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Formulation, Development and Evaluation of Taste Masked Effervescent Tablet of Paracetamol and Dicyclomine HCl

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ABSTRACT

The main objective of the current research work was to formulate and evaluate taste masked effervescent tablet. Dicyclomine HCl is very bitter in taste. The purpose of this research was to reduce the bitterness of Dicyclomine HCl using Hydroxyl Propyl Betacyclodextrin by inclusion complex method and formulate effervescent tablet with sufficient mechanical integrity and to achieve faster disintegration in the water.**:** Components excipients and Dicyclomine HCl HP-Betacyclodextrin inclusion complex were selected based on preliminary studies. A comparative evaluation of the taste masking was carried out for developed formulation. Citric acid, tartaric acid, sodium bicarbonate was used in 1:2:3.44 ratio for effervescent mixture. 32full factorial design was applied. Ratio of citric acid and hardness were taken as independent variables dissolution of Paracetamol and Dicyclomine HCl at 5 minutes, disintegration time, and friability were taken as dependent variables. Optimized formulation was then evaluated for general tablet evaluation and dissolution. Short term accelerated stability studies were performed for tablets prepared using optimized formulation. Optimized batch composition had ratio of Paracetamol: citric acid and hardness at concentration of 1:0.45 (mg) and 8 (kg/cm2) respectively. All the evaluation parameters of the optimized batch met the acceptance criteria. The taste masked effervescent tablet of Paracetamol and Dicyclomine HCl was formulated successfully by wet granulation method.

Keywords: Paracetamol, Dicyclomine HCl, Taste masking, Effervescent tablet, Wet granulation.

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INTRODUCTION

Effervescent mixtures have been moderately popular over the years since along with the medicinal value of the particular preparation. In addition, they provided a pleasant taste due to carbonation which helped to mask the objectionable taste of the drugs. The oral dosage forms are the most popular way of taking medication despite having some disadvantages like slow absorption and thus onset of action is prolong. This can be overcome by administrating the drug in liquid from but, many apis have limited level of stability in liquid form. So, effervescent tablets acts as an alternative dosage form.[1-6]

Taste masking technologies are increasingly focused on aggressively bitter tasting drugs like the macrolide antibiotics, non-steroidal anti-inflammatory drugs and penicillin's. Taste masking of water soluble bitter drugs, especially those with a high dose, is difficult to achieve by using sweeteners alone. [7-10]

The mechanism of taste masking by complex formation has two theoretical possibilities. Either the cyclodextrins wraps the bad tasting molecule to inhibit its interaction with the taste buds, or it interacts with the gate keeper proteins of the taste buds. β-cyclodextrin is widely used complexing for taste masking of drugs due to its sweet taste and is non-toxic in nature. [11-16]

Analgesic and anti-inflammatory relieves mild to moderate pain, and reduces inflammation and fever. These agents are effective for somatic pain. Paracetamol (PCM) also known as acetaminophen. It is Non-steroidal anti-inflammatory drug and belongs to a group of medicines known as analgesics or pain killer. Dicyclomine Hydrochloride is a synthetic tertiary amine antispasmodic. It is an anti-cholinergic drug. It acts by blocking muscarinic receptors in smooth muscle of the stomach and intestine and relieves muscle spasm and cramping in gastrointestinal tract (GIT). [17-21]

Rationale of Combination: Dicyclomine hydrochloride is an anti-cholinergic drug which controls the secretions of the body while Paracetamol is an analgesic. Thus Dicyclomine HCl + PCM combination used to treat running nose, common cold, flu, body ache, muscle pain. [22-24]

Paracetamol is an analgesic and antipyretic and Dicyclomine hydrochloride is antispasmodic used in management of pain. Due to effervescence, tablet will disperse in water, rapidly dissolve and get converted into the solution form which will be directly available for absorption hence fast onset of action is achieved as compared to conventional tablet. The bitter taste of Dicyclomine hydrochloride is masked using Hydroxyl Propyl Betacyclodextrin by inclusion complex method that leads to better patient compliance. [25-29]

MATERIALS AND METHOD

Chemicals

Paracetamol was purchased from Cadila Pharma.Ltd.. Dicyclomine Hydrochloride was purchased from Palam Pharma Pvt. Ltd.. HP-Beta-Cyclodextrin and Povidone-K-30 was purchased from Signet Chemical Corporation Pvt.Ltd.. Citric Acid (Anhydrous) was purchased from Dhruvika Chemicals Trading Pvt.Ltd. (Mumbai, India). Tartaric Acid was purchased from Carton Laboratories. Sodium Bicarbonate and Mannitol was purchased from Merck. Orange Flavour was purchased from Bell Flavours And Fragrances India Pvt.. Sodium Benzoate was purchased from Navyug Pharma Chem.. Magnesium Stearate was purchased from Accent Miervcell Industries. Neotame was purchased from Shangqiu Kangmeida Bio-technology Co., Ltd. Microcrystalline Cellulose was purchased from FMC Biopolymer. Other reagents and chemicals were of analytical grade.

METHODOLOGY

Identification of drug

Identification of drug is first step in research methodology. The sample of drug was identified by FT-IR, DSC and Spectrophotometry method.

FTIR Spectral Analysis

FTIR spectrum of drug sample was taken and compared with that of reference standard of Paracetamol and Dicyclomine HCl.

DSC Analysis

Thermal behavior of drug was examined using thermal analyzer. An accurately weighed sample (about 1 mg) was placed in sealed aluminium pan before heating at a scanning rate of 5 °C per minute from 50 to 180 °C. An empty aluminium pan was used as reference.

Determination of λ max of Paracetamol and Dicyclomine HCl

Determination of λmax of Paracetamol and Dicyclomine HCl was done by the UV- visible spectrophotometer. The standard stock solutions of Paracetamol and Dicyclomine HCl were diluted separately appropriately with methanol in a volumetric flask. The resulting solution was scanned between 200nm to 400nm in a double beam UV/ Visible spectrophotometer.

Preparation of standard calibration curve of Paracetamol and Dicyclomine HCl

Preparation of stock solution (Paracetamol)

Accurately weighed 10 mg Paracetamol was taken in 100 ml volumetric flask and 30 ml of methanol was added and drug was dissolved. Then volume was make up to the mark of 100 ml with methanol to give final strength 100 µg/ml.

Preparation of stock solution (Dicyclomine HCl)

Accurately weighed 10 mg Dicyclomine HCl was taken in 100 ml volumetric flask and 30 ml of methanol was added and drug was dissolved. Then volume was make up to the mark of 100 ml with methanol to give final strength 100 µg/ml.

Preparation of standard calibration curve

Accurately weighed quantities 50mg of Paracetamol and 50mg Dicyclomine HCl was taken then dissolve separately Paracetamol and Dicyclomine HCl in 50ml volumetric flask and volumes were make up to 50ml with methanol (1000 µg/ml) by using micro pipette aliquots of respective secondary stock of Paracetamol and Dicyclomine HCl were suitably diluted to get 6.5, 13, 19.5, 26, 32.5, 39 µg/ml for Paracetamol. 5, 10, 20, 30, 40, 50, 60, 70, 80 µg/ml of Dicyclomine HCl.

Method of preparation of effervescent tablet

Paracetamol granules and Dicyclomine HCl HP-β-Cyclodextrin complex granules were prepared separately.

