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Original Article

PART I: OPTIMIZATION OF HYDRALAZINE HYDROCHLORIDE IMMEDIATE RELEASE LAYER IN ANTIHYPERTENSIVE BILAYER TABLET

HARSH TRIVEDI[1*], KUNAL PATEL[2], NISHANT A. OZA[3], SWATI SAGAR[4]

[1,2]Shree Swaminarayan Sanskar Pharmacy College, Zundal, Gandhinagar, Gujarat, India, [3,4]C. U. Shah University, Wadhwan City, Gujarat, India-363030.
Email: harshtrivedi28@gmail.com

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ABSTRACT

Objective: Aim of the present study was the optimization of the immediate release (IR) layer containing hydralazine hydrochloride (HHC) 25 mg and compressed with a sustained-release (SR) layer of isosorbide dinitrate (ISDN) 40 mg to decrease the dosing frequency.

Methods: In this study, Drug-excipients compatibility study was carried out by FT-IR and a preliminary trial was conducted for screening of super disintegrating agents. The amount of sodium starch glycolate (SSG) (X_1) and the amount of ac-di-sol® (X_2) was chosen as independent variables in 3^2 full factorial design while wetting time (WT) (Y_1), disintegration time (DT) (Y_2) and *In vitro* drug release at 15 min (Q_{15}) (Y_3) were taken as dependent variables. Multiple linear regression analysis, ANOVA, and graphical representation of the influence of factor by 3D plots were performed by using sigma plot 13.0. In the present study, the following constraints were used for the selection of an optimized batch: WT<16 s, DT<25 s, and Q_{15}>90%. To validate the evolved mathematical models, a checkpoint batch was selected from its desirability value.

Results: FT-IR spectra show that the drug and excipients were compatible with each other. The calculated F values found for WT, DT, and Q_{15} were 045.559, 077.100 and 278.760, respectively. All Calculated F values are greater than tabulated values for all dependent variables. Prepared checkpoint was selected from its desirability value 0.935 and it gives a 100% drug release within 30 min.

Conclusion: These results confirm that the prepared HHC 25 mg IR layer is used for rapid control of hypertension.

Keywords: Bilayer tablet, 3^2 Full factorial design, Immediate release, Hydralazine hydrochloride, Isosorbide dinitrate

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INTRODUCTION

Hypertension affects around half of the adult population worldwide, being one of the most common cardiovascular disorders (CVD). It occurs when the high cardiac output exerts pressure on the arterial wall as the blood flow increases. The conventional dosage form used in the treatment of hypertension cannot produce the desired therapeutic effect for a prolonged period. The rationale for using fixed-dose combination therapy is to obtain increased blood pressure (BP) control by employing two antihypertensive drugs with different modes of action and enhance compliance by using a single tablet. Bilayer tablet is suitable for the sequential release of two drugs in combination, separate, and sustained release [1, 2].

HHC, directly acting as a potent peripheral vasodilator, is widely prescribed in the treatment of hypertension and congestive heart failure by direct relaxation of arteriolar smooth muscle. While, ISDN is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the later. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure. The combination consists of HHC 25 mg and ISDN 40 mg fixed-dose that functions as a nitric oxide enhancer and an antioxidant that helps to prevent tolerance to the prolonged use of nitrate. This combination also balanced after-load and preload reduction with a lowering of ventricular filling pressure and systemic and pulmonic vascular resistance. The hemodynamic effects of the combination drug in heart failure include increased cardiac output [3, 4].

Aim of the present study was to develop and optimize the IR layer containing HHC 25 mg using 3^2 full factorial designs, to give immediate effect on direct relaxation of arteriolar smooth muscle.

MATERIALS AND METHODS

Materials

HHC was kindly supplied as gift samples by Torrent Pharmaceuticals, Ahmedabad, Gujarat India. ISDN was supplied as gift samples from Cadila Pharmaceuticals Ltd, Ahmadabad, India. Microcrystalline cellulose (MCC) was procured from Colorcon Asia Pvt. Ltd., Ahmedabad, Gujarat, India. Magnesium stearates, Talc, sodium starch glycolate (SSG), and croscarmellose sodium (CCS) were purchased from SD Fine Chemicals, Mumbai, India. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Drug-excipients compatibility study

Drug excipient interaction plays a vital role in achieving the stability of the drug in dosage form. Fourier transform infrared spectroscopy (FT-IR) was used to study the physical and chemical interactions between drugs and excipients. FT-IR spectra of HHC and mixtures of drugs with other excipients were obtained by using the FT-IR instrument. (FT-IR-1700, Shimadzu, Kyoto, Japan) [5].

