Journal of **N**onlinear **A**nalysis and **O**ptimization
Vol. 12, No. 2, (2021),
ISSN : **1906-9685**

DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF HYDROCHLORTHIAZIDE

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ABSTRACT

The aim is to formulate various immediate release tablet formulations of Hydrochlorothiazide using different superdisintegrants (Indion 414, Crospovidone), MCC and Magnesium Stearate by Direct Compression Method. The pre-formulation study was carried out in order to establish, identity the compatibility study between drug and excipients/polymers by FTIR spectroscopy, melting points, solubility. Immediate release Hydrochlorothiazide was carried out by 2^3 factorial design varying concentration of super disintegrants. The tablet was prepared separately using 8 station tablet compression machine and evaluated for their performance. The results shown that the drug is compatible without any significant changes in chemical nature of drug. The drug release is zero order release pattern (r^2= 0.996) and A8 formulation containing superdisintegrant i.e. 10 % Indion 414 and 5 % Crospovidone showed rapid disintegration (1.43min) of immediate release tablet, and *in- vitro* drug release shows 99.8% drug release within 1 hr.

Key words: Hydrochlorothiazide, Immediate Release Tablets, Superdisintegrants, design of experiment.

INTRODUCTION

Oral route is one of the convenient and efficient routes of drug administration. It is effective to achieve the local and systemic effect of drug. Conventional dosage form is usually in the form of two or three daily doses, which can show the large fluctuations in the drug plasma concentration and cause side effects on the human body. These problems overcome by to develop innovative methods for drug delivery via the oral route. An immediate release dosage form allows a manufacturer to extend market exclusivity, while offering patients a convenient dosage form or dosage regimen. Immediate release tablets are those tablets which are designed to disintegrate and release their medication with no special rate, such as no special coatings and other techniques.

Immediate release and fast dispersing drug delivery system may offer a solution to these problems. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities [1].

Hydrochlorothiazide is a diuretic under class thiazide diuretics. It is act by inhibiting the water reabsorption in the nephron by inhibiting the sodium chloride symporter in the distal convoluted tubule which is responsible for 5% total sodium reabsorption. Once sodium entered in cell via sodium potassium ATPase, causing increasing the osmolarity of interstitum, thereby establishing osmotic gradients for water reabsorption. HCTZ effectively reduce the osmotic gradient and water reabsorption throughout nephron [2]. When it is given orally the Bioavailability of the drug is 70% and peak plasma concentrations and reached 1-2 hours. The drug is widely distributed, reaching concentrations in the CSF that are 50% of those in the plasma and excreted by the kidneys partly by glomerluar filtration and partly by tubular secretion. The plan of present research is to develop patient compliance and cost effective Hydrochlorothiazide immediate release tablets by wet granulation method. Thus eight different formulations were designed to obtain best optimized product by comparing with innovator.

MATERIAL AND METHODS

Materials:

Hydrochlorothiazide (HTZ) was received from Medo Pharma, Malur (Karnataka). Microcrystalline cellulose (MCC) (PH 102) was received a gift sample from Signet Chemicals Pvt. Ltd, India, Crospovidone (CP) from Gangawal Chemicals, Mumbai, Indion 414 from Ion Exchange, Mumbai. Magnesium stearate was obtained from S.D. Fine Chem Ltd. Mumbai, Talc was obtained from Sanjay biological museum, Amritsar, India. Colloidal Silicon Dioxide from Evonik Degussa, Mumbai, India As the method of preparation is direct compression technique; hence no specified reagent was required.[3, 4]

Method:

Preparation of Immediate Release Layer of Hydrochlorothiazide:

The immediate release tablets of Hydrochlorothiazide were formulated utilizing superdisintegrants crospovidone and Indion 414 at varying concentrations of 10%, 20%, 30% and combination of superdisintegrants (A4, A8) respectively. Using a scale and a sieve, we were able to measure out exactly how much medicine, crospovidone/Indion 414, microcrystalline cellulose, and lake sunset yellow we needed. We crushed and mortared the powders together for a whole ten minutes. Greasy with magnesium stearate and colloidal silicon dioxide, the powder was mixed in a mortar

and pestle for three minutes. The powder mixture was manually fed into 4 mm flat-faced punches on a 10-station rotating tablet machine (Rimek Mini Press-I), which then underwent direct compression to create tablets with a final weight of 50 mg.[1][6]

Table - 1: Formulation Design of Immediate Release Tablets of Hydrochlorothiazide