Preparation of Paracetamol granules

Wet granulation using a rapid mixer granulator (RMG) was employed for the preparation of paracetamol granules. Isopropyl alcohol was used as a non-aqueous granulating fluid to avoid acid-base reaction during processing. Initially, paracetamol, anhydrous citric acid, tartaric acid, sodium bicarbonate, mannitol, and orange flavor were sifted through a 24# sieve using a vibratory sifter. Separately, the required quantity of Povidone K-30 was dissolved in isopropyl alcohol under continuous stirring until a clear binder solution was obtained. The sifted materials were then dry mixed in the RMG using slow impeller speed with the chopper switched off for 5 minutes. Granulation was carried out by adding the binder solution to the dry mix while maintaining slow impeller speed and keeping the chopper off for 3 minutes. The wet mass obtained was further kneaded using slow impeller and slow chopper speed for 2 minutes. The prepared wet granules were dried in a rapid dryer at 50°C with an airflow of 40 until the loss on drying (LOD) was not more than 2%. Finally, the dried granules were sized through a 0.8 mm oscillating granulator.

Preparation of Dicyclomine Hydrochloride granules

Preparation inclusion complex: The inclusion complex of Dicyclomine hydrochloride with HP-β-Cyclodextrin was prepared in a 1:1 molar ratio by the kneading method. For this, 20.00 mg of Dicyclomine hydrochloride and 79.50 mg of HP-β-Cyclodextrin were accurately weighed and used for complex preparation. Initially, HP-β-Cyclodextrin was triturated with a small quantity of water to form a uniform paste. Dicyclomine hydrochloride was then added to the paste and the mixture was kneaded continuously in a mortar and pestle for 30 minutes to obtain a homogeneous complex. The prepared kneaded mass was dried in an oven and passed through a 60# sieve.

Both prepared granule portions were blended in a blender at 16 rpm for 20 minutes. After blending, sodium benzoate was added and lubrication was carried out for 5 minutes at 16 rpm. The extra granular part was then added to the lubricated granules. Finally, the prepared granules were compressed into tablets using a rotary punching machine fitted with 20 mm punches.

Drug-excipient compatibility study

Compatibility must be established between the active ingredients and other excipients to produce a stable, efficacious and safe product. FTIR of Paracetamol and Dicyclomine HCl with excipients were recorded.

EXPERIMENTAL DESIGN

Experimental runs as per 3^2 full factorial design

According to result of preliminary batches the factors were selected for DOE. The major factor that affects the disintegration time and drug release of the two factors were selected i.e. citric acid and hardness. For employing the design three levels were selected.

As per the above selection 3^2 full factorial design was selected. For Applying the DOE design expert version 10 Stat-Ease, Inc. used.

Polynomial Equation; $Y= Y = \beta o + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X2 + \beta_{11} X_{12} + \beta_{22} X_{22} + E$ ……. (1)

Table 1: List of independent variables

Independent variables	Low (-1)	optimum (0)	High (+1)
Paracetamol: citric Acid (mg)	1:0.25	1:0.35	1:0.45
Hardness (kg/cm2)	6	8	10

Proposed response variables

Y1 = Dissolution of Paracetamol at 5 min.

Y2 = Dissolution of Dicyclomine HCl at 5 min

Y3= Disintegration time

Y4 = Friability

Table 2: Experimental runs

Runs	Coded value		Actual value	
	X 1	X 2	PCM: citric acid ratio	Hardness
1	1	-1	1:0.45	6
2	-1	1	1:0.25	10
3	0	-1	1:0.35	6
4	1	0	1:0.45	8
5	0	0	1:0.35	8
6	-1	-1	1:0.25	6
7	0	1	1:0.35	10

8	-1	0	1:0.25	8
9	1	1	1:0.45	10

Table 3: Effervescent material ratio for design batches

Effervescent material	Standard ratio	Paracetamol: citric acid ratio (Paracetamol 325 mg)		
		1:0.25	1:0.35	1:0.45
Citric acid (anhydrous) (mg)	1	81.25	113.75	146.25
Tartaric acid (mg)	2	162.5	227.5	292.5
Sodium bicarbonate (mg)	3.44	279.5	391.5	503.1

Table 4: Experimental design batches composition

Batch code (mg/tab)	D1	D2	D3	D4	D5	D6	D7	D8	D9
Paracetamol	325	325	325	325	325	325	325	325	325
Citric acid (anhydrous)	146.25	81.25	113.75	146.25	113.75	81.25	113.75	81.25	146.25
Tartaric acid	292.5	162.5	227.5	292.5	227.5	162.5	227.5	162.5	292.5
Sodium bicarbonate	503.1	279.5	391.5	503.1	391.5	279.5	391.5	279.5	503.1
Mannitol	0	395	185	0	185	395	185	395	0
Orange flavour	13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3	13.3
Neotame	5	5	5	5	5	5	5	5	5
Povidone-k-30	39	39	39	39	39	39	39	39	39
Dicyclomine HCl HPβ-Cyclodextrin inclusion complex	99.5	99.5	99.5	99.5	99.5	99.5	99.5	99.5	99.5
Microcrystalline cellulose pH 112	85.5	85.5	85.5	85.5	85.5	85.5	85.5	85.5	85.5
Sodium benzoate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Magnesium stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Total	1500	1500	1500	1500	1500	1500	1500	1500	1500

Statistical analysis of design batches

The data obtained from the evaluation of all the design batches were validated by ANOVA and regression analysis using microsoft excel 2013. Response surface plots and contour plots were plotted by using design expert 10.0 trial version. Polynomial equations having the necessary terms of main and interaction effects were generated from the regression analysis data obtained using microsoft excel 2013. In addition, analysis of variance (ANOVA) was used to identify significance of the effects of factors on the response in terms of their regression coefficients.

Optimization of the formulation

After evaluation of response variables, optimization of formulation was carried out using microsoft excel 2013. The constraints of variables for selection were kept as following: amount of citric acid, hardness as specified in design; dissolution of Paracetamol and Dicyclomine HCl at 5 min., disintegration time, friability were optimized. Optimized batch was selected on the basis of desirability of the solutions provided by the MS excel, which should be as high as possible and preferably near to 1.

EVALUATION PARAMETERS

Pre compression parameter:

Determination of bulk density and tapped density:

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V0) measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus set for 10, 500, and 1250 taps and after that the volume (Vf) measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density calculated using the following formulae.

Bulk density = W/V0

Tapped density = W/Vf

Where, W= Weight of the powder

V0 = Initial volume

Vf = final volume

1) Angle of repose (θ)

The angle of repose of prepared products will be determined by glass funnel method, weigh required quantity of the prepared products using following equation.

θ = tan-1 h / r

Where, θ = angle of repose

h = height of the pile and

r = radius of the powder cone

2) Compressibility Index (Carr's Index)

$$\textbf{Carr's Index} = \frac{\textit{Tapped Density} - \textit{Bulk Density}}{\textit{Tapped Density}} \times 100$$

3) Hausner's Ratio

$$\textbf{Hausner's Ratio} = \frac{\textit{Tapped Density}}{\textit{Bulk Density}}$$

POST COMPRESSION PARAMETER:

Thickness:

The thickness of the press coated tablet will be measured by using Digital Vernier caliper.

Friability:

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W0) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by –

$\%F = 100\ (1-W_0/W)$,

% Friability of tablets less than 1% are considered acceptable.

Weight variation test

To study weight variation twenty tablets of the formulation were weighed using electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

Drug content analysis

A powder quantity equivalent to 325 mg Paracetamol and 20 mg Dicyclomine Hydrochloride was accurately weighed and transferred to volumetric flask of 100 ml capacity and volume was made up to the mark with methanol (3250 µg/ml Paracetamol and 200µg/ml Dicyclomine HCl). From this solution 5 ml was transferred to volumetric flask of 50 ml capacity (325 µg/ml Paracetamol and 20 µg/ml Dicyclomine HCl). From this solution Dicyclomine Hydrochloride were determined by measuring the absorbance of the prepared mixture at 217nm. And from the above solution 5ml was transferred to volumetric flask of 50 ml capacity (32.5 µg/ml Paracetamol) Paracetamol were determined by measuring the absorbance of the prepared mixture at 295nm and 217nm respectively for UV-spectrophotometric method.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using monsanto tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.

