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ORIGINAL ARTICLE **OPEN ACCESS**

Design, Formulation and Evaluation of Immediate Release Tablets Of Hydrochlorthiazide

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ABSTRACT
The aim is to formulate various formulations of immediate release tablet of Hydrochlorothiazide using different Superdisintegrants (Sodium Starch Glycolate, Croscarmellose, Crospovidone), Povidone K-30 and Magnesium stearate by wet granulation 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, the result shown that the drug compatible to excipients without any significant changes in chemical nature of drug. Immediate release Hydrochlorothiazide was carried out by 3^2 factorial design varying concentration of Polymers and super disintegrants. The tablet was prepared separately using 8 station tablet compression machine and evaluated for their performance. The drug release zero order release pattern (r2= 0.996) and H6 formulation containing super disintegrant i.e. 33.3% sodium starch glycolate and 23.3 % cross carmellose sodium shows rapid disintegration (1.43min) of immediate release tablet, and in vitro drug release shows 91.28% drug release within 1 hr with Hixson drug release pattern (r2 = 0.994).
Key words: Hydrochlorothiazide, immediate release tablets, superdisintegrants, design of experiment.

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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 usuallyin 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 is the gifted sample from (Flamingo pharmaceutical). Sodium Starch Glycolate, Croscarmellose, Crospovidone, Pvp K-30, magnesium stearate, Lactose and talc parches from (Thermosil fine chem.) [3, 4].

Method:

Formulation of Hydrochlorothiazide core tablet:

Core tablet of Hydrochlorothiazide were prepared by wet granulation technique with different concentration of excipients. Drug and other excipients is passing though sieve no 40# without lubricants to obtain a powder mixture. PVP K30 was dissolved in water and adds this solution into it to a mixture of drug and excipients to produced wet granules. Then the granules were dried at 50^0C for 30 min in oven. The dried granules were passed through sieve no 22 # to form uniform size granules. Then lubricants were passed through 40 # sieve and mixed with dried granules. Finally lubricated granules compressed in to tablet compression machine to obtained core tablet. [1][6]

Formulation Table:

Table 1: Formulation Table of the Immediate release tablet of Hydrochlorothiazide.

Ingredients	H1	H2	H3	H4	H5	H6	H7	H8	H9
HCTZ	25	25	25	25	25	25	25	25	25
SSG	30	40	50	30	40	50	30	40	50
CCS	25	25	25	35	35	35	45	45	45
PVPk30	5	5	5	5	5	5	5	5	5
Lactose	60	50	40	50	40	30	40	30	20
Talc	3	3	3	3	3	3	3	3	3
Mg stearate	2	2	2	2	2	2	2	2	2
Total (Mg)	150	150	150	150	150	150	150	150	150

Experimental design: [21]

A 3^2 full factorial design was selected for this experiment. It consists of 9 full factorial design points. This design generally involved Independent variable X and Dependent variable Y.

Sodium starch glycolate (X_1) and Cross carmellose sodium (X_2) 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: Sodium starch glycolate	Y1: hardness
X2: cross carmellose sodium	Y2: disintegration time

Table no.2: Factorial combination as per experimental design for Hydrochlorothiazide

Batches	Coded value	
	X1	X2
H1	-1	-1
H2	0	-1
H3	1	-1
H4	-1	0
H5	0	0
H6	1	0
H7	-1	1
H8	0	1
H9	1	1

Table no 3: Translation of experimental design of actual value Hydrochlorothiazide

Coded value	Actual value	
	X1	X2
-1	30	25
0	40	35
1	50	45

Pre-formulation study:

Identification test by U.V vis. 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].

Identification test by FTIR spectroscopy:

FTIR study of drug sample and identification studies was performed by potassium bromide (KBr) dispersion method (Perkin Elmer). Samples were prepared with KBr pellets (1 mg sample in 100 mg KBr) with a hydrostatic force of 100 PSI pressure for 1 minute. The scanning range was 400 to 4000 cm-1 [8].

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:

a. Qualitative Solubility Qualitative solubility analysis of drugs were done bydissolving 5 mg of drug in 5 ml differentsolvents such as distilled water, HCl (0.1N), phosphate buffer (pH 6.8),Phosphate buffer(pH 6.8), ethanol, methanol, acetone and chloroformwere used to determine the solubility of drug.