SL. No	Ingredients (mg)	A1	A2	A3	A4	A5	A6	A7	A8
1	Hydrochlorothiazide	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
2	Indion414	-	-	-	5	5	10	15	10
3	Crospovidone	5	10	15	10	-	-	-	5
4	MCC(PH102)	31	26	21	21	31	26	21	21
5	Magnesium stearate	1	1	1	1	1	1	1	1
6	Colloidal silicon dioxide	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
7	Lake sunset yellow	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Total Tablet weight		50	50	50	50	50	50	50	50

Experimental Design: (21)

A 2^3full factorial design was selected for this experiment. It consists of 8 full factorial design points. This design generally involved Independent variable X and Dependent variable Y. Indion 414 (X1) and Crosspovidone (X2) variable was selected as factor the levels of two factors were selected on the basis of preliminary studies carried out before implementing the experimental design.

Independent variable	Dependent variable
X1: Indion 414	Y1: Hardness
X2: Crospovidone	Y2: Disintegration Time

Table -2: Factorial combination as per Experimental Design for Hydrochlorothiazide

Batches	**Coded value**	
	X1	**X2**
A1	--	-1
A2	--	0
A3	--	1
A 4	-1	0
A 5	-1	--
A 6	0	--
A 7	1	--
A 8	1	0

Table -3: Translation of Experimental Design of actual value Hydrochlorothiazide

Coded value	Actual value	
	X1	X2
-1	5	5
0	10	10
1	15	15

Pre-formulation study:

Compatibility study:

FTIR Spectroscopy The drug-excipients interaction was studied by FTIR spectroscopy by KBr press pellet method. Sample for analysis and KBr were taken in 1:100 ratio and ground in motor for even distribution of sample in KBr. The pellet was prepared in the form of disk by applying pressure of 100 PSI for 1min using hydraulic press and subjected to FTIR. The pellet Scanned at 400 to 4000cm^{-1} IR range. Pre-compression evaluation [8][13][14]

Differential Scanning Colorimetry (DSC) study:

The study involves the evaluation of Pure Hydrochlorothiazide, physical mixtures of the drug with various excipients (as detailed in Table 6). Differential scanning colorimetric analysis was then performed on the samples. The differential scanning colorimetric analysis of the pure drug and excipients was conducted using a Shimadzu DSC 60 thermal analyzer. The analysis was performed at heating flow rates of 10^0C per minute, ranging from 50 - 300^0C under static air, using an aluminum pan. The onset peak and end set peaks were recorded for individual drugs and combinations of drugs and excipients.

Identification test by U.V Spectrophotometer:

The *In-vitro* dissolution study for the Hydrochlorothiazide immediate release tablets were carried out in USP type-II dissolution test apparatus (Electrolab TDT-08L) (Paddle type) using 900 ml of 0.1 N HCL at 50 rpm and temperature 37 ± 0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed by measuring the absorbance at 271.6 nm using UV Visible spectrophotometer and calculate the percentage drug release [7].

Melting Point Determination:

Melting point of drug sample was determined by using melting point apparatus. Small amount of drug sample was taken transferred in a thin walled capillary tube. The tube was approximately 10-12 cm in length with 1mm in diameter and closed at one end. The capillary which contain sample was placed in melting point apparatus and heated and when drug sample was melted the melting point of sample powder was noted [9].

Determination of solubility:

Qualitative Solubility:

Qualitative solubility analysis of drugs were done by dissolving 5 mg of drug in 5 ml different solvents such as distilled water, HCl (0.1N), phosphate buffer (pH 6.8),Phosphate buffer(pH 6.8), ethanol, methanol, acetone and chloroform were used to determine the solubility of drug.

Micromeritics Properties of Granules:

Bulk Density:

Bulk density was determined by placing the granules into measuring cylinder and total volume was measured and also total powder weight was measured. The bulk density was calculated by using formula.

Bulk density (BD) = weight of powder /bulk volume.

Tapped Density:

Tapped density of granules was determined by tapping the cylinder by using tapped density apparatus. Tapped the cylinder up to 100 times in tapped density apparatus and then measure the tapped volume and calculate the tapped density by using formula.

Tapped Density (TD) = weight of powder /tapped volume.

Hausner's Ratio:

Hausner's ratio is the number that is correlated to the flowability of a powder or granules. it is calculated using formula,

Hausner's ratio = tapped density / bulk density.