Disintegration time

Disintegration time was determined using the disintegration apparatus USP in water maintaining the temperature at 37 ± 2°C

Measurement of CO2 content

One effervescent tablet solved in 100 ml of 1N sulfuric acid solution and weight changes were determined after dissolution end. The obtained weight difference was shown the amount (mg) of CO2 per tablet. The CO2 content reports are averages of 3 determinations.

Evaluation of the water content by KF

Titration method used to determine the water content. In contrast to drying method, this is a specific method if no side reactions occur only water will be determined. While using drying method some problem occurs like apart from water, other volatile components of the sample and decomposition products are also determined. Titration method is rapid (few minutes), can be validated & therefore fully documented. With the Karlfischer (KF) titration both free and bound water can be determined e.g. surface water as crystals or the water content inside them. The method

works over a wide concentration range from ppm upto 100% and supplies reproducible and correct result.

Taste masking evaluation (sensory evaluation)

Taste evaluation was done by taste panels. The method chosen was ranking test. For this 6 human volunteers were selected. The dispersion of the pure drug and formulations were coded and given to the panelists. The intensity of bitterness was asked from panelists and best taste masking technique was screened from all the adopted taste masking methods.

In-Vitro dissolution studies

Drug release study of tablets will be studied using a USP Dissolution Apparatus II (Paddle type) at rotation speed of 100rpm using 0.1NHCl, the dissolution media maintained at 37±0.5^{o}C. Aliquots of 10ml will be withdrawn at different time intervals. Drug content in each sample was analyzed after suitable dilution by UV-spectrophotometric method.

Absorbance correction method is used for determination of percentage of drug release of drug Paracetamol and Dicyclomine hydrochloride in vitro dissolution testing

Short term accelerated stability study

The accelerated stability study was conducted as per ICH guideline. Accelerated stability study was carried out under the condition 40° C ± 2° C & 75%± 5% RH for 1 month.

Conditions for accelerated stability study:

For accelerated stability study the drug product were kept in walk in humidity chamber at 40° C ± 2° C & 75% ± 5% RH. The drug product were packed in plastic tube with fitted caps containing desiccants. After one month properly labeled tube were withdrawn for different tests.

RESULTS AND DISCUSSION

Identification of drug

Infrared spectroscopy

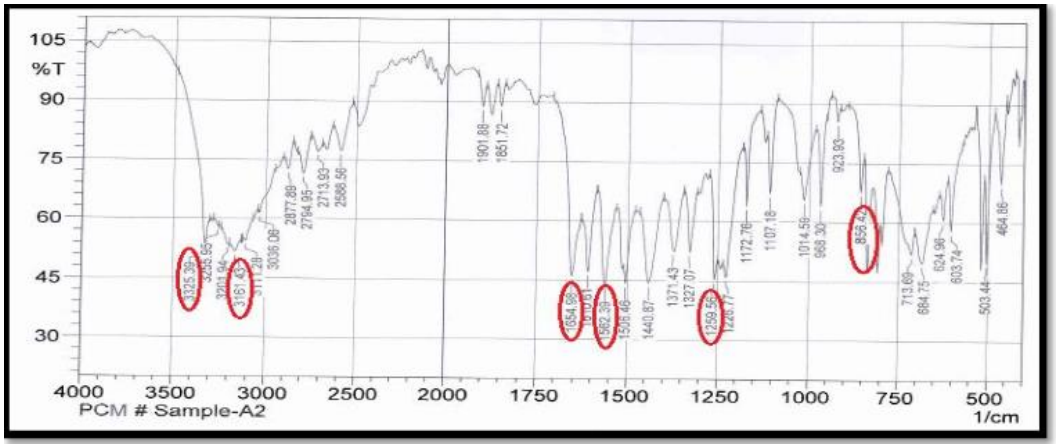

Figure 1: FTIR spectra of Paracetamol

Table 5: Values of functional group peak

Drug	Functional group	Peak observation (cm-1)	Range (cm-1)
Paracetamol	O-H	3325.05	3400-3200
	N-H	3161.11	3500-3100
	C=O	1650.95	1655-1620
	Amide II Band	1560.30	1570-1515
	C-NH group	1254.64	1250
	Para-disubstituted aromatic ring	804.26	850-750
Dicyclomine HCl	C-N	1134.10	1250-1020
	C-O	1193.83	1300-1000
	C-H	2929.64	3000-2840
	C=O	1718.46	1725-1700

Interpretation:

From the FTIR graph and the data table we can conclude that peaks of functional group are identical to the standard range.

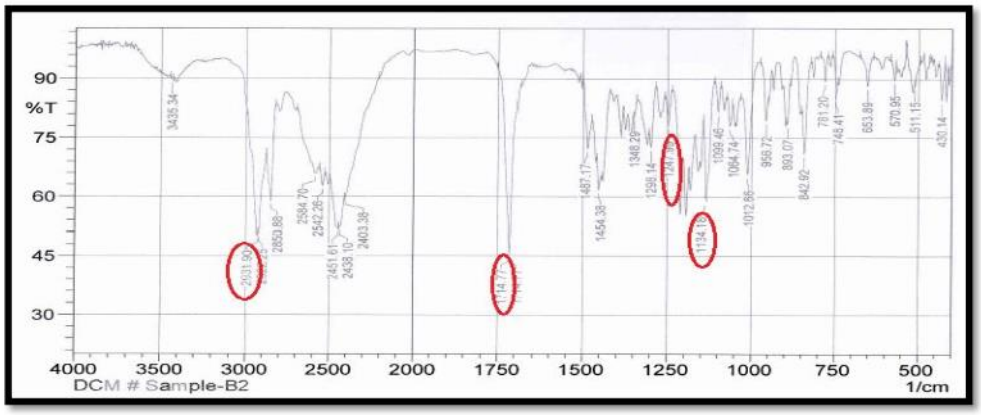

Figure 2: FTIR Spectra of Dicyclomine HCl

Differential scanning calorimetry (DSC)

The thermogram Of Paracetamol and Dicyclomine HCl was obtained by differential scanning calorimetry (Shimadzu, DSC-60 Thermal Analyzer). About 5 mg sample was taken in DSC aluminum cell and studied at temperature range 40 to 430ºC.The DSC thermograph of Paracetamol and Dicyclomine HCl shows endothermic peak at 173.5°C and 167°C respectively corresponding to its melting point.