Compatibility study:

b. 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]

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 morter 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 filterate 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:**

For immediate release tablet

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 [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.

Solubility: solubility of hydrochlorothiazide was found in freely soluble in acetone, sparingly soluble in methanol, slightly soluble in Distilled water, Soluble in ethanol.

Melting point: melting point was found to be 267^{0}C

Compatibility study: compatibility study of Hydrochlorothiazide was carried out by using FTIR the drug and excipients are compatible with each other.

Table no. 4: Preformulation study of Hydrochlorothiazide

Sr.No	Parameters	Observation
1	Identification by U.V visible spectrophotometer.	271.6 nm (ʎ max)
2	Melting Point	267^{0}C
3	Solubility	Freely soluble in acetone Sparingly soluble in methanol Slightly soluble in Distilled water Soluble in ethanol.
4	Compatibility study (FTIR)	Compatible

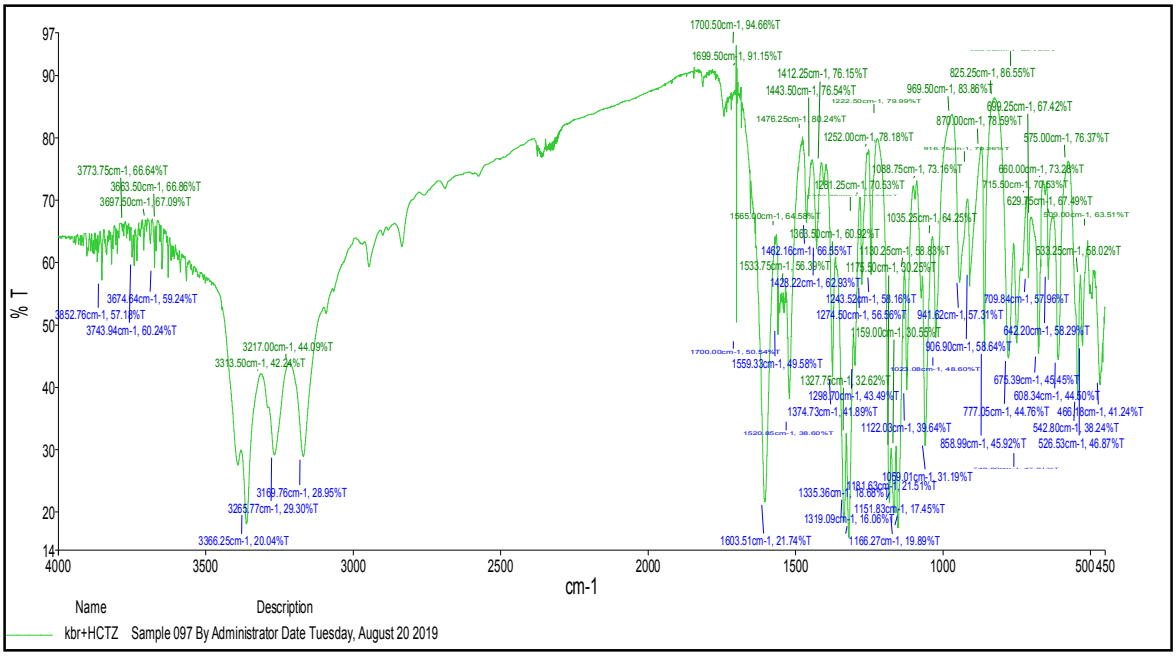

Fig 1 FTIR spectrum of Hydrochlorothiazide

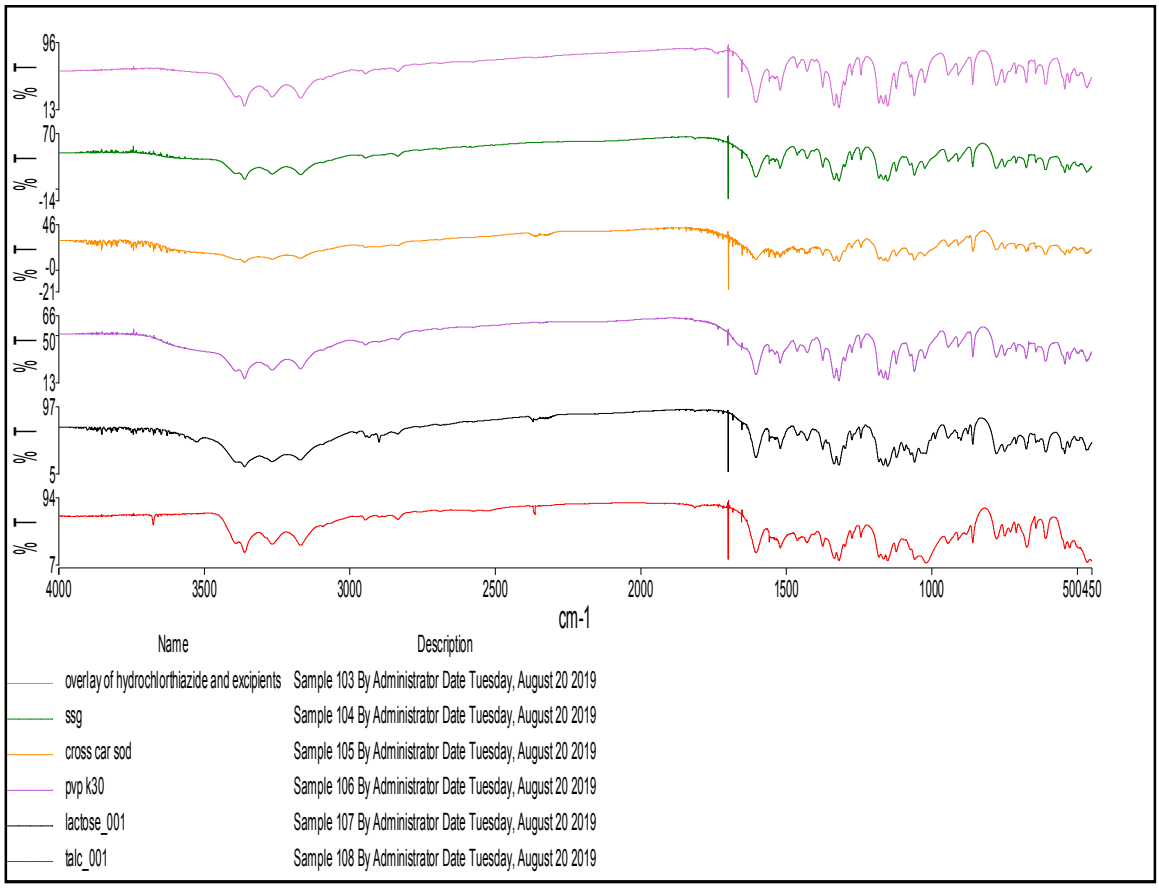

Fig. 2 Compatibility study by IR spectra of HCTZ+SSG+Cross car. Sod. + PVP k30 + lactose + talc.

