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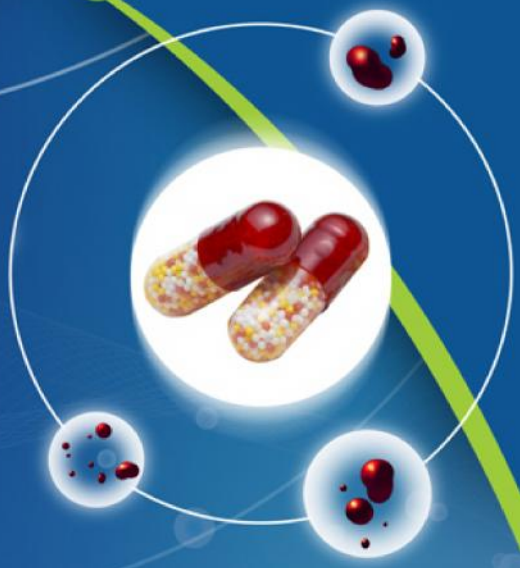

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Research Article

FORMULATION DEVELOPMENT AND OPTIMIZATION OF IMMEDIATE RELEASE LAYER FOR BILAYER GASTRORETENTIVE TABLET OF NIZATIDINE USING 3^2 FACTORIAL DESIGN MODEL

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ABSTRACT

The main objective of this study is to prepare and optimized the formula of Immediate Release layer for bilayer gastro retentive floating tablet of Nizatidine using 3^2 Factorial Design. Nizatidine having biological half life (1 to 2 hours), selected model drug as it is Competitive inhibition of histamine at H_2-receptors of the gastric parietal cells resulting in reduced gastric acid secretion, gastric volume and hydrogen ion concentration in the upper part of GIT hence it is suitable for gastro retentive system. In this study Immediate Release layer was prepared by superdisintegrant sodium starch glycolate, Crosspovidone and microcrystalline cellulose. The IR layer was characterized by initially Flow Property of blend and further characterized for Hardness, Friability, Disintegration time and drug content. Finalized the formula for IR layer on the basis of Friability and Disintegration time data study with design expert software 3^2 Model. Validation of Model has confirmed using linear correlation plots and residual plots.

Key words: *Nizatidine, Immediate Release, Factorial Design, Gastroretentive*

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly relief, and then maintain the desired drug concentration.[1] Most feasible approaches for achieving a prolonged and predictable drug delivery in the gastrointestinal tract which can control the gastric residence time and they are collectively called gastro retentive dosage forms. [2]

Optimization is "Choosing the best element from some set of available alternatives".

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It is the process of finding the best way of using the existing resources while taking in to the account of all the factors that influences decisions in any experiment**.** [3] Factorial designs are very frequently used response surface designs. A factorial experiment is one in which all levels of a given factor are combined with all levels of every other factor in the experiment. When we study two factors at three level $\mathbf{3^2}$ the total Number of run will be =09**.** [4]

EPERIMENTAL

Material and Methods

Drug Nizatidine and polymers Sodium starch glycolate, Crosspovidone, obtained from Dr. Reddy Lab Hyderabad as a gift sample and others chemicals used for present study are purchased from R. S. Chemicals Jaipur Rajasthan of Laboratory grade.

Drug Excipients Compatibility Studies: Excipients are integral components of almost all

pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to promote the consistent release, bioavailability of the drug and protect it from degradation.

The physicochemical compatibility between Drug and polymers used in the formulations was studied by using Fourier transform infrared (FTIR) spectroscopy and Differential scanning calorimeter (DSC).

IR Spectra of Drug and Excipients: The FTIR spectrogram of Nizatidine and Excipients were recorded using FTIR spectrophotometer by direct sample method and spectra were recorded in the wavelength region between 4000cm^{-1} to 400cm^{-1} and on the basis of comparison with spectra of pure drug confirmed the compatibility.

DSC of Drug and Excipients: In DSC analysis, the samples were weighed (5 mg), hermetically sealed in flat-bottom aluminum pans, and heated over a temperature range of 50 to 250ºC in an atmosphere of nitrogen (20 ml/min) at a constant increasing rate of 10ºC/min. The thermograms obtained for Drug and physical mixtures of drug with polymers were compared.