Compressibility Index:

Compressibility index was calculated by formula,

Carr's index (%) = Tapped density – bulk density/ tapped density* 100

Angle of Repose:

The angle of repose of granules was determined by fix funnel method. The blend was poured through funnel separately until apex of pile so formed just touch the tip of the funnel. The angle of repose was calculated by using formula

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

h is height of pile; r is radius of pile.

Drug Content Uniformity:

10 tablets were taken and crushed into mortar to form powder. From that, sample equivalent to 25 mg of drug was taken and transferred to 100ml volumetric flask. 0.1 N HCl (20ml) was added dissolve the drug and volume was made up to mark with 0.1N HCl, this was

filtered. From the filtrate 1ml was taken and diluted with 0.1N HCl and absorbance of this solution was measured by using U.V-spectrophotometer at 271.6 nm (SHIMADZU; U.V1800).

Disintegration Test:

Six tablets of HCTZ were selected randomly from each batch for the disintegration test. Disintegration test was performed in simulated gastric fluid 0.1 N HCl using disintegration testers. Disintegration time (DT) was measured for immediate release layer.

***In-vitro* Dissolution Study:**

The *In-vitro* dissolution study for the Hydrochlorothiazide immediate release tablets were carried out in USP type-II dissolution test apparatus (Electrolab TDT-08L) (Paddle type) using 900 ml of 0.1 N HCL at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed by measuring the absorbance at 271.6 nm using UV Visible spectrophotometer and calculate the percentage drug release.

RESULT AND DISCUSSION

Pre-formulation Study [22][23][24]

The UV absorption of 2-10 µg/ ml in water found 271.6nm at 200-400 nm rang exhibit maxima of hydrochlorothiazide. The results are tabulated in table-4 and show all the results are within limits.

Solubility: Solubility of hydrochlorothiazide was found in freely soluble in acetone, sparingly soluble in methanol, slightly soluble in Distilled water, Soluble in ethanol. The results are tabulated in table-4 and show all the results are within limits.

Melting Point: Melting point was found to be 268^0C. The results are tabulated in table-4 and show all the results are within limits.

Compatibility study: Fig – 1 & Fig – 2 shows the compatibility study of Hydrochlorothiazide. FTIR and DSC study shows that the drug and excipients are compatible with each other.

Table - 4: Preformulation study of Hydrochlorothiazide

Sr. No	Parameters	Observation
1	Identification by U.V visible spectrophotometer.	271.6 nm (λ max)
2	Melting Point	268^0C
3	Solubility	Freely soluble in acetone Sparingly soluble in methanol Slightly soluble in Distilled water Soluble in ethanol.

4	Compatibility study (FTIR)	Compatible

Pre-compression Evaluation of Granules:

Properties of granules such as Bulk Density, Tapped Density, Compressibility Index, Hausner's Ratio, angle of repose were studied and overall result include in table no 5. The compressibility index of the formulation 22.73 to 30.85 % indicating a good flow properties of powder which were further confirmed by determining the angle of repose, it is in the range of 23.8 to 27.02 which shows good flow properties.

Table -5: Pre-Compression Evaluation of Granules

Parameter	Batches							
	A1	A2	A3	A4	A5	A6	A7	A8
Bulk density	0.404	0.393	0.43	0.399	0.4171	0.384	0.423	0.41
Tapped density	0.554	0.576	0.541	0.553	0.571	0.527	0.576	0.565
Carr's index	28.24	27.58	25.28	24.71	26.96	22.73	24.26	30.85
Hausner's ratio	1.59	1.38	1.33	1.32	1.36	1.29	1.32	1.3
Angle of repose	25.00	23.8	25.2	24.45	25.78	23.67	27.02	24.57