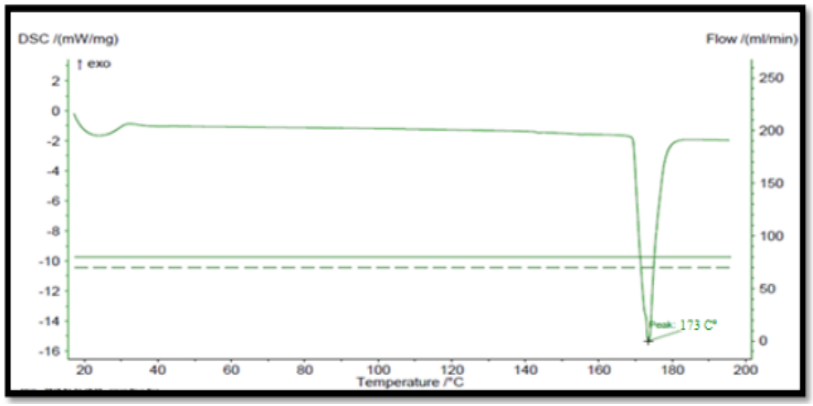

Figure 3: DSC thermogram of Paracetamol

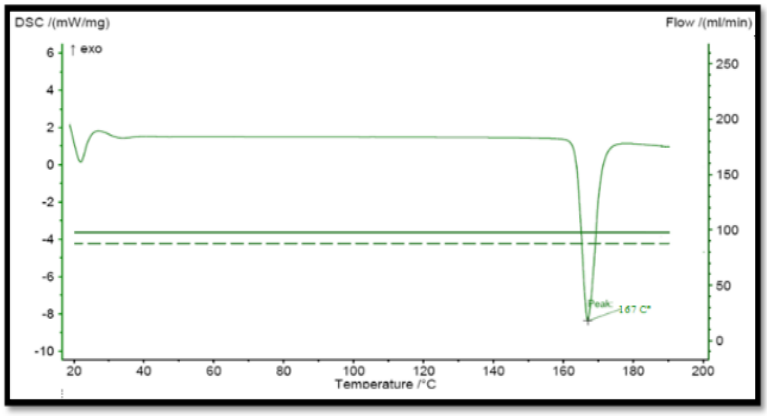

Figure 4: DSC thermogram of Dicyclomine HC

Determination of λ max of Paracetamol and Dicyclomine HCl

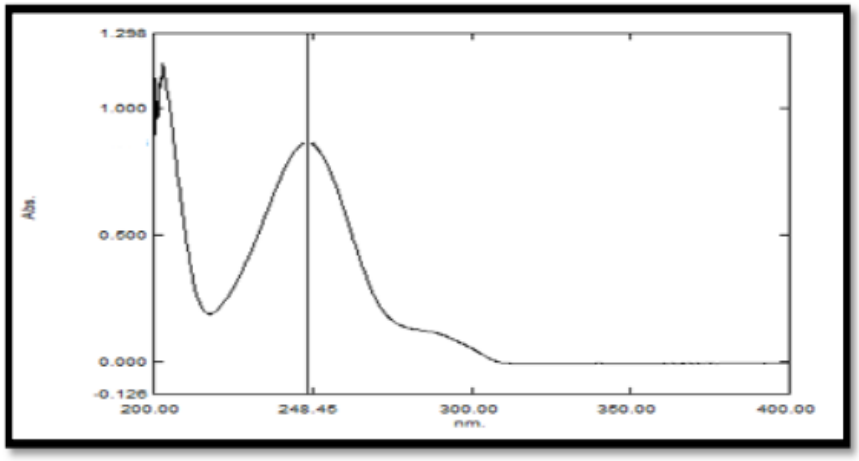

Figure 5: λ max of Paracetamol

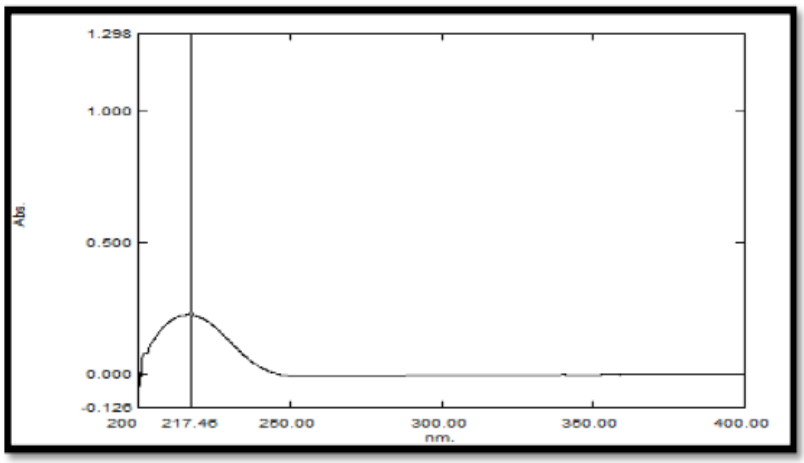

Figure 6: λ max of Dicyclomine HCl

λ max of Paracetamol	248nm
λ max of Dicyclomine HCl	217nm

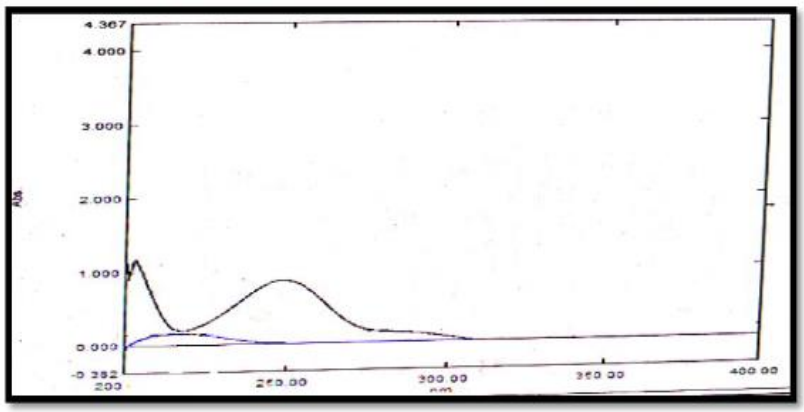

Figure 7: Overlay spectra of Paracetamol and Dicyclomine HCl.

Calibration curve of Paracetamol and Dicyclomine HCl

Calibration curve of Paracetamol at 295 nm

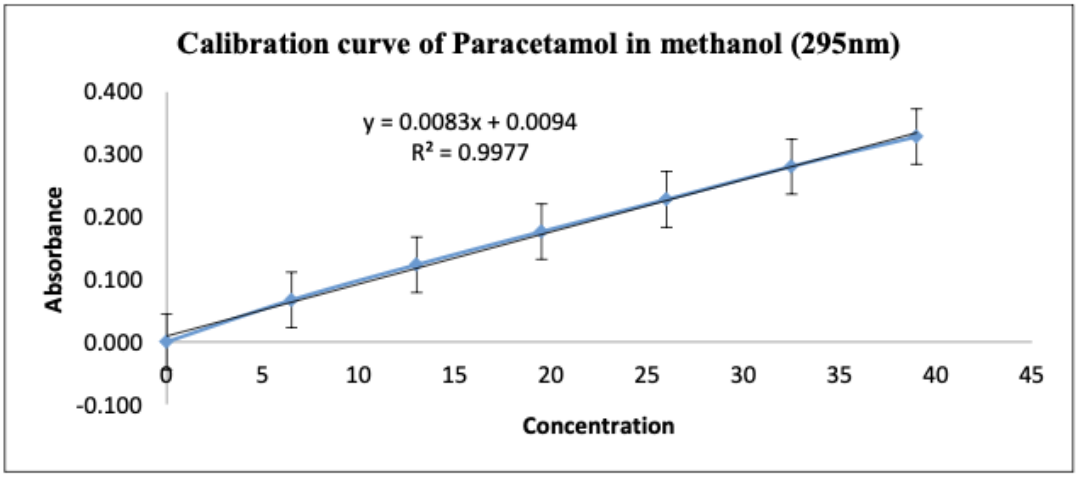

Figure 7: Calibration curve of Paracetamol at 295 nm (R^2 = 0.9977)