Prepration of Immediate Release layer of Tablet: Drug (Nizatidine), Sodium starch glycolate and Crosspovidone were sieved through # 30 sieve, and other Excipients were sieved through # 60 sieve prior to use. The amount of drug was kept constant in each formulation. All the materials were accurately weighed and blended, subsequently compressed on a manual single punch tablet compression machine into tablets using flat-faced, round punches 8 mm in diameter.

Pre compression characterization of Powder blend for IR layer

Angle of repose: The angle of repose of powder blends was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation**.** [5]

Bulk density and tapped density: Both Bulks density (BD) and tapped density (TD) was determined. A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at interval of one second. Tapping was continued until no further change in volume was noted. [5]

Compressibility Index: The flowability of powder can be evaluated by comparing the bulk density (ρo) and tapped density (ρt) of powder and the rate at which it packed down. The Compressibility Index of the powder blend was determined by Carr's compressibility index**.**

Hausner's ratio: The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hausner's ratio**.** [6]

Characterization and Evaluation of Immediate Release layer after compression

Appearance: Twenty tablets of each formulation were taken to check any discoloration or degradation of drug in the tablets by visual method. If any discoloration or black spots appears, it shows the degradation or decomposition of the drug in the tablet formulation**.** [7]

Hardness: The resistance of tablet to breakage under the condition of storage, transportation and handling before usage depends upon its hardness. The hardness of tablets of each batch was measured by Monsanto Hardness tester. Tablet hardness has been defined as the force required breaking a tablet in a diametric compression test. A tablet was placed between two anvils of hardness tester, force was applied to the anvils, and the crushing strength that causes the tablet to break was recorded in kg/cm^2**.** [8]

Friability: Tablets require certain amount of strength or hardness and resistance to withstand

mechanical shock of handling in manufacturing, packaging, and shipping. A pre-weighed sample (10 tablets) were placed in the friabilator, and operated for 100 revolutions, then again weighed the tablets. Percentage loss should not more than 0.5 to 1.0 % and the % friability was calculated using the formula**.** [9]

In-Vitro Disintegration Time: Tablets place in each of six tubes of disintegration apparatus. Suspend the assembly in 0.1 N HCl maintained at temperature of 37± 2^0C and operate the apparatus, simultaneously note the time taken to disintegrate by using stop watch. Ideally the IR Part of Tablet will completely disintegrate in few seconds**.** [10]

Uniformity of content: The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100 ml of 0.1N hydrochloric acid, followed by stirring for 30 minutes. The solution was filtered through a 0.45 µm membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at suitable wavelength maxima (λ_{max}) 325 nm for Nizatidine using 0.1 N hydrochloric acid as blank. [11]

Response surface analysis:

Response surface analysis is done by using Design Expert Software. The coefficient of the polynomial equation generated using MLRA for friability and Disintegration time of Immediate Release layer

$Y= \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1X_2 + \beta_4 X_1^2 + \beta_5 X_2^2$

Five coefficients (β_1 to β_5) were calculated representing β_0 as intercept, and β_1 to β_5 various quadratic and interaction terms. The 3D plot show the various three dimensional response surface plots for the studied response properties and the relationship between the different ratio of polymers on Response variables (friability and Disintegration time) of Immediate Release layer for gastro retentive Bilayer floating tablet of Nizatidine. [12-13]

Validation of Model: Five Check point formulations (three from overlay plot and two from grid and feasibility search) have been chosen for the purpose of validation. Subsequently studies carried out for various response variables. Validation will be confirmed using linear correlation plots, residual plots and magnitudinal comparison of observed versus predicted data. [14]

RESULTS AND DISCUSSION

The characterize peaks of pure drug Nizatidine remained unchanged in the IR spectra of Physical Mixture containing drug, polymers and other Ingredients (Figure- 1). IR analysis revealed that there was no known chemical interaction of drug with polymers and other ingredients.

The DSC of pure drug Nizatidine (Figure- 2) showed sharp endothermic peak at 132.05 ^{0}C corresponding to their melting point and physical mixture (Figure- 5.4) showed sharp endothermic peak at 131.86 ^{0}C representing drug. A slight decrease in the energy change of endotherm of physical mixture indicates a small reduction in crystallinity.