Preliminary screening of super-disintegrating agent for IR layer

The development of the IR layer containing HHC 25 mg by selecting ingredients in the appropriate amount and the super-disintegrants optimized thereafter. The IR layer of HHC was prepared by the direct compression method. SSG, CCS, and ac-di-sol® were used in varying amounts as shown in table 1. Batch T1 to T3 contained 2%, 3%, and 5% of SSG, respectively. Batch T4 to T6 contained 2%, 3%, and 4% CCS, respectively and batch T6 to T10 contained 2%, 3%, 4%, and 5% ac-di-sol® respectively. Prepared layer was evaluated for weight variation, thickness, hardness, friability, DT, WT, drug content, and Q_{15} [6, 7].

Optimization of the super-disintegrating agent by using 3^2full factorial design

A 3^2 full factorial designs were used for the optimization of the super disintegrating agent. The formulation of factorial batches as shown in table 2. Based on preliminary results, the amount SSG (X_1) and amount of ac-di-sol® (X_2) were chosen as independent variables in 3^2 full factorial designs, while WT (Y_1), DT (Y_2) and Q_{15} (Y_3) were taken as dependent variables. Multiple linear regression analysis,

ANOVA and graphical representation of the influence of factor by contour plots were performed using sigma plot 13.0 [8, 9]. The experimental runs and measured responses of 3^2 full factorial design batches of IR layer of HHC 25 mg were depleted in table 4.

Table 1: Preliminary screening of super disintegrating agent for IR layer

Ingredients (mg)	Qty. (mg/tab)									
	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
HHC *	25	25	25	25	25	25	25	25	25	25
MCC PH102	51	50	48	51	50	49	51	50	49	48
Tablettose	20	20	20	20	20	20	20	20	20	20
SSG #	2	3	5	0	0	0	0	0	0	0
CCS $	0	0	0	2	3	4	0	0	0	0
Ac-Di-Sol®	0	0	0	0	0	0	2	3	4	5
Magnesium stearate	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1
Total	100 mg/tab									

*HHC=hydralazine hydrochloride, #SSG =sodium starch glycolate, $CCS= croscarmellose sodium

Table 2: Formulation of factorial design batches for IR layer

Ingredients (mg)	Qty. (mg/tab)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
HHC *	25	25	25	25	25	25	25	25	25
MCC PH102	49	48	47	48	47	46	47	46	45
Tablettose	20	20	20	20	20	20	20	20	20
SSG #	2	3	4	2	3	4	2	3	4
Ac-Di-Sol®	2	2	2	3	3	3	4	4	4
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Total	100 mg/tab								

*HHC=hydralazine hydrochloride, #SSG =sodium starch glycolate

Development of bilayer tablet

The bilayer tablets of IR layer HHC 25 mg and SR layer ISDN 40 mg were prepared separately and the two layers were compressed together. The IR layer of HHC was prepared using a direct compression method. The active ingredient, tablettose, MCC PH-102, and different super disintegrate mixed in a geometrically order. Magnesium stearate and talc added to the above blend. The whole blend passed through 40# mesh and compressed using an 8 mm flat punch on a 12-station rotary tablet machine to form an IR layer [10, 11]. SR layer of ISDN also post optimized using 3^2full factorial designs and it was prepared using a direct compression method. The SR layer was compressed using a rotary tablet punching machine by using an 8 mm flat punch on a 12-station rotary tablet machine [12, 13].

Evaluation of bilayer tablet

The prepared tablets were evaluated for thickness, hardness, friability, and DT of the IR layer were evaluated as described by Nivedithaa VR *et al.*, and Fridrun P *et al*. [14, 15].

Wetting time (WT): It was evaluated by using five circular tissue papers of 10 cm in diameter, which was placed in a petridish of 10 cm diameter. 10 ml of eosin solution was adding to the petridish. A tablet was carefully placed on the surface of the tissue paper. The time-required water to reach the upper surface of the tablet was noted as the WT [14, 15].

HPLC was used for estimation of HHC and ISDN: The drug concentration was evaluated using reverse phase high-performance liquid chromatography. Analysis of the sample was performed using a cyberlab HPLC system equipped with a LCP-100 pump, cyber lab LC-UV100 UV detector, and RP C18 column (250 × 4.6 mm ID, particle size 5µ) at ambient temperature. The mobile phase used was a mixture of methanol and distilled water 1000 ml containing 0.1 ml TEA each (60: 40). The pH was adjusted to 6.5. The flow rate was 1.0 ml per min. The detection was carried out at 215 nm. A calibration curve was plotted for HHC and ISDN. A good linear relationship was observed between the concentration of the drug and the peak area of the drug with a correlation coefficient [16].