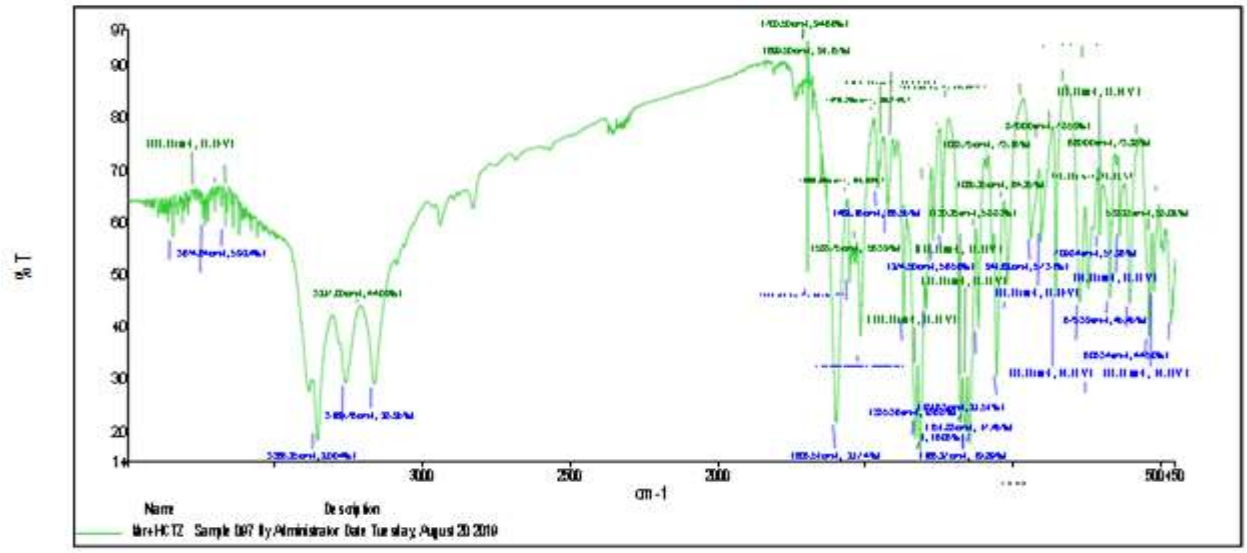

Fig – 1: FTIR Spectrum of Hydrochlorothiazide

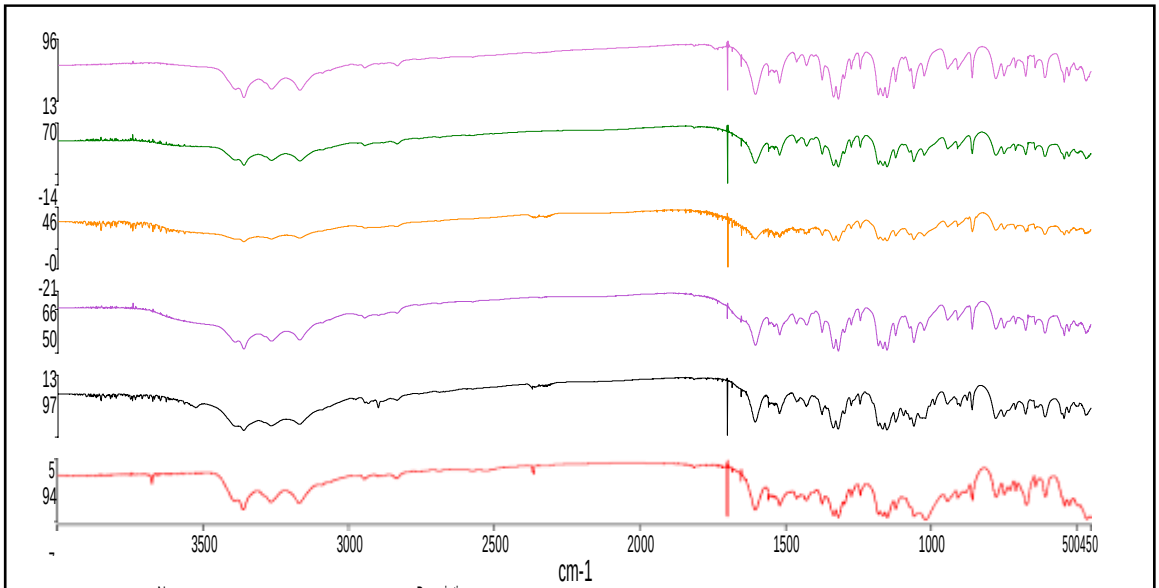

Fig – 2: Compatibility Study by IR Spectra of HCTZ with Physical Mixture

Formulation and Development [21]

Formulation development of immediate release tablet of Hydrochlorothiazide by full factorial design (2^3) was done by using DESING-EXPERT 12.32. Bits (STATE-EASE) free trial version software. The 2^3 full factorial designs were used in the study. In this design, three factor each in two levels (table -6) were evaluated experimentally by all 8 possible combination. Indion 414 (X1) and Crosspovidone (X2) were selected as independent variable. Hardness and Disintegration time were selected as independent variable.