The flow property of IR blend show that they have good flow property as well as good compressibility characteristics and hardness and friability values are in proper range an disintegration time is around 45 seconds.

The physical parameters of the compressed IR layer were determined. The friability 0.63 to 0.70 was within limit and hardness of the formulation was found to be 3.27 to 3.81 kg/cm^2. The hardness was sufficient to prevent all chipping and breaking during transportation.

In Optimization study we observed following equations

Response-1 Disintegration Time

$$\mathbf{Y= 42.33 -2.83 X_1 – 4.5X_2 - 0.5 X_1 X_2 + 0.5 X_1^2 + 0.5 X_2^2}$$

Response-2 Friability

$$\mathbf{Y = 0.715 + 0.07 X_1 + 0.088 X_2 - 0.0025 X_1 X_2 -0.043 X_1^2 +0.011 X_2^2}$$

While locating the optimized formulation using overlay plots, the following criteria were taken into consideration

Friability < 0.7 and Disintegration time < 45 seconds

A region was marked in the overlay plot corresponding to optima and corresponding levels and responses predicted for optima in the current investigation came out to be identical.

All responses were fitted to linear, interaction and quadratic model using Design Expert software. Contor plot and 3D response curve for disintegration time and friability showed that combination of both polymer Sodium starch Glycolate (SSG) and Crospovidone (CP) increase the disintegration time and individually SSG are more effective while combination of both polymer reduce the friability as compare to individual effect. So with the help of Design Expert we selected the require quantity of both polymer to produce required effect.

The value of prob > F where found to be < 0.05 for all the responses again indicating that the model are significant and closeness of observed and predicted value of check point formulation also confirms the goodness of Model. On the basis of the above observation, finalize the formula of IR layer for further study. In validation study the high values of r^2, indicating excellent goodness of fit. The residual plots were also found to exhibit quite uniform and randomized scatter of the residual points, when plotted against the observed values of the response variables.

Table-1 Formulation of IR layer as per the experimental design [3^2]

Batch Code	N1	N2	N3	N4	N5	N6	N7	N8	N9
Nizatidine	75	75	75	75	75	75	75	75	75
SSG(X_1)	8	8	8	12	12	12	16	16	16
CP (X_2)	6	8	10	6	8	10	6	8	10
Lactose	46	44	42	42	40	38	38	36	34
Avicel	35	35	35	35	35	35	35	35	35
Magnesium Stearate	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10

All the quantities of Drug and excipients are given in mg per Tablet.

Table- 2 Flow Property of IR layer blend used for Gastro retentive Bilayer Tablet

Formulation Code	**Bulk Density g/cm^3**	**Tapped Density g/cm^3**	**Compressibility Index (%)**	**Hausner's Ratio**	**Angle of Repose(Degree)**
NI-1	0.645±.0112	0.862±.0125	15.45±.0084	1.280±.0024	28.43±.0124
NI-2	0.672±.0105	0.870±.0164	14.42±.0042	1.192±.0039	27.54±.00135
NI-3	0.694±.0141	0.882±.0148	14.61±.0024	1.178±.0088	25.73±.0145
NI-4	0.702±.0135	0.859±.0168	15.14±.00078	1.241±.0017	26.52±.00162
NI-5	0.684±.0125	0.884±.0178	15.72±.0089	1.236±.0097	28.84±.0098
NI-6	0.689±.0106	0.856±.0121	16.27±.0018	1.475±.0047	26.92±.0138
NI-7	0.715±.0175	0.889±.0119	15.02±.0089	1.354±.0028	27.79±.0175
NI-8	0.704±.0123	0.897±.0097	15.42±.0077	1.413±.0049	25.73±.0164
NI-9	0.731±.0117	0.901±.0105	16.08±.0068	1.395±.0037	25.38±.0094