Drug content for HHC: The drug content was determined by weighing 20 tablets from each batch and calculated the average weight. Then the tablets were triturated to get a fine powder. From the resulting triturate, the powder was weighed accurately, which was equivalent to 100 mg HHC and dissolved in 100 ml volumetric flask containing 100 ml of 0.1N HCl and volume was made to 100 ml with solvent. The volumetric flask was shaken using a sonicator for 1 h. and after suitable dilution with 0.1 N HCl. The drug content was determined using HPLC at 215 nm.

In vitro drug release study: In vitro drug release of bilayer tablets was determined using a USP type-II dissolution test apparatus at 100 rpm. The dissolution was studied using 900 ml of simulated gastric fluid 0.1N HCl (without enzyme, pH 1.2) for the first 2 h and half dissolution model was followed for the sustained release layer for 12 h. Filter through Whatman filter paper and replaced by an equal volume of dissolution medium sample were suitably diluted and analyzed by HPLC at 215 nm.

Stability study: Optimized batch was packed in aluminum foil and was placed for stability study at 40°C/75% RH for 6 mo. The sample was evaluated after 6 mo for physical parameters and In vitro dissolution. The dissolution profile of the product was compared using the similarity factor, f_2, which was calculated by the following formula.

$$f_2 = 50 \log \left[\{1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\}^{-0.5} x100\right]$$

Where a log is the logarithm to the base 10, n is the number of time points, $\sum$ is the summation over all time points, R_t is the mean dissolution value of the reference profile at time t and T_t is the mean dissolution value of the test profile at the same time point. The USFDA draft guidance document contains more information on the similarity factor (f_2). The value of the similarity factor (f_2) between 50 and 100 suggests that the two dissolution profiles are similar [17, 18].

RESULTS AND DISCUSSION

Drug-excipients compatibility study by FT-IR

Fourier transform infrared spectroscopy (FT-IR) was used to study the physical and chemical interactions between drugs and excipients. FT-IR spectra of HHC, and HHC with excipients were recorded using KBr mixing method on FT-IR instrument. The FT-IR spectra of the pure drug are shown in fig. 1(A). HHC exhibited peaks

due to C=C, N-H, C=N, C–H, and C-C stretching. The same peaks of the functional group remain unchanged with all the excipients individually, which was shown in fig. 1(B). Even the functional group shows no change with all the excipients together; all the peaks of major functional groups remain similar to the pure drug as formulation. So, from FT-IR spectra, we can conclude that the drug and excipients were compatible with each other and they were suitable to use for formulation [19].

