. Swelling was a strong enough to avoid premature disintegration as well as burst effect and retarded the release of drug for a long period of time. Usually swelling is essential to ensure the drug release from the system and there should be appropriate balance between swelling and water uptake. Swelling index values starts decreasing when polymer erosion starts in medium.

Swelling study of individual formulation was carried out using eight station USP dissolution apparatus type I (Basket) (TDT – 08 T, Electrolab, Mumbai, India) at 100rpm and respective buffer solution was used as medium and the temperature was maintained at 37 ± 0.5^0 C. Weight of individual tablet was taken prior to the swelling study (W_1). The tablet was kept in a basket. The weight of tablet was taken at predetermined time interval (W_2). Percentage of hydration (swelling index) was calculated using the following formula.

$$\text{Swelling index} = (W_2 - W_1) \times 100 / W_2$$

Where, W_1 is the initial weight of tablet and W_2 is the weight of hydrated tablet.

***In-vitro* drug release study**

In-vitro drug release studies from prepared tablets were conducted according to the method described by Fayed *et al*. [30] for a period of 12 hrs using eight station USP dissolution apparatus type II (Paddle) (TDT – 08 T, Electrolab, Mumbai, India) at 37 ± 0.5^0 C and 100 rpm speed. The dissolution studies were carried out in triplicate for a period of 12 hrs (initial 2 hrs in 700 ml 0.1 N HCl, and rest 10hrs add 200 ml 0.2 Mtrisodium phosphate to maintain pH 6.8) under sink condition. At predetermined time interval 5 ml samples were withdrawn from the vessel, filtered through 0.45 µm membrane filters and replaced with fresh medium to maintain the constant volume. The absorbance of the filtrate was measured at 276 nm using UV double beam spectrophotometer (UV 1800, Lab India, Mumbai,India). The amounts of drug present in the samples were calculated with help of appropriate calibration curves. Drug dissolved at specific time periods was plotted as percentage release versus time.

Mathematical modelling of release data [31]

The release of drug from different formulations was evaluated by fitting the release data to the following mathematical equations for describing the release pattern.

Zero order equation

Zero order release would be predicted by the following equation:

$$C_t = C_0 - K_0 t$$

Where,$C_t$is the amount of the drug released at time t, $C_0$is the initial amount of drug in the tablet and $K_0$is the zero-order rate constant (hr^{-1}).

First order equation

First order release would be predicted by the following equation:

$$\log C = \log C_0 - K_1 t/2.303$$

Where, C is the amount of drug remaining as a solid state at time t, C_0 is the initial amount of drug in the matrix and $K_1$is the first order rate constant (hr^{-1}).

Higuchi model equation

Drugreleasedfromthematrixdevicesbydiffusion has been described by following Higuchi's classical diffusion equation:

$$Q = 2 C_0 (Dt / \pi)^{1/2}$$

Where,Q is amount of drug released per unit area, C_0 is the initial drug concentration, t is time of release and D is diffusion coefficient of the drug in the matrix and can be calculated according to the following equation:

$$D = (Slope / 2 C_0)^2 \pi$$

Korsmeyer- Peppasequation

Thereleaseratesfromcontrolledrelease polymericmatricescanbedescribed by the equation proposed by Korsmeyer*et al*.

$$Mt / M\infty = K. t^n$$

Where,Mt / M∞ is the fraction released by the drug at time t, K is a constant incorporating structural and geometric characteristic and n is the release exponent indicating drug transport mechanism.

Scanning Electron Microscopy (SEM) study

The scanning electron microscopy study was performed to examine the surface topography, texture, and morphology of the tablet. SEM analysis was done before and after dissolution of the tablet using JEOL, JSM6360 scanning electron microscope. Images may be scanned on a digital imaging system by computer enhancement.

Optimization by statistical analysis

Analyse-it + General 1.73 software demo version was used for **Linear Regression Analysis.** In this study design, two factors were evaluated. The ratios of HPMC K4M (X_1) and HPMC K15M (X_2) were selected as independent variables. The zero order rate constant (K_0), Higuchi rate constant (K_h), diffusion exponent (n), initial burst release (X_{120}) and times required for 50% drug release (t_{50}) were selected as dependent variables.A new set of formulation (F 8) was prepared by taking the same polymers in different ratio (4:1) of the total weight of the polymer and analysed the values with predicted one.

RESULTS AND DISCUSSION

Evaluation of rheological parameters of powder mixture:

The rheological characteristics of the powder blends of different batches were evaluated in order to get free flowing of powder which helped trouble free tableting resulting in accuracy of dosage. The values of different parameters were tabulatedin **Table 2**. Results indicated that all powder blends were "excellent" to "good" category according to USP 29 NF 24 and ranging from 25.1293 ± 1.6721 to 29.7922 ± 1.3767 ^{0} for angle of repose; 0.3029 ± 0.0092 to 0.3161 ± 0.0156 g/cm^3 for poured density; 0.3250 ± 0.0097 to 0.3639 ± 0.0190 g/cm^3 for tapped density; 6.4957 ± 0.6139 to 15.7209 ± 2.8561% for Carr's index and 1.0695 ± 0.0070 to 1.1874 ± 0.0408 for Hausner's ratio respectively.