Table-3 Physical Parameters of the IR layer of Nizatidine

Formulation	Hardness kg/cm^2	Friability	Disintegration Time (Seconds)	% Drug Content
NI-1	3.48±0.0025	0.63	45	99.12±.0012
NI-2	3.31±0.0039	0.64	43	99.35±.0018
NI-3	3.81±0.0037	0.66	41	99.24±.0035
NI-4	3.27±0.0068	0.67	40	99.41±.0018
NI-5	3.47±0.0069	0.67	38	99.46±.0028
NI-6	3.43±0.0075	0.68	37	99.57±.0039
NI-7	3.46±0.0087	0.64	39	99.42±.0017
NI-8	3.67±0.0039	0.67	36	99.19±.0028
NI-9	3.29±0.0078	0.70	34	99.11±.0057

Table-4 Validation Batches of IR Layer according to Overlay plot

Check Point Formulation	X1	X2	Friability (%)		Floating lag Time (Second)	
			Predicted	Observed	Predicted	Observed
V1	-0.91	0.63	0.60	0.65	36.53	38.50
V2	-0.59	-0.32	0.60	0.62	36.77	37.00
V3	-0.33	-0.83	0.59	0.58	36.49	39.00
V4	-0.81	0.72	0.61	0.60	36.42	38.15
V5	-0.62	-0.28	0.62	0.61	36.15	38.25

Table-5 Final Formula of IR layer of Drug Nizatidine

Name of Ingredient	Quantity in mg per Tablet
Nizatidine	75
SSG(X_1)	10
CP (X_2)	8
Lactose	40
Avicel	38
Magnesium Stearate	9.5
Talc	9.5