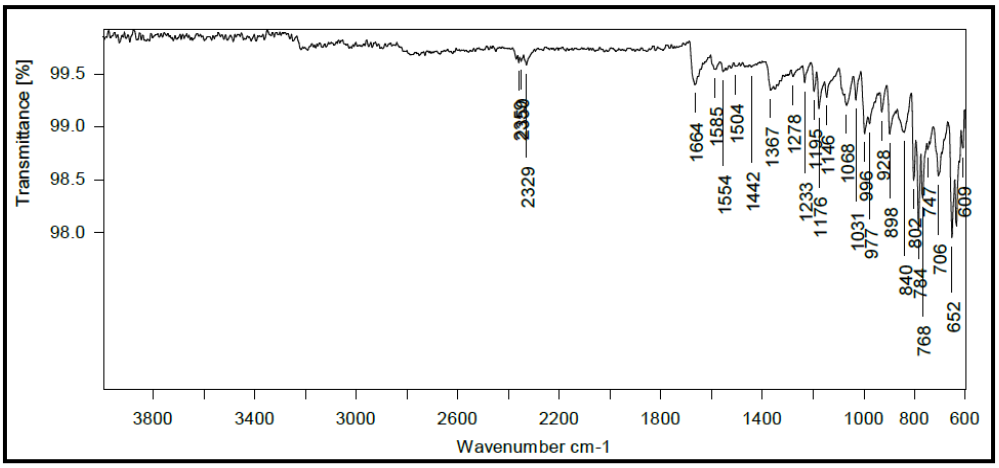


Fig. 1(A): FT-IR of HHC

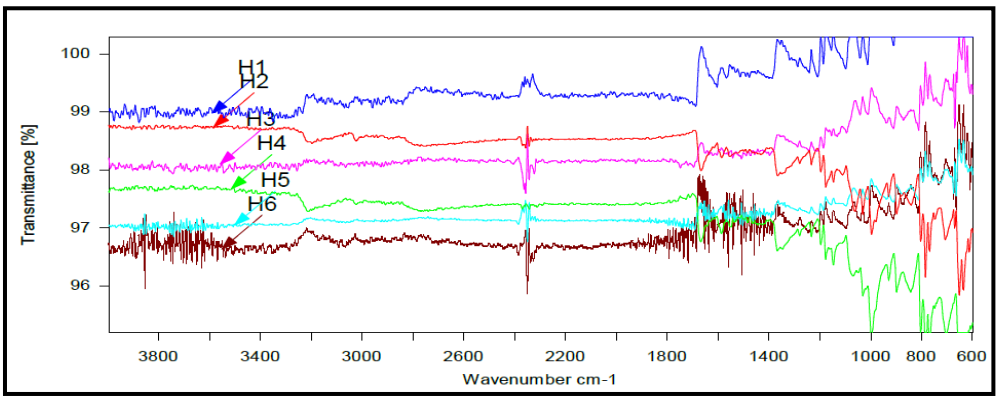


Fig. 1(B): Overlay Spectra of HHC with all excipients, (H1 = Pure HHC, H2 = HHC+MCC PH102, H3 = HHC+Tablattose, H4 = HHC+SSG, H5 = HHC+Ac-Di-Sol®, H6 = HHC+CCS)

Preliminary screening of super disintegrating agent for IR layer

The batches T1-T10 were prepared to achieve an optimized concentration of super disintegrant and the most efficacious one among the three super disintegrants incorporated to prepare IR layer of HHC 25 mg as shown by table 1. Batch T1 to T3 containing SSG, among that batch T2 exhibited the lowest WT, DT, and more drug release was found as shown in table 3. Above 5% of SSG increased DT and WT. This might be due to the reason that SSG swells in 3D. Batch T4-T6 was containing CCS, but it has shown higher WT, and DT compared to other batches. Batch T7 to T10 containing ac-di-sol® among that batch T9 depicted lowest WT, DT and more drug release was found but they do not achieve desired constraints. Hence, further trials were carried out by using a combination of SSG and ac-di-sol® to understand their effect and optimize the concentration of both for the desired release profile [20].

Table 3: Preliminary screening of super disintegrating agent

Batch	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)	DT (s)	WT (s)	Drug content (%)	Q_{15}
T1	100.70±0.14	2.55±0.04	3.50±0.05	0.43±0.02	37±1	28.10±0.06	99.17±0.07	75.4±2.81
T2	100.70±0.05	2.54±0.02	3.10±0.04	0.46±0.15	36±2	27.05±0.17	98.58±0.04	77.9±2.51
T3	100.70±1.07	2.54±0.04	2.98±0.14	0.46±0.03	38±1	28.06±0.04	98.41±0.08	77.3±1.25
T4	100.10±0.45	2.54±0.02	3.60±0.11	0.46±0.01	44±1	35.04±0.05	99.17±0.06	70.5±1.39
T5	100.90±0.78	2.57±0.05	3.20±0.09	0.47±0.06	42±2	34.05±0.09	100.5±0.05	72.3±1.15
T6	100.40±0.34	2.54±0.05	2.98±0.07	0.47±0.02	41±2	34.13±0.12	102.4±0.09	75.3±2.87
T7	100.70±1.89	2.54±0.03	3.50±0.03	0.46±0.02	33±1	27.14±0.14	98.17±0.04	81.4±2.44
T8	100.50±0.22	2.55±0.03	3.12±0.05	0.49±0.03	32±1	26.12±0.16	98.48±0.17	83.3±2.34
T9	100.90±0.67	2.56±0.04	2.98±0.08	0.49±0.02	31±2	23.10±0.14	101.4±0.11	86.9±1.46
T10	100.80±1.35	2.55±0.04	2.97±0.08	0.40±0.32	33±1	24.95±0.13	102.5±0.13	86.9±1.12

*All values are mean±SD (n=6)