Drug excipient compatibility study

Differential scanning calorimetry (DSC)

The thermal profiles of pure drugand formulations were depicted in the **Figure 1 and 2**. The sharp melting peak of pure drug was observed at 154.35^{0}Cindicating crystalline nature of the drug in pure form. The matrix forming polymers exhibited a broad endothermal effectdue to a dehydration process and superimposed each other as they were in mixed form, indicated in the first curve of **Figure 2**. The second curve of **Figure 2** indicated thermogram of the formulation. Here we observed that the dehydration band was shifted to lower temperature and a small shoulder following the broad endothermic effect was revealed probably due to a partial recrystallization of polymer blends and or due to the evolution of water associated with both polymers as a result of energies evolved during compression process. The thermal profiles of all the mixture remained almost unchanged after compression, indicating compatibility of the drug with all the examined polymers.

Fourier transforminfra-red spectroscopy (FT-IR)

FT-IR study was then performed in order to obtain more information and support the DSC results. FT-IR spectra of pure drug and formulation were reported in **Figure 3** and **4**.The appearance of characteristic peaks of drug at 1112.96 cm-1 region due to alcoholic O-H bond in bending and C-N vibration, at 1198.80 cm-1regiondue to C-O bond in bending, peaks at 1245.09 cm-1 region due to C-N bond, peaks at 1379.15 cm-1 and 1385.90 cm-1 due to phenolic C-O bond in stretching were well retained in the formulation, thus indicating the absence of interactions and confirming DSC findings.

X-ray powder diffraction (XRD)

Powder diffraction spectra of pure drug, 1:1 physical mixture of drug and polymers before compression and formulation were shown in **Figure 5**to **7**. The characteristic high intensity peaksof pure drug were observed at

2θbecause of crystalline nature of drug. But the intensity of these characteristic peaks gradually decreased in 1:1 physical mixture before compression and formulation respectively. This observation indicated that amorphous polymer molecules shielded the drug molecules completely and the presence of low intensity characteristic peaks indicated there was no interaction occurs between drug and polymer before and after compaction.

Evaluation of physicochemical parameters

The physicochemical parameters of the formulations were mentioned in the **Table 3** and were within the pharmacopoeial specification. The mean weight values of tablets ranged from 119.85±2.23 to 120.5±2.09 mg, whereas mean diameter and thickness ranged from 6.14±0.12 to 6.25±0.18 mmand 4.17±0.01 to 4.27±0.13 mm respectively. All formulations showed good hardness (> 5kg) in the range of 5.76±0.37 to 6.06±0.36 kg/cm^2, having a percentage friability of less than 1%. The physical strength of a tablet depends on its dimension which is related to the compression force applied during tableting. Breaking strength does not provide the actual physical strength of the tablet even if fixed compression force applied for all batches. This problem has been circumvented in part by the calculation of the tensile strength of the tablet. The values were ranged from 138.45±1.39 to 143.89±1.25 N.In general, highest hardness value showed highest values of tensile strength which will result in less porosity and slow drug release. Mean drug content value obtained was found satisfactory within 97.33±1.52 to 98.66±1.02%for all formulations.

***In-vitro* swelling and drug release study**

The results obtained from the *in-vitro* swelling and drug release study was depicted in the **Table 4** and **5**respectively.Here we observed that in first two hours about 14 to 21%swelling occurred indicating higher water uptake into the matrix which results in increase of tablet area and promote higher drug release (X_{120}) ranging between 2.4833 mg (≈ 35%) to 2.9881 mg (≈ 37%) from the system. After that, up to 4 to 5 hours the rate of swelling was gradually increasedabout 19 to 35%. In this stage water molecules were gradually entered into the matrix and form a viscous gel layer. The viscosity of this gel layer depends on the amount and viscosity of the polymer present into the system. With time when the penetration of water in the gel matrix exceeds a critical concentration (i.e. the concentration at which the interactions between water and polymer increase, with a consequent reduction of polymer – polymer interaction), the polymer chains begin to separate, extending the spaces through which leaching of drug occurs. The t_{50} value (i.e. time required for 50% drug release) of all the formulations were almost close to each other indicating steady state release. After 4 to 5 hoursthe swelling index was gradually decreased and the rate of erosion of polymeric bed increases and water molecules are trying to enter to the dry core of the tablet exists which indicate decrease of tablet area. In this stage, polymer dissolution is more significant than the polymer swelling. As a result the total drug release was varied significantly from batch to batch ranging between 86.5681 to 96.8421%.

Kinetic analysis of release data

The drug release kinetic of salbutamol sulphate was described by various mathematical models and equations. **Table 6** and **Figure8,** to **10**explain the release kinetics of the eight formulations. The higher correlation coefficient (r^2) values for Higuchi diffusion model obtained in all the formulations indicate diffusion mechanism of drug release. In addition, the magnitude of the Higuchi rate constant (K_h) was found to be dependent on composition i.e. amount of individual polymer used for the system. It has been seen that the rate constant values decreases with increasing the HPMC K15M concentration due to formation of more viscous gel layer which retard drug release from the system. The n exponent of Korsmeyer – Peppas model can be used to characterize the drug release mechanisms from the system. The data indicated that drug release follow anomalous transport i.e. both diffusion and erosion as they lies between > 0.43 to < 0.85.

Scanning Electron Microscopy (SEM)

The SEM images of the tablet were taken before and after dissolution as shown in **Figure 11** and **12**. The images of the tablet before dissolution showed intact surface without any perforations, channels or troughs. After dissolution we revealed many pores with increasing diameter. The solvent font enters the matrix and moves slowly toward the centreof the tablet. The drug diffuses outfrom the matrix after it comes in contact with dissolution medium, which clearly indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of drug from the formulations.

Statistical optimization

The effects of combination two polymers in varying ratios on different dependent variables were shown in the **Table 7**. Putting these values to the statistical software following mathematical **equations 1**to**5**was derived. Using these equations optimization of new formulation containing same polymers was carried out.