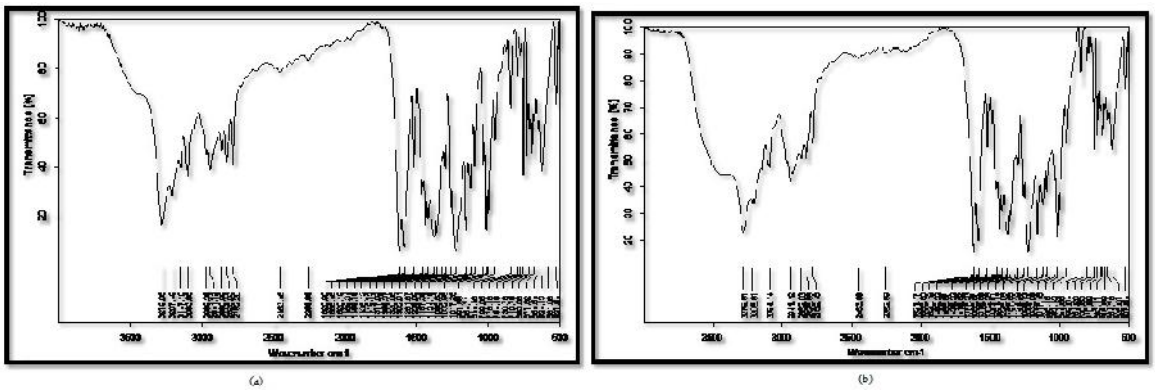


Fig.-1 (a) IR of pure drug Nizatidine (b) IR of drug Nizatidine and excipients

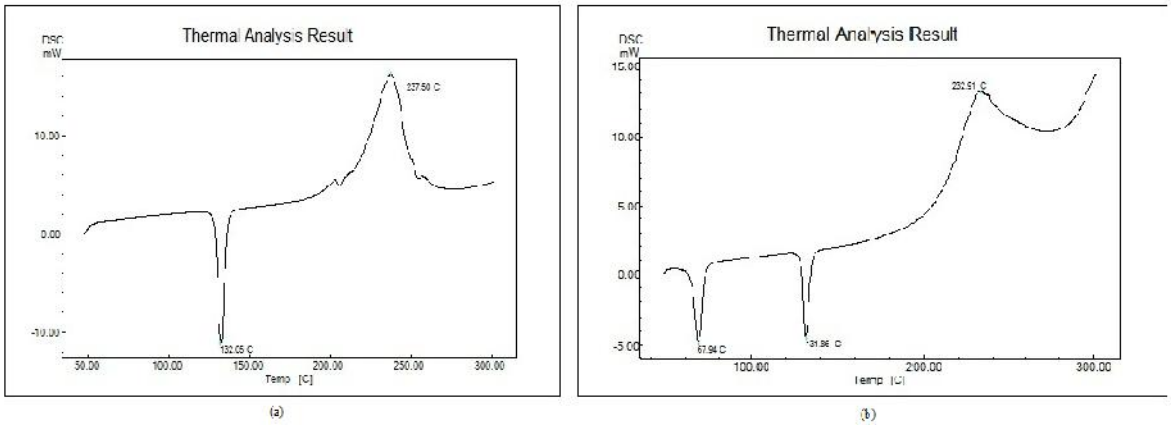
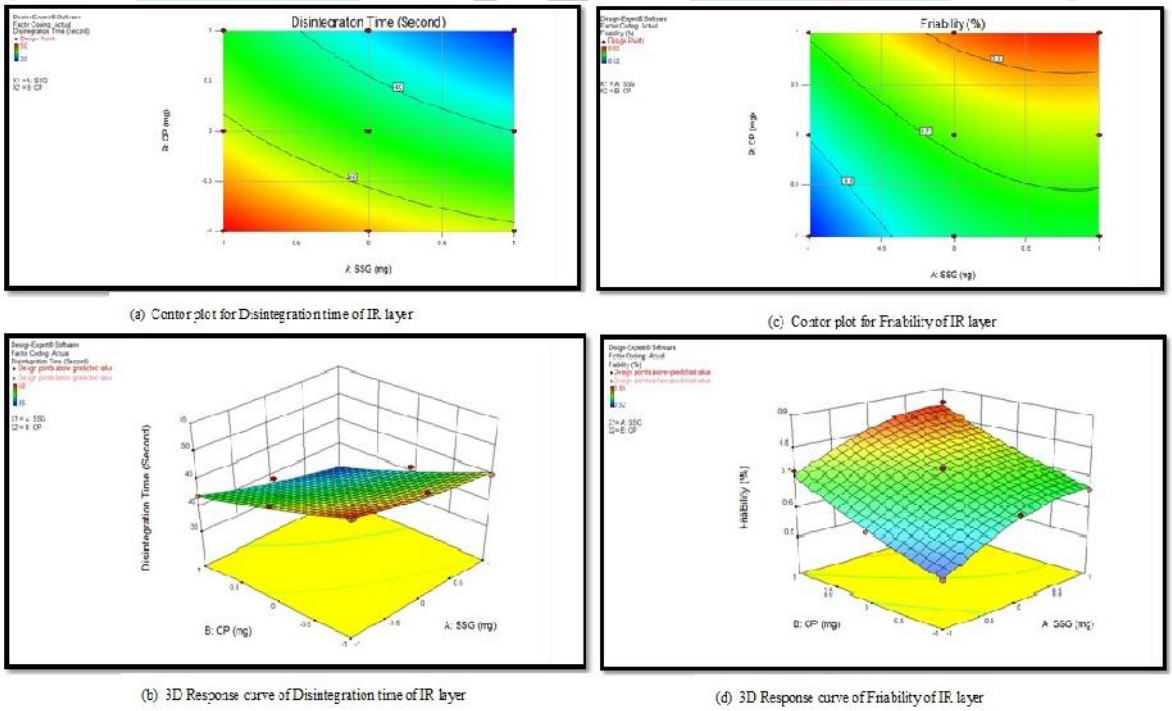


Fig.-2 (a) Thermogram of pure drug Nizatidine (b) Thermogram of drug Nizatidine and excipients