Calibration curve of Paracetamol at 217 nm

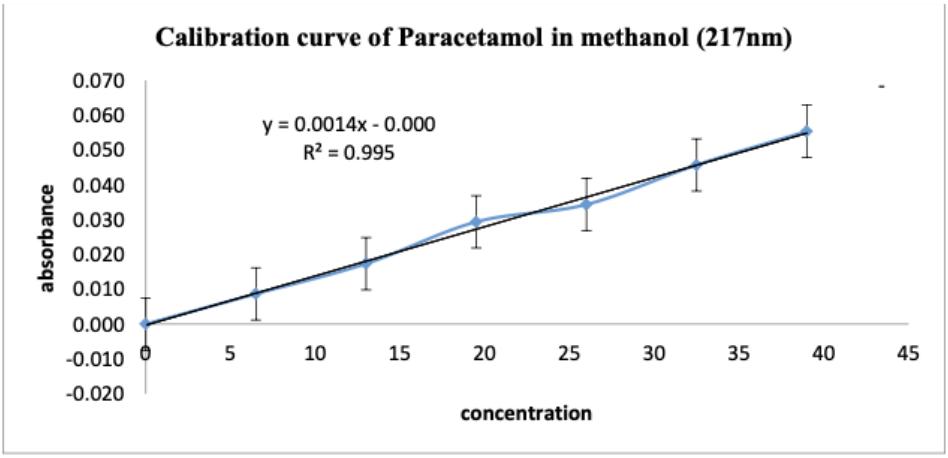

Figure 8: Calibration curve of Paracetamol at 217 nm (R^2 = 0.995)

Calibration curve of Dicyclomine HCl at 217nm

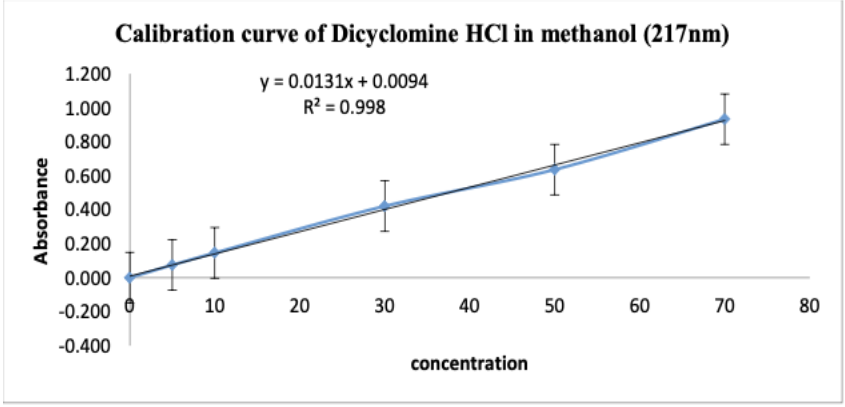

Figure 9: Calibration curve of Dicyclomine HCl in methanol at 217nm (R^2 = 0.998)

Correction on absorbance of drugs

From the overlay spectrum of Paracetamol and Dicyclomine HCl in methanol, it was observed that Dicyclomine Hydrochloride have zero absorbance at 295nm, whereas Paracetamol has significant absorbance. Thus Paracetamol was estimated directly at 295nm without interference of Dicyclomine Hydrochloride. For estimation of Dicyclomine Hydrochloride absorbance of Paracetamol were measured at 217nm using standard solution of Paracetamol 10µg/ml. The contribution of Paracetamol was deducted from the total absorbance of sample mixture at 217nm. The calculated absorbance is the corrected absorbance for Dicyclomine Hydrochloride.

Experimental design

Table 6: Results of evaluation parameters of design batches.

Formulation code	D1	D2	D3	D4	D5	D6	D7	D8	D9
Pre compression parameters									
Angle of repose (θ^0)	30.7	29.1	23.9	30.9	29.4	23.5	31.1	29.2	24.1
Bulk density (g/ml)	0.64	0.57	0.51	0.63	0.56	0.55	0.65	0.57	0.52
Tapped density (g/ml)	0.80	0.69	0.61	0.80	0.69	0.66	0.80	0.70	0.63
Carr's index (%)	20.0	17.39	16.39	21.25	18.84	16.66	18.75	18.57	17.4 6
Hausner's ratio	1.25	1.21	1.19	1.26	1.23	1.20	1.23	1.22	1.21
Post compression parameters									
Hardness (kg/cm2)	6	10	6	8	8	6	10	8	10
Weight variation (mg)	1479.5 - 1521.3	1480.7 - 1522.5	1485.1 - 1519.2	1489.5 - 1520.2	1487.5 - 1526.2	1486 - 1520	1479.5 - 1521.3	1485.7 - 1520.5	1486.2 - 1521.3
Friability (% w/w)	1.37	0.08	1.14	0.22	0.2	1.05	0.11	0.19	0.15
Disintegration time (sec.)	35	205	55	50	90	58	190	98	185
Water content by KF (%)	1.53	1.49	1.61	1.12	1.21	1.71	1.46	1.57	1.41
Carbon dioxide content(gm)	0.251	0.160	0.212	0.230	0.23	0.24	0.167	0.251	0.153
Drug content (%) Paracetamol	98.7	98.9	99.9	99.8	99.3	98.9	98.8	96.9	99.4
Drug content (%) Dicyclomine HCl	98.3	98.6	99.5	99.4	99.1	98.2	96.7	97.1	99.1

In vitro dissolution results of design batches.

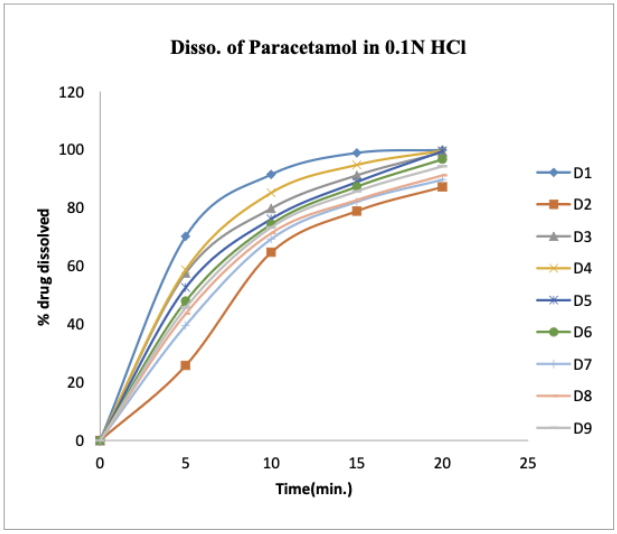

Figure 10: In-vitro dissolution profile of Paracetamol (design batches)

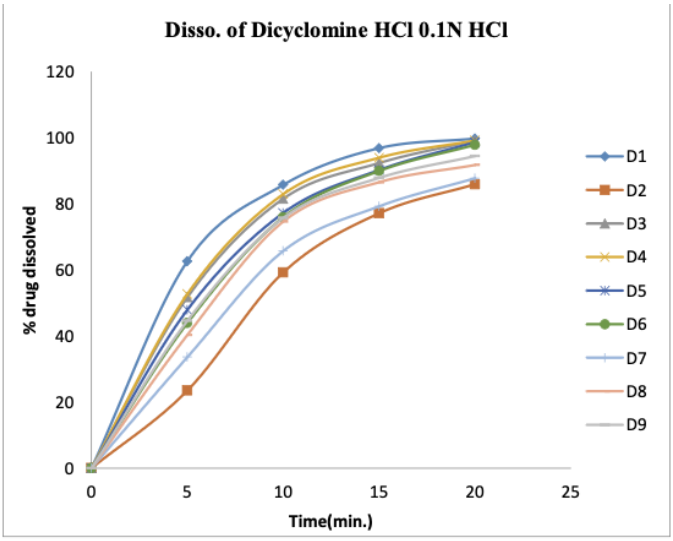

Figure 11: In-vitro dissolution of Dicyclomine HCl (design batches)

Generation of full model for selected full factorial design

The Table shows the design layout of full factorial design with response variables. The results were subjected to multiple regression analysis and equations were evolved.