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 15 to 17% Indicating a good flow properties of powder which were further confirmed by determining the angle of repose, it is in the range of 11^0 to 15^0 which shows good flow properties.

Table 5: pre-compression evaluation of granules

	Batches								
Parameter	**H1**	**H2**	**H3**	**H4**	**H5**	**H6**	**H7**	**H8**	**H9**
Bulk density	0.4015	0.3893	0.43	0.399	0.4171	0.3884	0.4223	0.41	0.3797
Tapped density	0.5564	0.5376	0.5741	0.53	0.571	0.5027	0.5576	0.5365	0.5
Carr's index	28.16	27.58	25.28	24.71	26.96	22.73	24.26	30.85	31.68
Hausner's ratio	1.38	1.38	1.33	1.32	1.36	1.29	1.32	1.3	1.31
Angle of repose	25.56	23.8	25.2	24.45	25.78	23.67	27.02	24.57	22.81

Formulation and Development [21]

Formulation development of immediate release tablet of Hydrochlorothiazide by full factorial design (3^2)

DESING-EXPERT 12.32. Bits. (STATE-EASE) Free trial version software was used for formulation development. The 3^2 full factorial designs were used in the study. In this design, two factor each in three levels (table no 9.9) were evaluated experimental trials were performed in all 9 possible combination. Sodium starch glycolate (X1) and Cross carmellose sodium (X2) were selected as independent variable. Hardness and Disintegration time were selected as independent variable.