$K_0 = 5.9613 + 0.5335\ X_1 + 0.1210\ X_2$ (1) $R^2 = 0.9983$

$K_h = 21.9527 + 1.6691\ X_1 + 0.4073\ X_2$ (2) $R^2 = 0.9880$

$n = 0.3642 + 0.0539\ X_1 + 0.0183\ X_2$ (3) $R^2 = 0.9508$

$X_{120} = 56.5477 - 5.4551\ X_1 - 1.5348\ X_2$ (4) $R^2 = 0.9680$

$t_{50} = 2.2500 + 0.7051\ X_1 + 0.1218\ X_2$ (5) $R^2 = 0.9433$

We observed that all the values of each dependent variable were in close proximity to each other, indicating significant effect of the polymer concentration which can be further confirmed by analysis of variance study ($p < 0.05$) shown in **Table 8**. Higher value of the correlation coefficient (**Equation 1 – 5**) clearly indicates that the response is strongly dependent on the factor studied. The linear regression equation 1 and 2 can be used to draw a conclusion that with increasing the amount of HPMC K4M, zero order rate constant will gradually increase which indicates drug released occurred through swelling of polymeric bed whereas with increasing the amount of HPMC K15M, Higuchi rate constant gradually decreased indicating diffusion or erosion mechanism of drug release. These two observations were further established by the diffusion exponent (n) of Korsmeyer – Peppas model. The n values of all the formulations indicate that drug release follows anomalous transport i.e. both swelling and diffusion or erosion. The linear equation 4 and 5 helps to draw a conclusion that with increasing the amount of HPMC K4M, drug release in first two hours (X_{120}) also increased may be due to less viscous gel layer formation occurs initially whereas with increasing the amount of HPMC K15M, more time is required to release 50% of drug from the dosage form because of the formation of more viscous gel layer which retard the release of drug from the system. The correlation between actual and predicted values of all the dependent variables was graphically presented in **Figure 13 to 17**.

Table 9 showed the comparison between the predicted and observed data of all dependent variables of the new formulation **F8**. It was found that the deviations of the responses between predicted and observed data were in close proximity (within 5%). So, it can be concluded that the process of matrix tablet formulation with any combination of HPMC K4M and HPMC K15M is statistically optimized and can be reproduced by following similar process conditions.

CONCLUSION

The objective of the present work was to develop salbutamol sulphate matrix tablet for sustained release dosage form to treat the chronic obstructive pulmonary disease (COPD). Direct compression technique was employed for the preparation matrix tablets by combination of two hydrophilic polymersHPMC K4M and HPMC K15Min different ratio. Drug excipient compatibility study was performed by infrared spectroscopy, differential scanning calorimetry and X-ray powder diffractometry. All the seven formulations showed acceptable pharmaco-technical properties and complied with the in-house specifications for tested parameters. *In-vitro* drug release data were fitted into different mathematical models and compare the correlation coefficient (R^2) value. The result reveals that all the formulations predominantly follow the Higuchi kinetic model ($R^2 \leq 1$), the main kinetic model to describe the drug release behaviour from a matrix system. The diffusion coefficient (n) value indicates a coupling of diffusion and erosion mechanisms for drug release from the systems. Scanning electron microscopy study was performed to find out the morphological changes of the dosage form before and after the drug release study. To check the reproducibility of HPMC K4M and HPMC K15M combination, statistical analysis was carried out with a new formulation F-8 (4:1 ratio) and was found that the deviations of the responses between the predicted and observed data were in close proximity. So, it can be concluded that the process of matrix tablet formulation with any combination of HPMC K4M and HPMC K15M is statistically optimized and can be reproduced by following similar process conditions.

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Table 1: Composition of matrix tablets of salbutamol sulphate (Each tablet weight 120 mg)

Ingredients (mg/ tablets)	F 1 (1:1)	F 2 (1:2)	F 3 (1:3)	F 4 (2:1)	F 5 (2:3)	F 6 (3:1)	F 7 (3:2)	F 8 (4:1)
Salbutamol sulphate	12	12	12	12	12	12	12	12
HPMC K4M	30	20	15	40	24	45	36	48
HPMC K15M	30	40	45	20	36	15	24	12
Avicel PH 101	44.4	44.4	44.4	44.4	44.4	44.4	44.4	44.4
Talc	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Magnesium stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2

Table 2: **Rheological parameters of powder blends**

Formulation code	Angle of repose (^{0})	Poured density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio
F 1	25.12±1.67	0.30±0.01	0.32±0.01	6.49±0.61	1.06±0.01
F 2	28.27±0.66	0.30±0.01	0.32±0.01	8.15±1.04	1.09±0.01
F 3	26.89±1.41	0.31±0.01	0.33±0.02	7.88±2.31	1.09±0.03
F 4	29.79±1.37	0.31±0.01	0.35±0.01	9.75±1.46	1.11±0.02
F 5	27.30±1.41	0.31±0.01	0.34±0.01	11.2±1.15	1.13±0.01
F 6	27.82±1.62	0.30±0.01	0.35±0.02	12.58±2.06	1.14±0.03
F 7	26.38±1.35	0.31±0.01	0.36±0.02	15.72±2.86	1.18±0.04
F 8	26.23±0.96	0.30±0.01	0.36±0.03	14.43±3.75	1.17±0.05

Mean ± SD (n = 3)