Table 7: Data transformation of 3^2 full factorial design

Batch	Coded value		Actual value		Responses			
	X 1	X 2	PCM : citric acid ratio (mg)	Hardness (kg/cm2)	Dissolution of Paracetamol At 5 min. (Y_1)	Dissolution of Dicyclomine HCl At 5 min. (Y_2)	Disintegration Time (Y_3) (sec.)	Friability (Y_4) (%)
D1	1	-1	1:0.45	6	70.2	71.6	35	1.37
D2	-1	1	1:0.25	10	25.8	23.5	205	0.08
D3	0	-1	1:0.35	6	57.6	51.3	55	1.14
D4	1	0	1:0.45	8	58.7	52.7	50	0.22
D5	0	0	1:0.35	8	52.6	47.6	90	0.2
D6	-1	-1	1:0.25	6	47.9	43.9	58	1.05
D7	0	1	1:0.35	10	39.6	33.6	190	0.11
D8	-1	0	1:0.25	8	43.6	40.3	98	0.19
D9	1	1	1:0.45	10	45.7	44.6	185	0.15

Table 8: Summary output of regression for effect of X_1& X_2 on Y_1

Regression statistics for effect of X_1 and X_2 on Y_1		
Multiple R	0.991727	
Standard Error	2.670275	
Coefficients		
Coefficient	Coefficient values	P-value
b_o	52.48889	0.00012
b 1	9.55	0.003133

b_2		-10.7667		0.002207	
b_{11}		-1.28333		0.545459	
b_{22}		-3.83333		0.13532	
b_{12}		-0.6		0.683631	
Equation					
Full Model $Y_1=52.48889+9.55X_1 -10.7667X_2 -1.28333X1X_2 -3.83333X_1^2 -0.6X_2^2$					
ANOVA					
Source of Variation	df	SS	MS	Calculated F	Significance F
Regression	5	1276.864	255.3729	35.81481	0.007075
Residual	3	21.39111	7.13037		
Total	8	1298.256			

Effect of X_1& X_2 on Y_1

For response Y_1, full mathematical model was evolved by adopting multiple regression analysis. Polynomial term X_{11}, X_{22} and interaction term X_1X_2 were found insignificant as P value was more than 0.05. From the equation of the full model as shown in Table 8, it can be concluded that factor X_1 i.e. amount of citric acid increases, the dissolution of Paracetamol increases. The value of X_2 co-efficient is less that indicate X2 had significant effect on the response Y_1 i.e. hardness decreases, the dissolution of Paracetamol increases. Hardness (b_2) has minimum value which means it has inverse effect on % drug release.

Full Model Y_1=$52.48889+9.55X_1 -10.7667X_2 -1.28333X1X_2 -3.83333X_1^2 -0.6X_2^2$

The interaction term b_{12} and polynomial term b_{11}, b_{22} have p- value greater than 0.05. But as their co-efficient values are very low, their effect on dependent variables is negligible.

The result of ANOVA suggested that F calculated value of dissolution of Paracetamol at 5 min. (Y_1 response) was 35.81481 (Table 8) Tabulated F value was found to be 9.013. Calculated F value was greater than tabulated value for this dependent variable. So, selected factor has significant effect on dependent variable (Y_1 response). R^2 value is 0.991727which explains that about 99.17% of variability is expresses by this model. The effect of different levels of X_1 and X_2 on Y_1 is expressed in 3D surface response plot (Figure 13) and counter plot (Figure 12).

Generation of plots of dissolution of Paracetamol at 5 min. (Response Y_1)

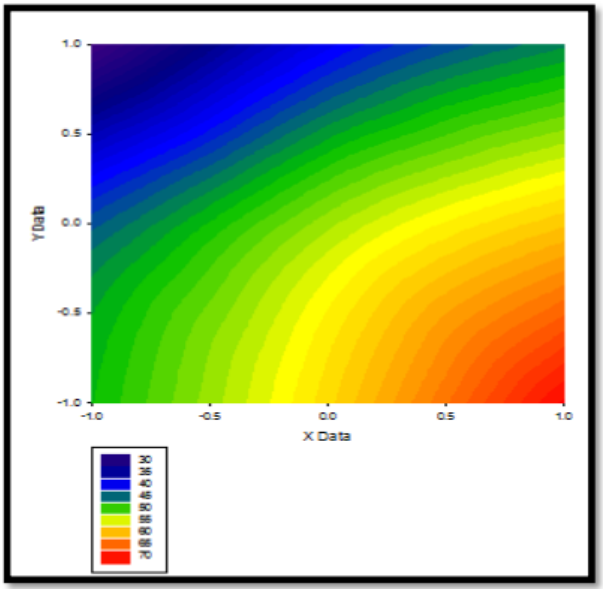

Figure 12: Contour plot of Y1

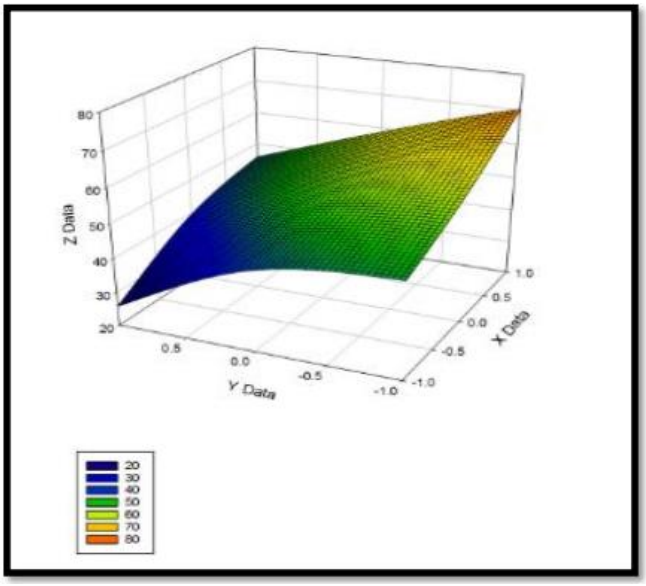

Figure 13: 3D Response surface plot of Y1

Table 9: Summary output of regression for effect of X_1& X_2 on Y_2

Regression statistics for effect of X_1 and X_2 on Y_1		
Multiple R	0.975453	
Standard Error	4.802816	
Coefficients		
Coefficient	**Coefficient values**	**P-value**
b_0	45.57778	0.001045
b 1	10.2	0.013803
b_2	-10.85	0.011631
b_{11}	1.933333	0.609
b_{22}	-2.11667	0.577282
b_{12}	-1.65	0.541372
Equation		

Full Model Y2=45.57778+10.2X1-10.85X2+1.933333X1X2-2.11667$X1^2$-1.65$X2^2$					
ANOVA					
Source of Variation	df	SS	MS	Calculated F	Significance F
Regression	5	1357.901	271.5802	11.77352	0.034686
Residual	3	69.20111	23.06704		
Total	8	1427.102			

Effect of X1& X2 on Y2

For response Y2, full mathematical model was evolved by adopting multiple regression analysis. Polynomial term X_{11}, X_{22} and interaction term X_1X_2 were found insignificant as P value was more than 0.05. From the equation of the full model as shown in Table 9, it can be concluded that factor X1 i.e. amount of citric acid increases, the dissolution Of Dicyclomine HCl increases. The value of X2 coefficient less that indicate X2 had significant effect on the response Y2 i.e. hardness decreases, the dissolution of Dicyclomine HCl increases. Hardness (b2) has minimum value which means it has inverse effect on % drug release.

Full Model Y2=45.57778+10.2X1-10.85X2+1.933333X1X2-2.11667$X1^2$-1.65$X2^2$

The interaction term b12 and polynomial term b11, b22 have p- value greater than 0.05. But as their co-efficient values are very low, their effect on dependent variables is negligible.

The result of ANOVA suggested that F calculated value of dissolution of Dicyclomine HCl at 5 min. (Y2 response) was 11.77352 (Table 9) Tabulated F value was found to be 9.013. Calculated F value was greater than tabulated value for this dependent variable.