The Statistical model:

$$Y_i = b_0 + b_1X_1 + b_2 X_2 + b_{12}X_1X_2\ b_1X_1^2 + b_2X_2^2$$

Where Yi 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_1^2 and X_2^2 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) SSG	(X2) CCS
-1	30	25
0	40	35
1	50	45

Post compression evaluation (Tablet):

Post compression parameter of immediate release tablet of Hydrochlorothiazide:[22][23][24]

The tablet of different formulation (H1 to H9) were subjected in various evaluation parameter such as thickness, hardness, Weight variation, friability, Disintegration time, drug content, and *In-vitro* dissolution study.

Table 7 : Evaluation of H1 to H9 tablet formulation of immediate release tablet of Hydrochlorothiazide

Batches	Thickness	wt variation	Hardness	DT	friability	drug content	% release
H1	2	148.6±2.61	3	1	0.754	89.21	85.34
H2	2	150.05±2.57	4	1.15	0.547	91.34	89.22
H3	2	150.1±3.3	4.5	1.37	0.532	87.6	83.45
H4	2	150.7±2.72	3.5	1.3	0.768	93.56	90.23
H5	2	150.3±2.41	4	1.5	0.592	92.34	89.93
H6	**2**	149.9±2.7	**3.5**	**1.3**	**0.431**	**94.1**	**91.28**
H7	2	150.8±2.52	4	1.2	0.612	90.52	88.92
H8	2	149.7±2.3	4.5	1.26	0.432	94.26	90.1
H9	2	151.7±2.23	5	1.57	0.354	95.23	91

***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. The *in-vitro* release of immediate release tablet H6 batch shows best result i.e. 91.28 % drug release at 60 min.

Table No 8 : *In-vitro* drug release of immediate release tablet of Hydrochlorothiazide.

Time in min	H1	H2	H3	H4	H5	H6	H7	H8	H9
5	15.37	16.98	13.2	19.89	20.21	19.58	18.12	20	19.92
10	29.01	31.05	29.23	38.29	32.83	36.34	31.2	34.58	31.49
20	41	43.82	38.62	49.2	47.03	50	49.78	51.29	49.74
30	54.72	56.92	49.93	56.78	58.9	62.7	58.9	62.7	61.38
40	63.13	67.1	66.05	68	69.42	71.62	67.89	71.1	74.8
50	76.31	78.07	75	79.09	78.17	82.5	78.12	80.51	83.69
60	85.34	89.22	83.45	90.23	89.93	91.28	88.92	90.1	91.8

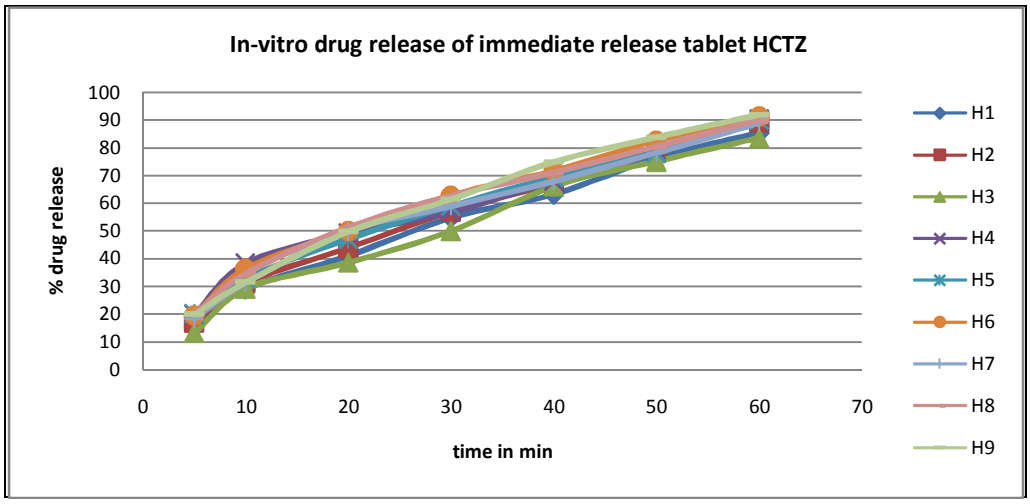

Fig no.3 *In-vitro* drug release of immediate release tablet HCTZ

Kinetics model fitting of % drug release:

Dissolution data of above immediate release tablet was fitted in Zero order, First order, Higuchi equation, Hixson, and Kors-peppas equations.