Table 3: Physicochemical properties of various tablet formulations

Batch code	Parameters						
	Weight variation (mg)	Diameter (mm)	Thickness (mm)	Hardness (kg/cm2	Friability (%)	Tensile strength (N)	Drug content (%)
F 1	120.30±2.15	6.14±0.13	4.18±0.21	5.76±0.37	0.33	140.19±2.39	97.34±2.31
F 2	120.25±2.45	6.16±0.18	4.22±0.18	5.92±0.26	0.16	142.25±2.58	98.57±1.44
F 3	120.05±1.96	6.25±0.18	4.23±0.13	5.86±0.44	0.12	138.45±1.39	98.13±1.69
F 4	120.10±1.20	6.14±0.13	4.27±0.13	6.00±0.41	0.21	142.95±1.92	98.26±1.68
F 5	120.20±1.82	6.19±0.07	4.25±0.11	6.06±0.36	0.12	143.89±1.25	98.43±1.29
F 6	120.50±2.06	6.19±0.07	4.17±0.09	5.84±0.37	0.21	140.64±2.24	97.33±1.52
F 7	119.85±2.23	6.22±0.11	4.25±0.08	5.94±0.31	0.21	141.27±1.78	98.66±1.02
F 8	120.50±2.09	6.24±0.13	4.25±0.07	6.04±0.27	0.24	140.85±1.68	97.43±1.59

Mean ± SD (n = 3)

Table 4: *In-vitro* swelling study of various formulations

Time (hour)	Formulation code							
	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)
1	16.39	15.13	12.39	13.71	13.93	13.45	14.05	14.75
2	21.31	19.33	14.88	18.55	17.21	16.81	16.53	18.85
3	24.59	24.37	19.83	24.19	20.49	21.85	20.66	25.41
4	29.51	27.73	26.45	28.23	24.59	26.89	24.79	32.79
5	27.05	30.25	31.40	29.03	27.87	29.41	27.27	35.25
6	25.41	28.57	29.75	27.42	30.33	28.57	31.40	33.61
7	22.13	26.05	28.93	25.81	28.69	26.05	29.75	30.33
8	20.49	25.21	27.27	22.58	27.05	24.37	26.45	28.69

Table 5: *In-vitro* drug release parameters of various formulations

Parameters	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
X_{120} (mg)	2.7088	2.5601	2.4833	2.7579	2.5961	2.8260	2.7434	2.9881
t_{50} (hrs.)	4.7	5.1	5.6	4.7	4.9	4.6	4.7	4.4
t_{90} (hrs.)	10.5	10.4	10.8	10.4	11.9	10.7	10.9	10.1
Total drug release at 12 hrs. (%)	94.5898	96.8421	93.5682	93.9921	86.5681	96.0284	92.1148	96.4489

Table 6: *In-vitro* release kinetics parameters of various formulations

Batch code	Zero order		Higuchi		First order		Korsmeyer - Peppas	
	R^2	K_0 (h^{-1})	R^2	K_h ($h^{-1/2}$)	R^2	K_1 (h^{-1})	R^2	n
F 1	0.9522	6.8475	0.9804	26.929	0.9345	-0.0929	0.9482	0.4939
F 2	0.9579	6.5663	0.9876	25.670	0.8905	-0.1014	0.9734	0.5292
F 3	0.9552	6.3054	0.9801	24.708	0.9275	-0.0879	0.9525	0.4937
F 4	0.9245	7.0935	0.9781	27.829	0.9701	-0.0998	0.9454	0.5280
F 5	0.9554	6.8155	0.9827	26.674	0.9687	-0.0651	0.9591	0.5088
F 6	0.9518	7.1785	0.9861	28.511	0.8903	-0.0959	0.9722	0.4895
F 7	0.9538	6.9339	0.9765	27.184	0.9284	-0.0784	0.9425	0.4804
F 8	0.9581	7.2748	0.9858	28.528	0.9214	-0.1090	0.9770	0.5338

Table 7: Release data of formulations used to study linear regression analysis

Formulation code	X_1 (parts)	X_2 (parts)	K_0 (h^{-1})	K_h ($h^{-1/2}$)	n value	X_{120} (mg)	t_{50} (hr)
F 1	1	1	6.8475	26.929	0.4939	2.7088	4.7
F 2	1	2	6.5663	25.670	0.5292	2.5601	5.1
F 3	1	3	6.3054	24.708	0.4937	2.4833	5.6
F 4	2	1	7.0935	27.829	0.5280	2.7579	4.7
F 5	2	3	6.8155	26.674	0.5088	2.5961	4.9
F 6	3	1	7.1785	28.511	0.4895	2.8250	4.6
F 7	3	2	6.9339	27.184	0.4804	2.7434	4.7

Table 8: ANOVA for dependent variables from linear regression analysis

Source	SS	dfMS	F – value	Probability
K_0 (h^{-1})				
Regression	1.306	2	0.653	1193.27 < 0.0001
Residual	0.002	4	0.001	
Total	1.308	6		
K_h ($h^{-1/2}$)				
Regression	12.783	2	6.392	164.41 0.0001
Residual	0.156	4	0.039	
Total	12.939	6		
n value				
Regression	0.013	2	68.422	60.45 0.0010
Residual	0.001	4	1.132	
Total	0.014	6		
X_{120} (mg)				
Regression	136.843	2	68.422	60.45 0.0010
Residual	4.528	4	1.132	
Total	141.371	6		
t_{50} (hr)				
Regression	2.291	2	1.145	33.24 0.0032
Residual	0.138	4	0.034	
Total	2.429	6		

SS – sum of squares; df – degree of freedom;
MS – mean of squares; F – Fischer's ratio