Table 4: Runs and measured responses of 3^2factorial design batches

Batch code	SSG *(X_1)	Ac-di-sol® (X_2)	WT (S) (Y_1)	DT (S) (Y_2)	Q_{15} (Y_3)
F_1	-1	-1	25.0±0.45	31.10±0.17	78.4±2.43
F_2	0	-1	24.33±0.57	29.20±0.29	81.9±2.33
F_3	1	-1	22.62±0.87	28.23±014	83.3±1.55
F_4	-1	0	22.66±0.87	30.34±0.27	82.5±1.89
F_5	0	0	19.34±0.59	28.54±0.24	85.3±1.67
F_6	1	0	18.66±0.32	26.34±0.17	86.3±2.57
F_7	-1	1	15.33±0.25	26.54±0.14	89.4±2.89
F_8	0	1	14.63±0.78	24.43±0.27	91.3±2.40
F_9	1	1	13.16±0.85	23.46±0.89	93.9±1.97
Factors and the levels in the design					
Independent variables			Low (-1)	Medium (0)	High (1)
Amount of SSG *(X_1)			2	3	4
Amount of ac-di-sol® (X_2)			2	3	4

*****All values are mean±SD (n=6), *SSG =sodium starch glycolate, *WT = wetting time, #DT= disintegration time, $$Q_{15}$= *In vitro* drug release at 15 min

Table 5: Evaluation of 3^2factorial design batches

Batch	Hausner's ratio	Angle of repose(θ)	Weight variation (mg)	Thickness (mm)	Friability (%)	Drug content (%)
F_1	1.15±0.035	22.54±0.02	099.40±0.14	2.56±0.04	0.45±0.06	99.17±0.05
F_2	1.14±0.015	22.36±0.09	100.60±0.07	2.53±0.05	0.44±0.05	98.58±0.07
F_3	1.14±0.057	22.38±0.09	100.80±1.08	2.54±0.07	0.45±0.04	99.41±0.06
F_4	1.16±0.05	23.82±0.07	099.50±0.56	2.57±0.05	0.47±0.07	99.17±0.05
F_5	1.18±0.07	23.38±0.06	100.70±0.57	2.58±0.04	0.44±0.05	100.5±0.07
F_6	1.12±0.071	24.80±0.05	100.90±0.78	2.55±0.07	0.47±0.03	100.4±0.06
F_7	1.16±0.025	23.81±0.03	100.40±1.55	2.55±0.06	0.49±0.04	99.17±0.05
F_8	1.16±0.025	23.86±0.31	099.40±0.67	2.55±0.04	0.46±0.06	99.48±0.06
F_9	1.11±0.011	23.85±0.07	100.70±0.56	2.53±0.06	0.44±0.05	99.54±0.07

*****All values are mean±SD (n=6)

Table 6: Results of the ANOVA for dependent variables

Source of variation	DF	SS	MS	F value	P value
WT*					
Regression	5	144.055	28.811	45.559	0.005
Residual	3	1.897	0.632		
Total	8	145.952	18.244		
DT #					
Regression	5	057.111	011.422	077.100	0.002
Residual	3	000.444	000.148		
Total	8	057.556	007.194		
$Q_{15}$$					
Regression	5	193.583	038.717		
Residual	3	000.417	000.139	278.760	<0.001
Total	8	194.000	024.250		

*WT = wetting time, #DT= disintegration time, $$Q_{15}$= *In vitro* drug release at 15 min

Table 7: Summary of regression output of factors for measured responses

Responses	Model	Coefficient of regression parameters						
		b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2
WT*	Full	19.629	1.423	4.663	0.0567	0.663	0.365	0.987
	Reduced	19.629	1.423	4.663				
DT#	Full	27.778	-1.667	-2.500	0.333	1.167	0.000	0.992
	Reduced	27.778	-1.667	-2.500	-	1.167	-	
$Q_{15}$$	Full	84.667	2.167	5.167	0.500	1.500	0.250	0.998
	Reduced	84.667	2.167	5.167	-	1.500	-	

*WT = wetting time, #DT= disintegration time, $$Q_{15}$= *In vitro* drug release at 15 min