Table No.9: Kinetics model fitting of % drug release:

Time (min)	Cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remainining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining (Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
10	16.8	83.2	3.162	1.920	1.000	1.225	16.8	4.366	0.276
20	38.34	61.66	4.472	1.790	1.301	1.584	21.54	3.951	0.691
30	53.3	46.7	5.477	1.669	1.477	1.727	14.96	3.601	1.041
40	63.7	36.3	6.325	1.560	1.602	1.804	10.4	3.311	1.331
50	74.81	25.19	7.071	1.402	1.699	1.874	11.11	2.931	1.711
60	81.59	18.41	7.746	1.265	1.778	1.912	6.78	2.640	2.002
120	95.21	4.79	10.954	0.680	2.079	1.979	13.62	1.686	2.956

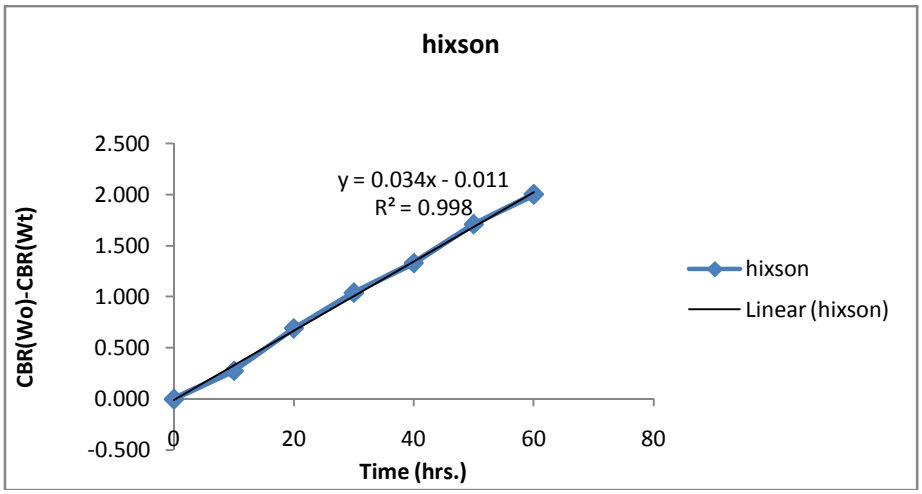

Fig no. 4 drug release kinetics

Evaluation of dependent variable and mathematical modeling:

Table.10 :Result of all batches of immediate release tablet:

Batches	Hardness	DT
H1	3	1
H2	4	1.15
H3	4.5	1.37
H4	3.5	1.3
H5	4	1.5
H6	**3.5**	**1.3**
H7	4	1.2
H8	4.5	1.26
H9	5	1.57

Table no 11: ANOA for linearity model Response 1: hardness of immediate release tablet

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2.42	2	1.21	12.43	0.0074	significant
A-ssg	2.04	1	2.04	21.00	0.0038	
B-ccs	0.3750	1	0.3750	3.86	0.0972	
Residual	0.5833	6	0.0972			
Cor Total	3.00	8				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**
The **Model F-value** of 12.43 implies the model is significant. There is only a 0.74% chance that an F-value this large could occur due to noise.
P-values less than 0.0500 indicate model terms are significant.

Table no.12 Fit Statistics of hardness of immediate release tablet

Std. Dev.	0.3118		**R^2**	0.8056
Mean	4.00		**Adjusted R^2**	0.7407
C.V. %	7.80		**Predicted R^2**	0.5782
			Adeq Precision	9.2582

The **Predicted R^2** of 0.5782 is in reasonable agreement with the **Adjusted R^2** of 0.7407; i.e. the difference is less than 0.2.
Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 9.258 indicates an adequate signal. This model can be used to navigate the design space.

Table no 13 Final Equation in Terms of Actual Factors of hardness of immediate release tablet

hardness	=
+0.791667	
+0.058333	ssg
+0.025000	ccs

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor.