Table 9: Comparison between the Predicted and Observed Data

Responses	Predicted Data	Observed Data	Deviation
K_0 (h^{-1})	8.2163	7.2748	**-0.9415**
K_h ($h^{-1/2}$)	29.0364	28.5280	**-0.5084**
n	0.5981	0.5338	**-0.0643**
X_{120} (%)	33.1925	37.4739	**+4.2814**
t_{50} (hr.)	5.2	4.4	**-0.8**

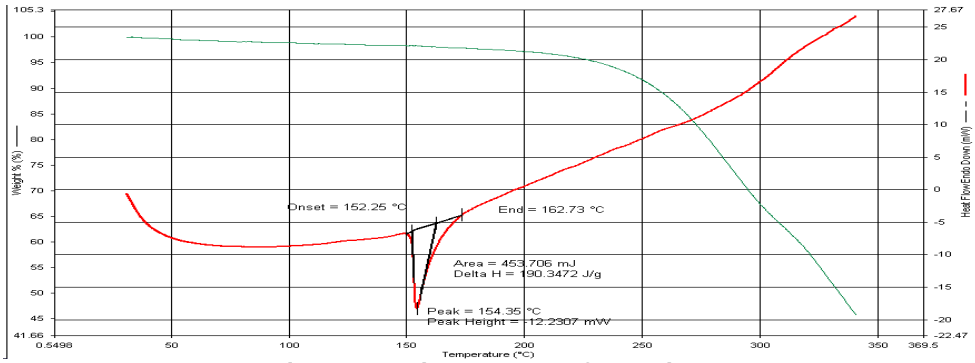

Fig. 1: DSC thermogram of pure drug

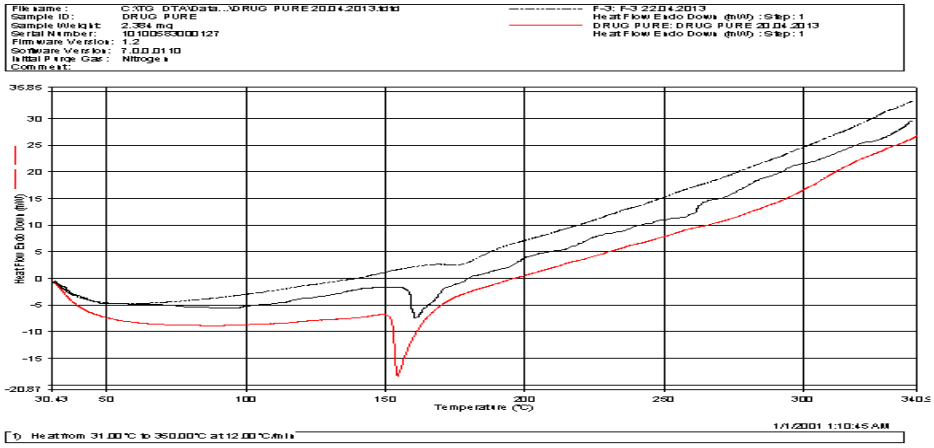

Fig. 2: DSC thermogram of formulation

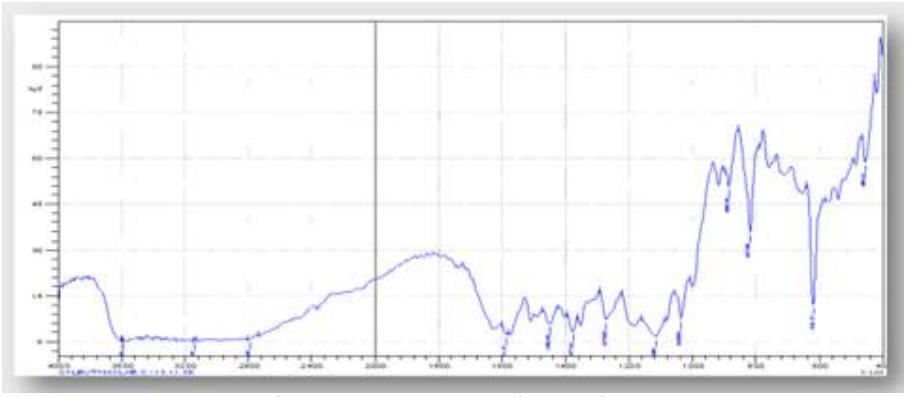

Fig. 3: FTIR spectra of pure drug