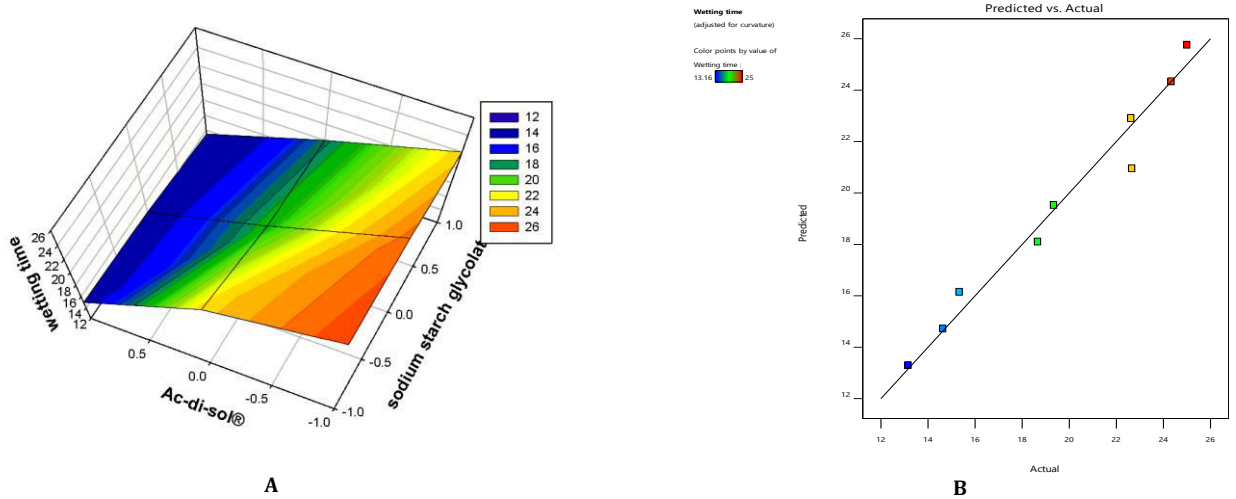
3^2 Full factorial design model evaluation

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses:

$$Y=b_0+b_1X_1+b_2X_2+b_{11}X_1^2+b_{22}X_2^2+b_{12}X_1X_2$$

where, Y is the dependent variable, b_o is the arithmetic mean response of the 9 runs and any bi is the estimated coefficients for the related factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The interaction term "X_1X_2" shows how the response changes when the two factors change simultaneously. Evaluation data for the IR layer of HHC 25 mg were presented in table 4 and table 5. The fitted equations relating the responses that are, WT (Y_1), DT (Y_2), and Q_{15} (Y_3) to the transformed factor are shown in table 7.

The polynomial equations used to draw conclusions after considering the magnitude of coefficient and mathematical sign it carries (i.e. positive or negative). The results of ANOVA suggested that calculated F values for WT, DT, and Q_{15} were 045.559, 077.100 and 278.760, respectively, shown in table 6. Tabulated F value was found to be 9.013 at α = 0.05. Calculated F values are greater than tabulated for all dependent variables. Therefore, the factors selected have shown significant effects. From the results of multiple regression analysis, it was found that all factors had a statistically significant influence on all dependent variables as p<0.05 [21, 22].



A **B**

Fig. 2(A): 3D plot showing the effect of SSG and ac-di-sol® on WT (B) Predicted Vs actual value of WT

Full and reduced model for WT

$$WT= 19.629-(1.423 * X_1)-(4.663 * X_2)+(0.0567 * X_1^2)-(0.663 * X_2^2)+(0.365 * X_1 X_2)$$

Based on the analysis of variance (ANOVA) the result showed that the developed linear model was highly significant, as was evident from a very low probability value 0.005. The value of R^2 was found to be 0.987. The plot of observed WT versus predicted WT (fig. 2B) shows a straight line. Therefore, it may be concluded that the equation has good predictive ability. From the 3D plot (fig. 2A) and regression coefficient values of factors, it was concluded that when the amount of SSG and amount of ac-di-sol® were increased WT was decreased. Due to the higher hydration capacity of ac-di-sol® it gives a faster WT compared to the SSG. For WT, the significance levels of the coefficients b_{11}, b_{22}, and b_{12} were found to be P= 0.926, 0.323and 0.426, respectively, so they were omitted from the full model to generate a reduced model. The reduced or the refined model for WT,

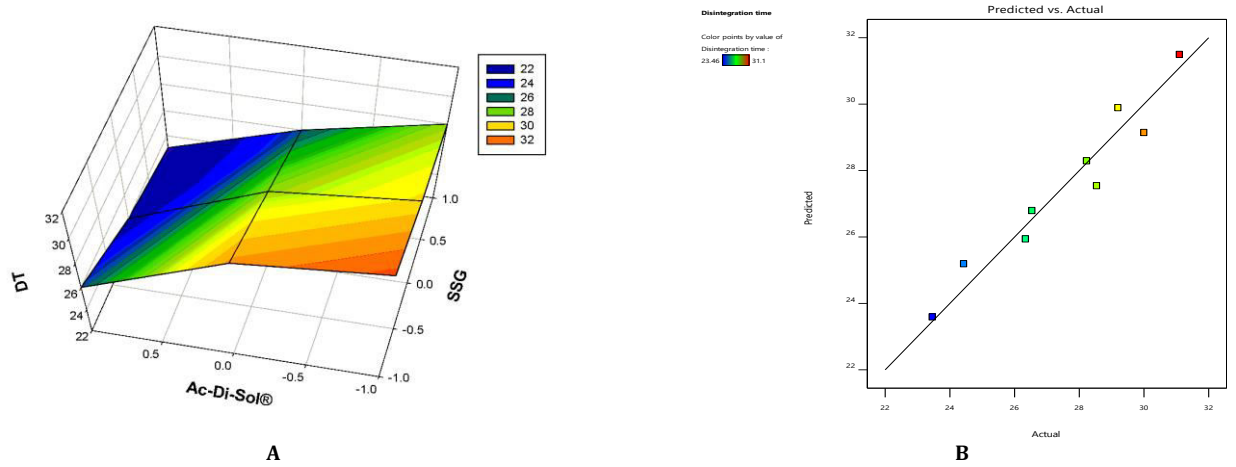
$$WT= 19.629-(1.423 * X_1)-(4.663 * X_2)$$