The Statistical model: $Y_i = b_0 + b_1X_1 + b_2 X_2 + b_{12}X_1X_2\ b_1X_{12} + b_2X_{22}$

Where Y_i is the level of response variable; b is regression coefficient; X_1& X_2 stand for main effect; X_1X_2 is interaction between the main effects; and X_{12} and X_{22} are quadratic term of the independent variables.

Table - 6: Variable and their levels used in formulation Immediate Release Tablet of Hydrochlorothiazide.

Coded value	Actual value (Independent variable)	
	(X1) Indion 414	(X2) Crospovidone
-1	5	5
0	10	10
1	15	15

Post Compression Parameter of Immediate Release Tablet of Hydrochlorothiazide:[22][23][24]

The tablet of different formulation (A1 to A8) were subjected to various post compression evaluation parameter such as thickness, hardness, Weight variation, friability, Disintegration time, drug content, and *In-vitro* dissolution study.

Table-7: Evaluation of A1 to A8 tablet formulation of immediate release tablet of Hydrochlorothiazide

Formulation	Evaluation Parameters

Code	Thickness (mm)	Hardness (Kg/Cm^2)	Friability	Avg. Weight Variation (mg)	Drug Content (%)	Disintegration Time (Sec)
A1	2.4	3.1	0.34	49.5	99.3	25.1
A2	2.2	3.3	0.31	49.1	98.8	19.5
A3	2.6	3.5	0.35	49.8	98.4	14.6
A4	2.4	3.9	0.49	50.1	99.9	11.9
A5	2.7	3.6	0.36	50.0	98.2	22.2
A6	2.1	3.4	0.35	49.4	99.1	19.4
A7	2.6	3.7	0.35	49.6	98.9	14.5
A8	2.4	3.8	0.42	51.2	99.2	10.9

***In-Vitro* Dissolution Test:**

The dissolution media used was 0.1N HCl prepared and used. The comparative dissolution rate profiles generated for the Hydrochlorothiazide following the testing of the IR Layer tablets using USP apparatus 2 are shown in table-8. The in-vitro release of immediate release tablet A8 batch shows best result i.e. 99.8% drug release at 60 min.

Table- 8: *In-vitro* Drug Release of Immediate Release Tablet of Hydrochlorothiazide.

Time (min)	A1	A2	A3	A4	A5	A6	A7	A8
5	15.37	16.98	13.2	19.89	20.21	19.58	18.12	20
10	29.01	31.05	29.23	38.29	32.83	36.34	31.2	34.58
20	41	43.82	38.62	49.2	47.03	50	49.78	51.29
30	54.72	56.92	49.93	56.78	58.9	62.7	58.9	62.7
40	63.13	67.1	66.05	68	69.42	71.62	67.89	71.1
50	76.31	78.07	75	79.09	78.17	82.5	78.12	80.51
60	85.34	89.22	83.45	98.88	89.93	91.28	95.67	99.87