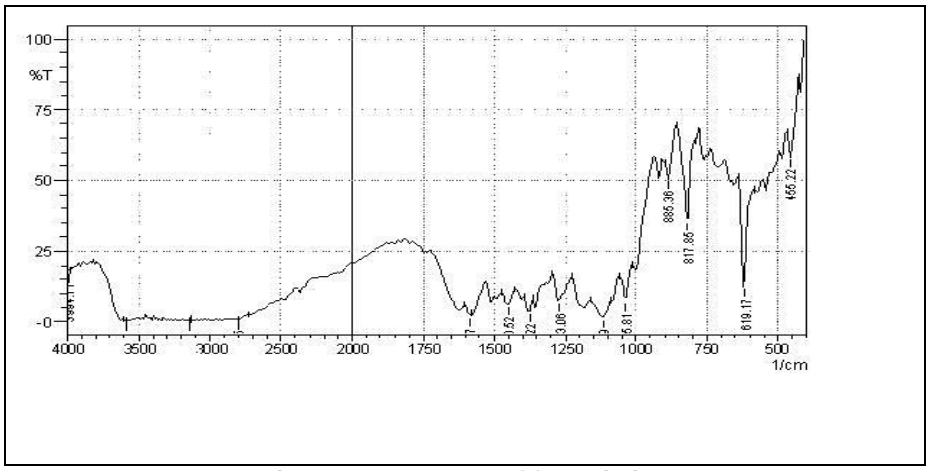

Fig. 4: FTIR spectra of formulation

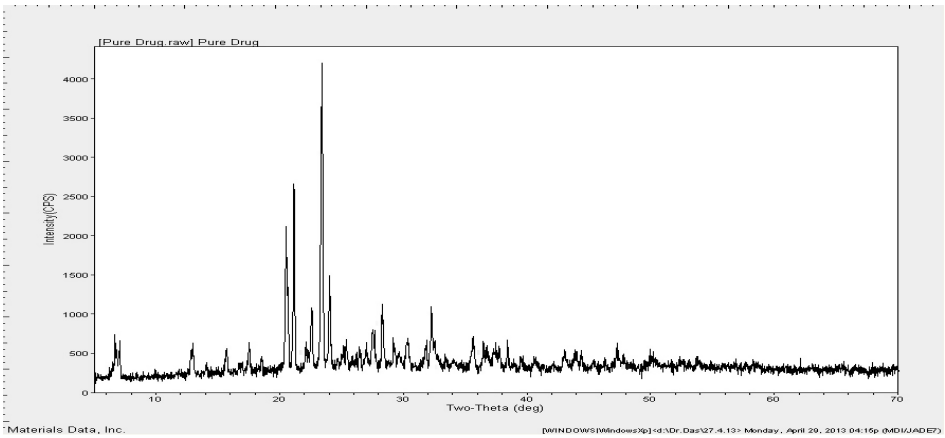

Fig. 5: X- ray diffraction spectra of pure drug

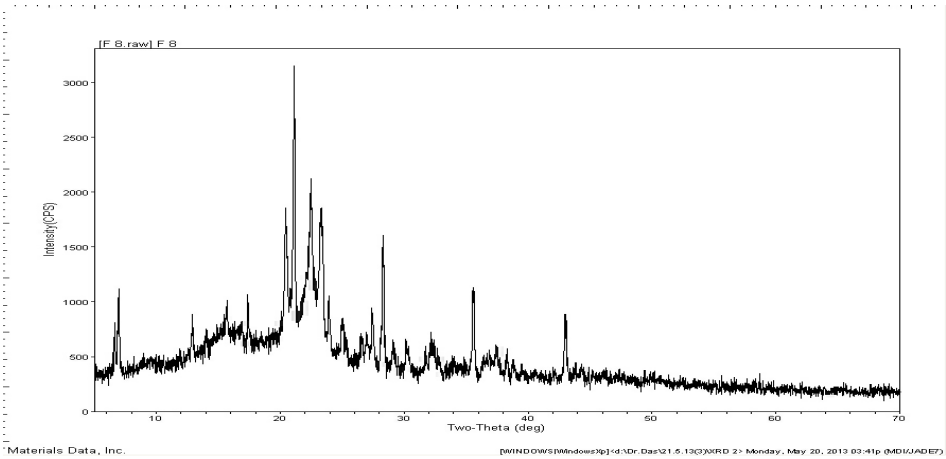

Fig. 6: X- ray diffraction spectra of physical mixture before compression

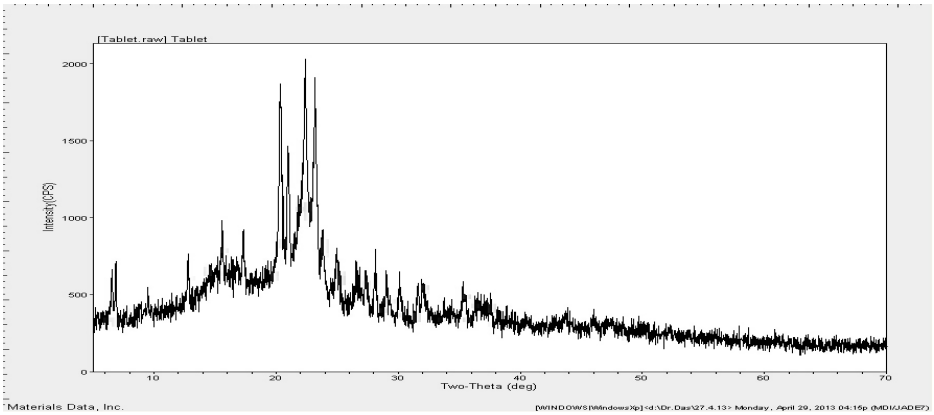

Fig. 7: X- ray diffraction spectra of formulation

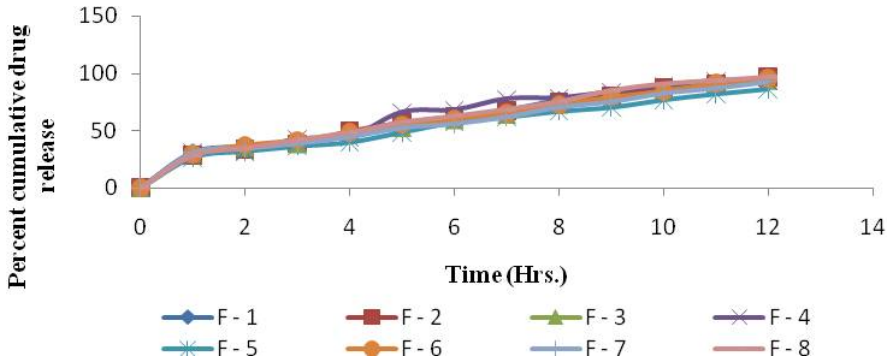

Fig. 8: *In-vitro* release profiles from formulations (Zero order model)