So, selected factor has significant effect on dependent variable (Y2 response). R2 value is 0.975453 which explains that about 97.54% of variability is expresses by this model. The effect of different levels of X1 and X2 on Y2 is expressed in 3D surface response plot (Figure 15) and counter plot (Figure 14).

Generation of plots of dissolution of Dicyclomine HCl at 5 min. (Response Y_2)

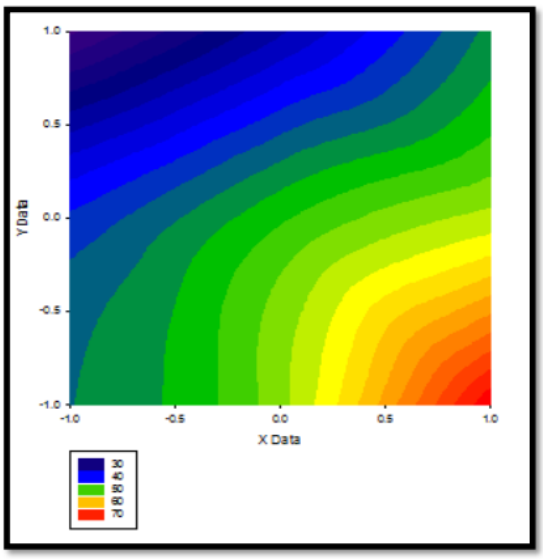

Figure 14: Contour plot of Y2

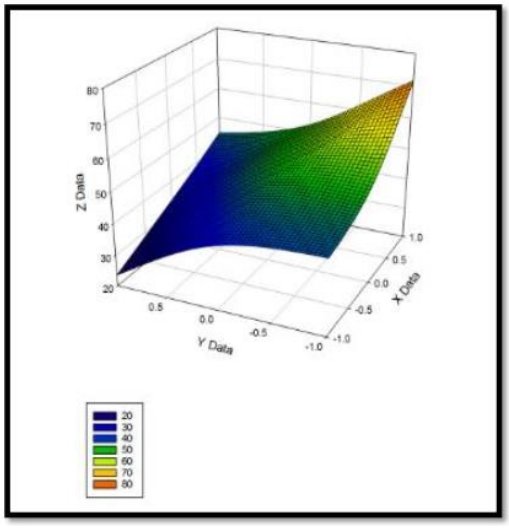

Figure 15: 3D Response surface plot of Y2

Table 10: Summary output of regression for effect of X1& X2 on Y2

Regression statistics for effect of X_1 and X_2 on Y_1		
Multiple R	0.994709	
Standard Error	11.32966	
Coefficients		
Coefficient	**Coefficient values**	**P-value**
b_0	83.66667	0.002187
b 1	-15.1667	0.046459
b_2	72	0.000576
b_{11}	-6.5	0.476557
b_{22}	42	0.013511
b_{12}	0.75	0.903052
Equation		
Full Model Y3=83.66667-15.1667X1+72X2-6.5X1X2+42$X1^2$ +0.75$X2^2$		
ANOVA		

Source of Variation	df	SS	MS	Calculated F	Significance F
Regression	5	36098.92	7219.783	56.24588	0.003647
Residual	3	385.0833	128.3611		
Total	8	36484			

Effect of X1& X2 on Y3

For response Y3, full mathematical model was evolved by adopting multiple regression analysis. Polynomial term X11 and interaction term X1X2 were found insignificant as P value was more than 0.05. From the equation of the full model as shown in Table 10, it can be concluded that factor X1 i.e. amount of citric acid increases, the disintegration time decreases. The Value of X1 Coefficient less that indicate X1 had significant effect on the response Y3 i.e. hardness decreases, the disintegration time decreases. Amount of citric acid (b1) has minimum value which means it has inverse effect on % drug release.

Full Model Y3=83.66667-15.1667X1+72X2-6.5X1X2+42$X1^2$ +0.75$X2^2$

The interaction term b12 and polynomial term b11 have p- value greater than 0.05. But as their co-efficient values are very low, their effect on dependent variables is negligible.

The result of ANOVA suggested that F calculated value of disintegration time (Y3 response) was 56.24588 (Table 10) Tabulated F value was found to be 9.013. Calculated F value was greater than tabulated value for this dependent variable.

So, selected factor has significant effect on dependent variable (Y3 response). R2 value is 0.994709which explains that about 99.47% of variability is expresses by this model. The effect of different levels of X1 and X2 on Y3 is expressed in 3D surface response plot (Figure 17) and counter plot (Figure 16).

Generation of plots of disintegration time (Response Y3)

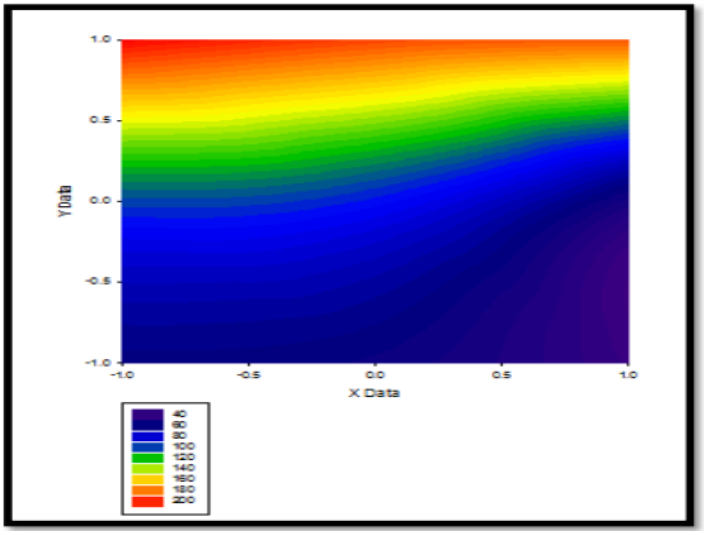

Figure 16: Contour plot of Y3

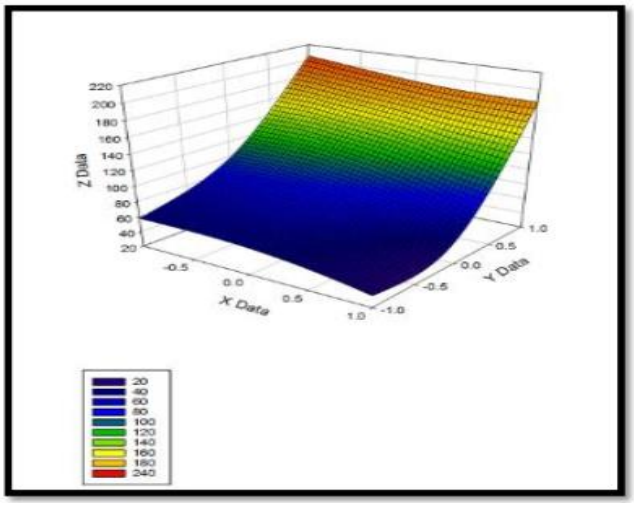

Figure 17: 3D Response surface plot of Y3

Table 11: Summary output of regression for effect of X1& X2 on Y4

Regression statistics for effect of X_1 and X_2 on Y_1					
Multiple R			0.99749		
Standard Error			0.060423		
Coefficients					
Coefficient	**Coefficient values**		**P-value**		
b_o	0.185556		0.025914		
b 1	0.07		0.065769		
b_2	-0.53667		0.000213		
b_{11}	0.026667		0.576777		
b_{22}	0.446667		0.001868		
b_{12}	-0.0625		0.130398		
Equation					
Y4=0.185556+0.07X1-0.53667X2+0.026667X1X2+0.446667 $X1^2$-0.0625$X2^2$					
ANOVA					
Source of Variation	df	SS	MS	Calculated F	Significance F
Regression	5	2.173536	0.434707	119.0677	0.0012
Residual	3	0.010953	0.003651		
Total	8	2.184489			

Effect of X1& X2 on Y4

For response Y4, full mathematical model was evolved by adopting multiple regression analysis. X1, X11 and interaction term X1X2 were found insignificant as P value was more than 0.05. From the equation of the full model as shown in Table 11, it can be concluded that factor X1 i.e. amount of citric acid increases, had no effect on Friability. The Value Of X2 Co-Efficient is less that indicate X2 had significant effect on the response Y4 i.e. Hardness decreases, Friability increases. Hardness (b2) has minimum value which means it has inverse effect on % drug release.