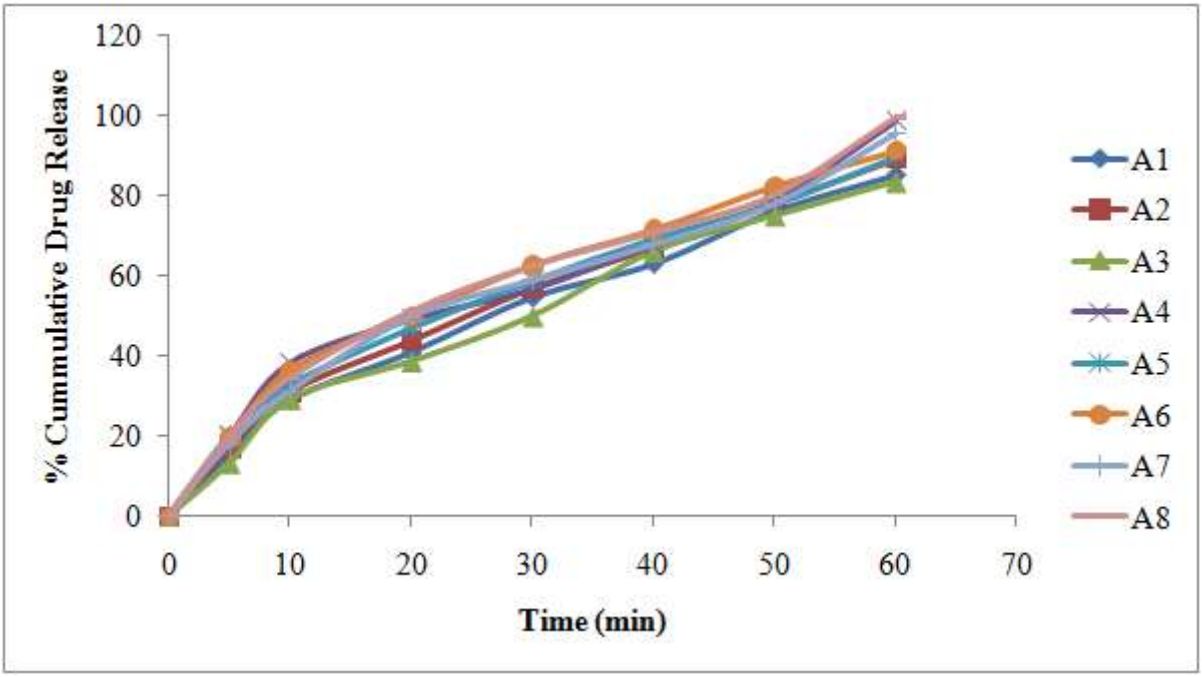

Fig-3: *In-vitro* Drug Release of Immediate Release Tablet HCTZ

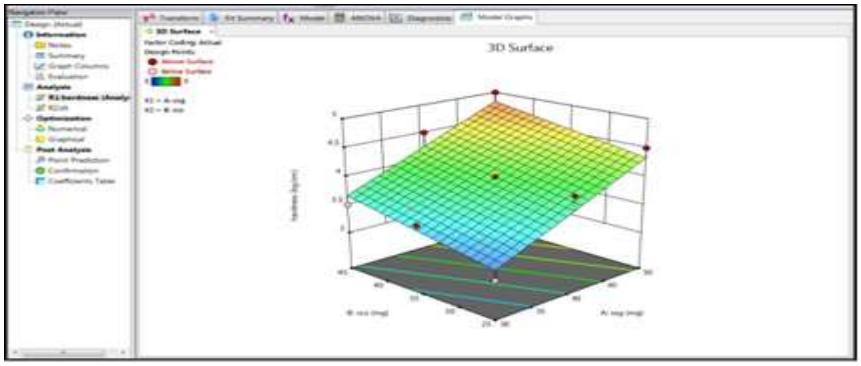

Fig – 4: Response Surface Plot Hardness of Immediate Release Tablet

Fig – 4 shows positive coefficients of X1 and X2 indicating, increasing the concentration of superdisintegrant Indion 414 and Crospovidone decreased the hardness which is essential for Immediate Release of drug.

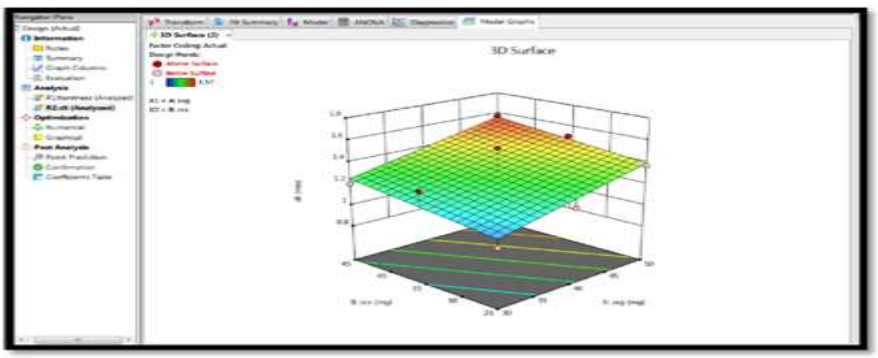

Fig -5: Response Surface Plot Disintegration Time of Immediate Release Tablet

Fig – 5 shows positive coefficients of X1 and X2 indicating, increasing the concentration of

superdisintegrant Indion 414 and Crospovidone decreased the disintegration time which is essential for Immediate Release of drug.

CONCLUSION:

The prepared tablet indicate satisfactory results for various evaluation parameter such as hardness, thickness, weight uniformity, friability, drug content, in-vitro dissolution study. All preformulation parameters study such as melting point, solubility, Drug Authentication by UV spectroscopy, FTIR spectroscopy and compatibility study was conducted and their results show satisfactory limits. The post compression parameter suggested that Hardness, Friability, Weight variation, were in acceptable limit. The drug content, *In-vitro* drug release of immediate release tablet carried in 0.1 N HCl up to 1 hr and its A8 batch shows better drug release.

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