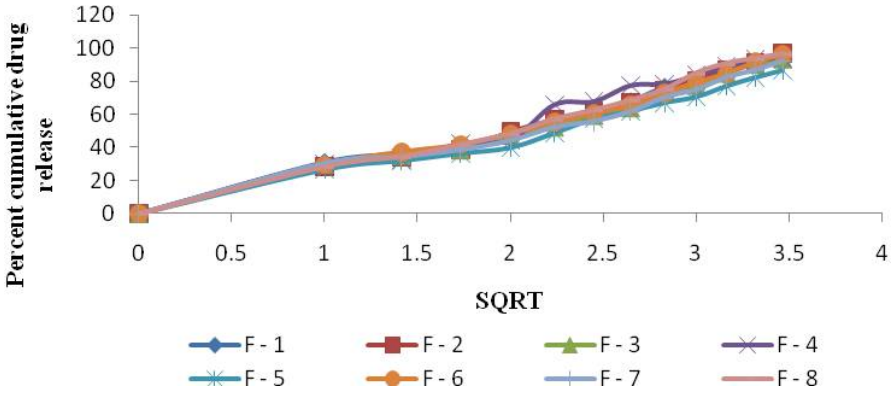

Fig. 9: *In-vitro* release profiles from formulations (Higuchi model)

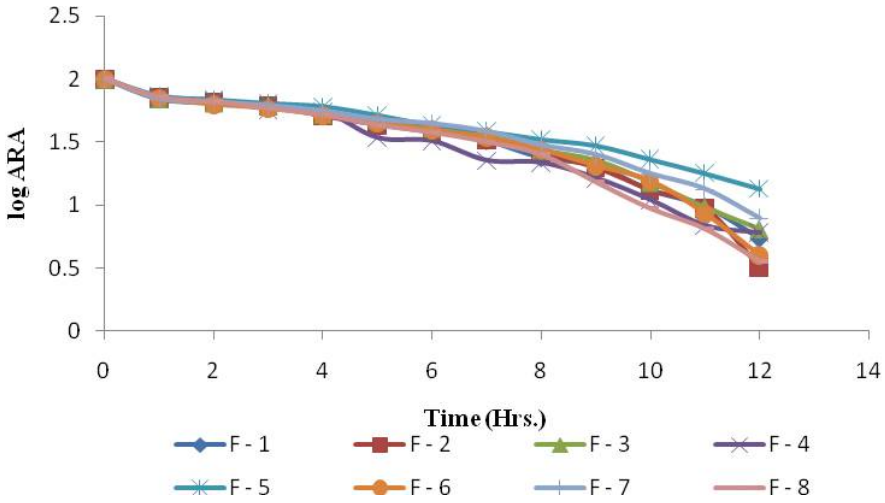

Fig. 10: *In-vitro* release profiles from formulations (First order model)