(a) Contor plot for Disintegration time of IR layer

(c) Contor plot for Friability of IR layer

(b) 3D Response curve of Disintegration time of IR layer

(d) 3D Response curve of Friability of IR layer

Fig.-3 Contor plot and 3D Response curve of Response variables

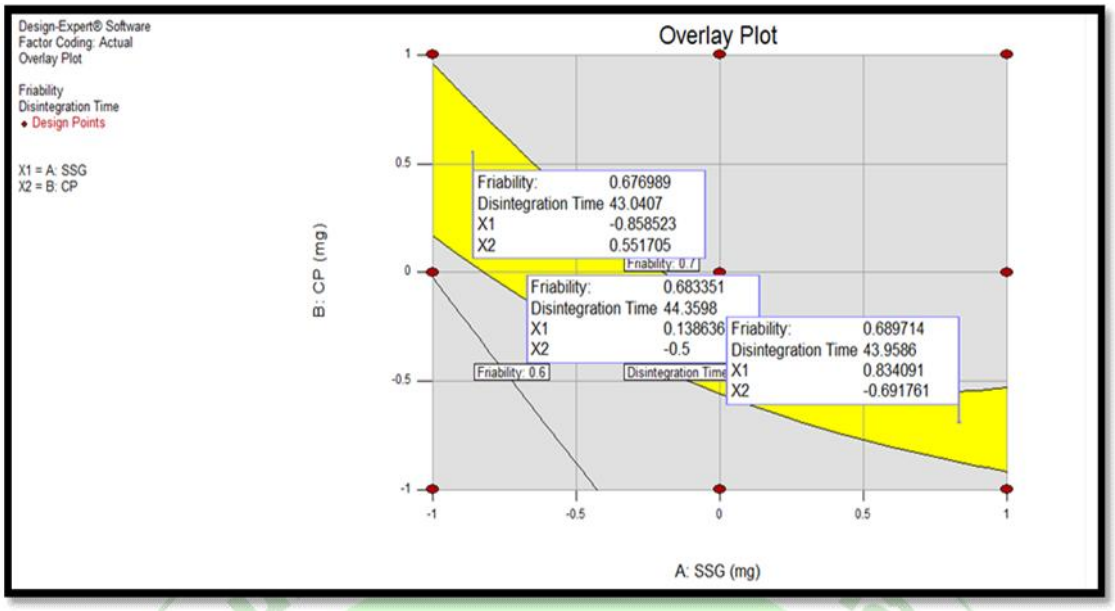
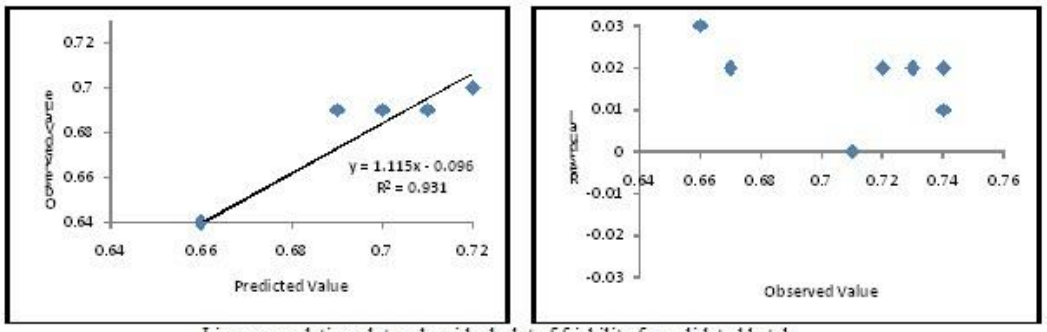
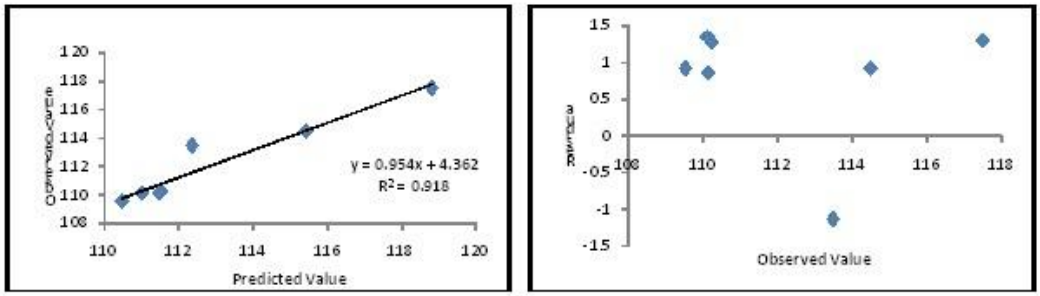


Fig. -4 Overlay plot for disintegration time and friability of IR layer



Linear correlation plot and residual plot of friability for validated batch



Linear correlation plot and residual plot of Floating lag Time for validated batch

Fig.-5 Validation of Model

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