Full and reduced model for DT

$$DT= 27.778-(1.667* X_1)-(2.500* X_2)+(0.333* X_1^2)-(1.167* X_2^2)-(-0.000* X_1 X_2)$$

Based on the analysis of variance (ANOVA) the result showed that the developed linear model was highly significant, as was evident from a very low probability value 0.002. The value of R^2 was found to be 0.992. The plot of observed DT versus predicted DT (fig. 3B) shows a straight line. Therefore, it may be concluded that the equation has the good predictive ability. From the 3D plot (fig. 3A) and the regression coefficient values of factors, it was concluded that when the amount of SSG and amount of ac-di-sol® were increased, disintegration time was decreased. The results also indicated that ac-di-sol® was given a more significant effect on DT. Higher swelling capacity of ac-di-sol leads to faster disintegration compared to sodium starch glycolate. For DT, the significance levels of the coefficients b_{11} and b_{12} were found to be P= 0.308 and 1.000, respectively, so they were omitted from the full model to generate a reduced model. The coefficients b_1, b_2, and b_{22} were found to be significant at P<0.05; hence, it was retained in the reduced model. The reduced or the refined model for DT,

$$DT= 27.778-(1.667 * X_1)-(2.500 * X_2)-(1.167 * X_2^2)$$



A **B**

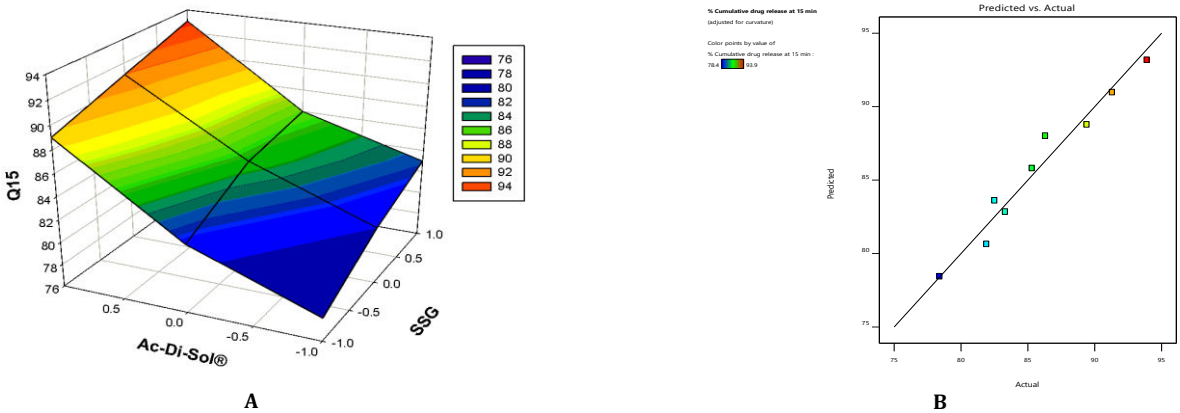
Fig. 3(A): 3D plot showing the effect of SSG and ac-di-sol® on DT (B) Predicted Vs actual value of DT