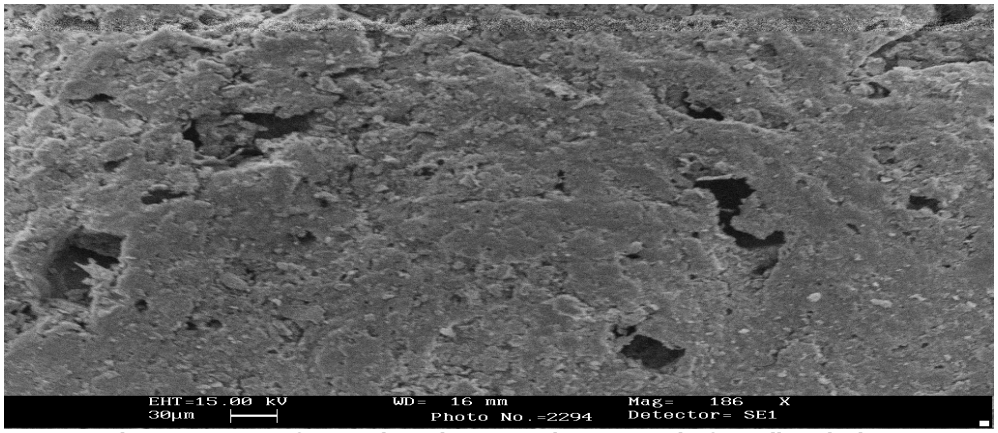

Fig. 11: Image of scanning electron microscopy before dissolution

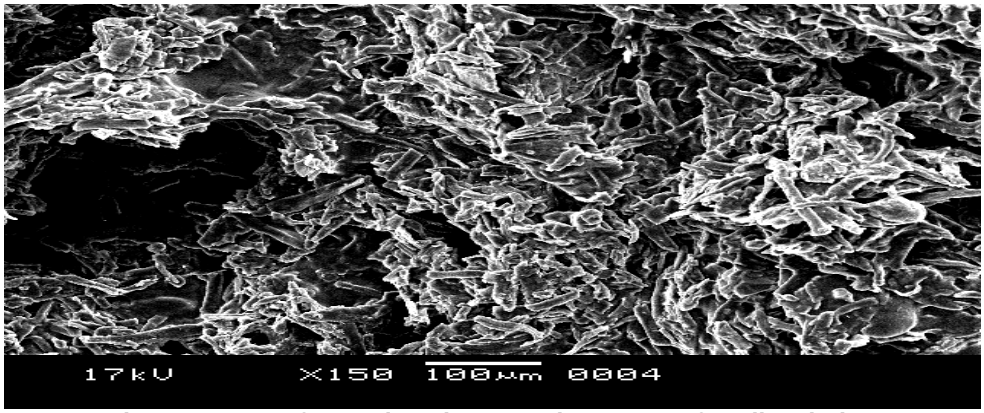

Fig. 12: Image of scanning electron microscopy after dissolution

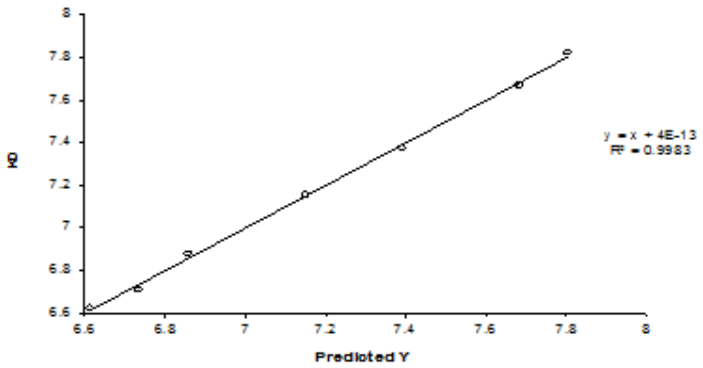

Fig. 13: Correlation between actual and predicted value of K_0

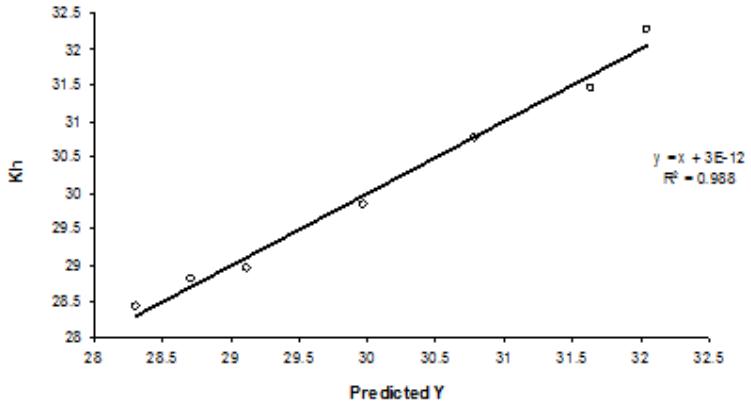

Fig. 14: Correlation between actual and predicted value of K_h

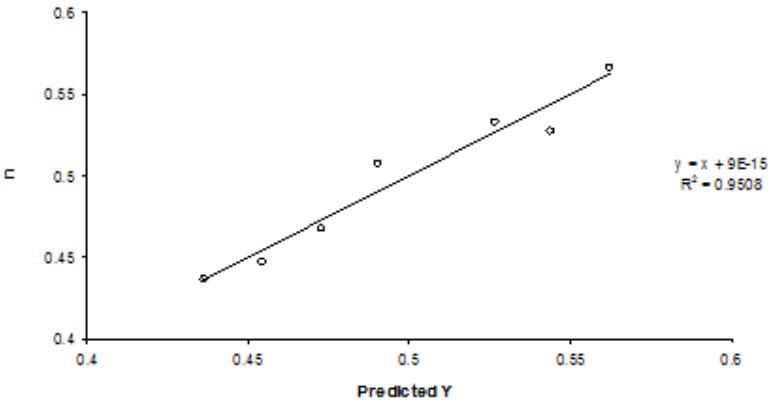

Fig. 15: Correlation between actual and predicted value of n

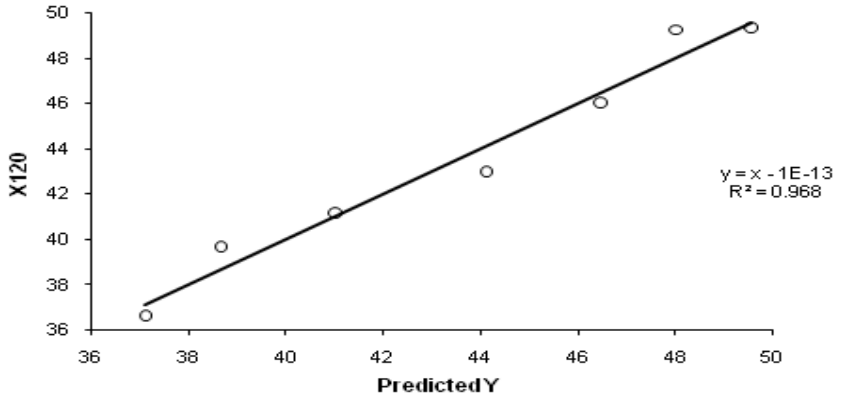

Fig. 16: Correlation between actual and predicted value of X_{120}

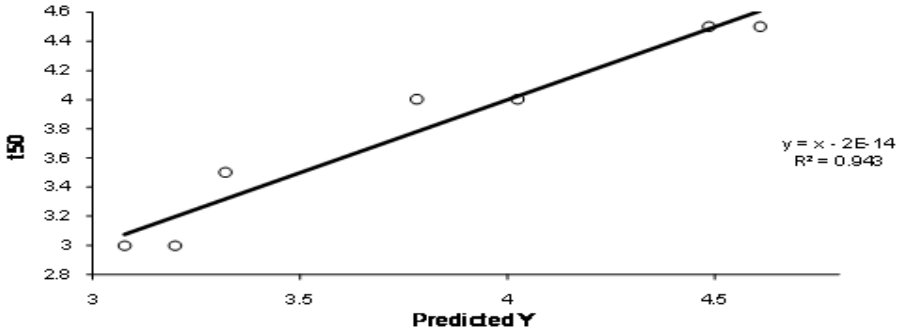

Fig. 17: Correlation between actual and predicted value of t_{50}

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