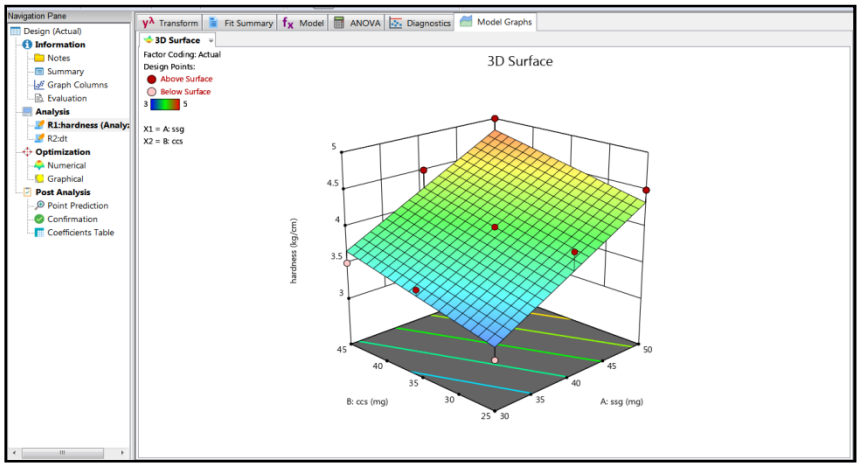

Fig no.4 Response surface plot hardness of immediate release tablet

Table no 14ANOA for linearity model Response 2: D.T of of immediate release tablet

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.1906	2	0.0953	5.69	0.0412	Significant
A-ssg	0.1473	1	0.1473	8.78	0.0252	
B-ccs	0.0434	1	0.0434	2.59	0.1589	
Residual	0.1006	6	0.0168			
Cor Total	0.2912	8				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**
The Model F-value of 5.69 implies the model is significant. There is only a 4.12% chance that an F-value this large could occur due to noise.
P-values less than 0.0500 indicate model terms are significant.

Table no 15 Fit Statistics D.T of of immediate release tablet

Std. Dev.	0.1295		**R^2**	0.6546
Mean	1.32		**Adjusted R^2**	0.5395
C.V. %	9.81		**Predicted R^2**	0.3955
			Adeq Precision	6.4658

The Predicted R^2 of 0.3955 is in reasonable agreement with the Adjusted R^2 of 0.5395; i.e. the difference is less than 0.2.
Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 6.466 indicates an adequate signal. This model can be used to navigate the design space.

Table no 16 : Final Equation in Terms of Actual Factors of disintegration time of immediate release tablet

dt	=
+0.395833	
+0.015667	ssg
+0.008500	ccs

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. The positive coefficients of X1 and X2 indicate increasing the concentration of superdisintegrant Sodium starch glycolate and Cross carmellose sodium which decrease the disintegration time.

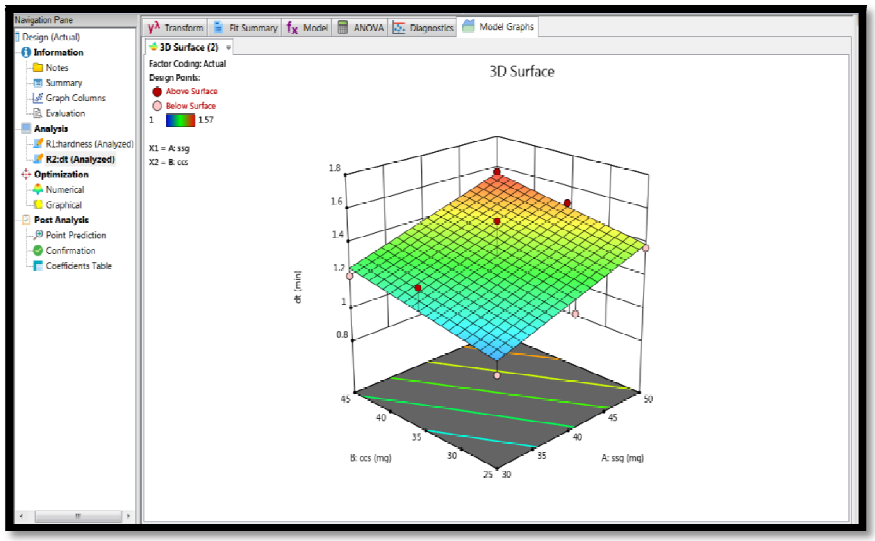

Fig no.5: Response surface plot disintegration time of immediate release tablet

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, DrugAuthentication by UV spectroscopy, FTIR spectroscopy and compatibility study was conducted and their results show in satisfactory limits.
Immediate release layer of Hydrochlorothiazide prepared using Sodium starch glycolate, cross carmellose sodium by wet granulation method. The post compression parameter suggested that Hardness, Friability, Weight variation, were in acceptable limit. The drug content *In vitro* release of immediate release tablet carried in 0.1 N HCl up to 1 hr and its H6 batch shows better drug release.

ACKNOWLDGMENT

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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