Full and reduced model for Q_{15}

$$Q_{15}= 84.667+(2.167 * X_1)+(5.167 * X_2)-(0.500 * X_1^2)+(1.500 * X_2^2)-(0.250 * X_1 X_2)$$

Based on the analysis of variance (ANOVA) the result showed that the developed linear model was highly significant, as was evident from a very low probability value<0.0001. The value of R^2 was found to be 0.998. The plot of observed Q_{15} versus predicted Q_{15} (fig. 4B) shows a straight line. Therefore, it may be concluded that the equation has good predictive ability. From the 3D plot (fig. 4A) and the regression coefficient values of factors, it was concluded that when the amount of SSG and amount of ac-di-sol® were increased that time, Q_{15} was increased. The results also indicated that ac-di-sol® was given a more significant effect on Q_{15}. For Q_{15}, the significance levels of the coefficients b_{11} and b_{12} were found to be P= 0.154 and 0.272, respectively, so they were omitted from the full model to generate a reduced model. The coefficients b_1, b_2 and b_{22} were found to be significant at P<0.05; hence, it was retained in the reduced model. The reduced or the refined model for % cumulative drug release,

$$Q_{15}= 84.667+(2.167 * X_1)+(5.167 * X_2)+(1.500 * X_2^2)$$



A B

Fig. 4(A): 3D plot showing the effect of SSG and ac-di-sol® on Q_{15} (B) Predicted Vs actual value of Q_{15}

Search for the selection of optimized formulation

The optimized IR layer containing HHC 25 mg was identified by numerical optimization by selecting the desired ranges for the response variables as WT<16 s, DT<25 s, and Q_{15}>90%. Further, the optimized bilayer tablet formulation was demarcated in the design space overlay plot shown in fig. 5. To validate the evolved mathematical models, a check-point was selected from its desirability value 0.935. Check-point batch CP1 was prepared and evaluated. The observed and predicted values for batch CP1 as shown in table 8. A good correlation was found between observed and predicted values. Hence, it was concluded that the evolved models might be used for the theoretical prediction of responses within the factor space. Optimized IR layer gives a 100% drug release within 30 min. It was kept for stability study and *in vitro* release profile at initial and after 6 mo was compared using similarity factor, f_2, value which was found to be 91.50% for HHC. There is no significant difference in the similarity factor.

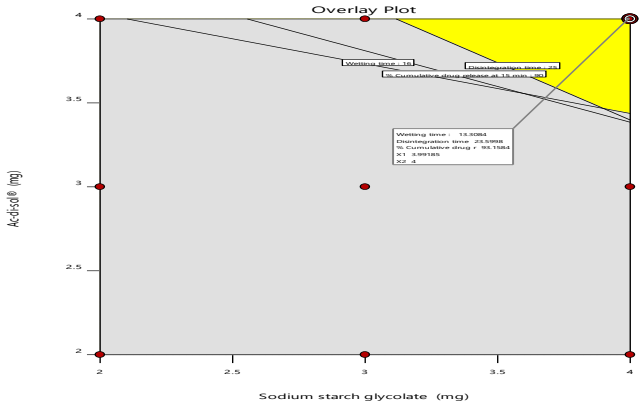


Fig. 5: Overlay plot depicting yellow color region design space and flagged point as the optimized IR layer containing HHC 25 mg

Table 8: Formulation and evaluation of checkpoint batches

Formulation of checkpoint batches				
Batch Code	Variable Level Coded Value		Actual Value	
	X_1	X_2	X_1(mg)	X_2(mg)
CP1	0.99	1	3.99	4.00
Evaluation of checkpoint batches and comparison with the predicted value				
Parameter	**Actual value**		**Predicted value**	
WT *	14.50±0.45		13.307	
DT #	23.40±1.29		23.599	
$Q_{15}$$	91.40±0.88		93.160	

(n=6), *WT = wetting time, #DT= disintegration time, $$Q_{15}$= *In vitro* drug release at 15 min

CONCLUSION

The present investigation was to formulate, evaluate, and optimize the layer containing HHC in a bilayer tablet. There was no Drug-excipient interaction in the FT-IR study. From the results of preliminary studies SSG, (X_1) and the amount of ac-di-sol® (X_2) were chosen as independent variables in 3^2 full factorial designs while WT (Y_1), DT (Y_2) and Q_{15} (Y_3) were taken as dependent variables. The effect of independent variables on dependent variables was studied by analyzing the response surface plot and polynomial equation. Optimization of the IR layer of HHC was performed by the overlay plot. A checkpoint batch was designed according to the results of the desirability value and evaluated for all the parameters. The results of the comparison of predicted response and obtained response were found in good agreement. The formulation was found to be stable during accelerated stability study. Quick disintegration and fast release of the HHC give a rapid control of hypertension. Further study was conducted for optimizing the SR layer containing ISDN 40 mg and compressed with the IR layer of HHC. The final formulation was decreasing the dosing frequency. It works as a nitric oxide enhancer and an antioxidant that helps to prevent tolerance to the prolonged use of nitrate.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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