Y4=0.185556+0.07X1-0.53667X2+0.026667X1X2+0.446667 $X1^2$-0.0625$X2^2$

The interaction term b12 and polynomial term b1, b11 have p- value greater than 0.05. But as their co-efficient values are very low, their effect on dependent variables is negligible.

The result of ANOVA suggested that F calculated value of disintegration time (Y4 response) was 119.0677 (Table 11) Tabulated F value was found to be 9.013. Calculated F value was greater than tabulated value for this dependent variable.

So, selected factor X2 has significant effect on dependent variable (Y4 response). R^2 value is 0.99749 which explains that about 99.74% of variability is expresses by this model. The effect of different levels of X1 and X2 on Y4 is expressed in 3D surface response plot (Figure 18) and counter plot (Figure 17).

Generation of plots of friability (Response Y_4)

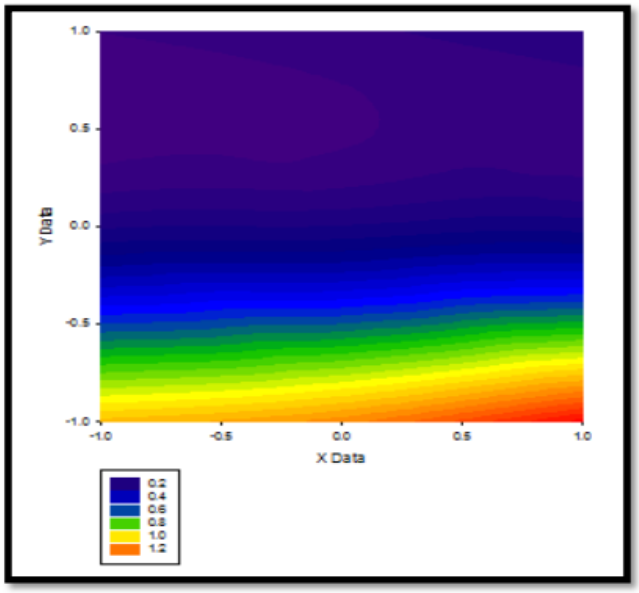

Figure 17: Contour plot of Y_4

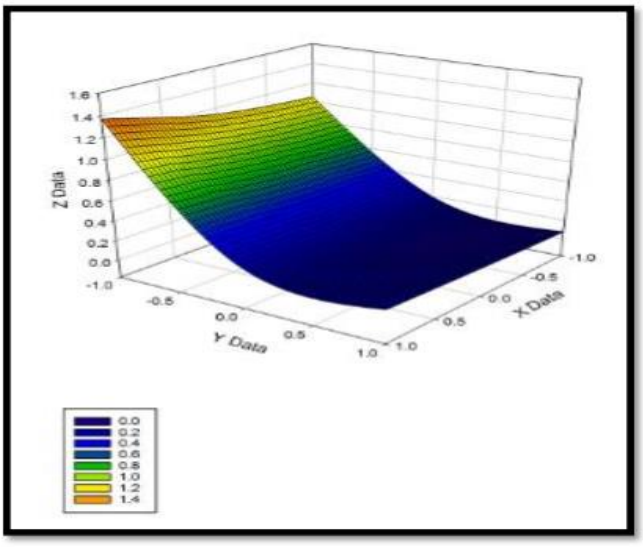

Figure 18: 3D Response surface plot of Y_4

Optimization of formulation

Table 12: Constraints

Parameters	Targeted Product Profile	
	Minimum	Maximum
Dissolution of Paracetamol at 5 min,	45%	60 %
Dissolution of Dicyclomine HCl at 5 min.	40%	55%
Disintegration time (Sec.)	<60 sec.	
Friability (%)	<1%	

Table 13: Selection of optimize batch

Batch	Y_1 (min.)	Y_2 (min.)	Y_3 (sec.)	Y_4 (%)	Overall Desirability
D1	0	0	1	0	0.25
D2	0	0	0	1	0.25
D3	1	1	1	0	0.75
D4	1	1	1	1	1
D5	1	1	0	1	0.75
D6	1	1	1	0	0.75
D7	0	0	0	1	0.25
D8	0	1	0	1	0.50
D9	1	1	0	1	0.75

Table 14: Optimization of formulation

Batch No.	PCM: citric acid ratio (mg)	Hardness (kg/cm2)	Dissolution at 5 min. (%)		DT (Sec.)	Friability (%)	Desirability
			Paracetamol	Dicyclomine HCl			
S1	1:0.45	8	58.7	52.7	50	0.22	1.00

As shown in the Table 14, one solution were presented by Microsoft Excel 2013.

Characterization of optimized batch

Primary evaluation

All the parameters which were considered for evaluating the design batches were also selected for evaluation of optimized formulation. The software has given the predicted values for all the responses which are shown in Table 2. In general, the optimized batch should be prepared and evaluated for the same parameters and then observed and predicted results are processed for determining % Bias. This should be within ±10%. As this optimized batch was from amongst the design batches, there was no need to prepare the batch. Batch no. D4 was taken for the purpose. Now it is said to be the formulation D4 and optimized batch.

Table 15: Evaluation of optimized batch

Sr.No.	Parameter	Predicted Value	Observed Value	t_{cal}
1.	Dissolution of Paracetamol at 5 min,	60.75	56.63	2.95

2.	Dissolution of Dicyclomine HCl at 5 min.	57.71	55.66	1.16
3.	Disintegration time (Sec.)	61.99	59	0.37
4.	Friability (%)	0.28	0.17	2.93

t_{tab}=3.17

Primary evaluations were done for optimized batch having $t_{cal}<t_{tab}$ are shown in Table 15. It was found that t_{cal} for all the parameters was within the limits.

Taste masking evaluation

0 = Acceptable, 1 = Slightly bitter, 2= Bitter, 3= Very bitter, 4= Extremely bitter.

Ranking of taste given by volunteer

Table 16: Taste masking evaluation for optimized batch

Volunteer	Pure Drug (Combination)	F13
1	4	0
2	4	0
3	4	0
4	4	0
5	4	0
6	4	0

Table 17: Evaluation of optimized Batch (pre compression and Post compression)

Sr.No.	Parameters	Values
1.	Angle of Repose(Ɵ)	31.1
2.	Bulk Density	0.65
3.	Tapped Density	0.80
4.	Compressibility Index	18.75
5.	Hausner's Ratio	1.23
6.	Hardness (kg/cm2)	8
7.	Weight variation (mg)	1486.5-1520.3
8.	Friability (% w/w)	0.21
9.	Disintegration time (sec.)	52
10.	Water content by KF (%)	1.11
11.	Carbon dioxide content	0.234
12.	Drug content (%) Paracetamol	99.6
13.	Drug content (%) Dicyclomine HCl	99.2

Short term accelerated stability study

Stability study of optimized batch was carried out for one month at 40°C in the lower chamber. At the end of 30 days, the dissolution studies, disintegration time and % drug content of tablets were carried out. The profiles are shown in Table 18 and Table 19. The dosage form did not show any significant difference as shown in Table.

Table 18: Comparison of % drug content of optimized batch after stability study

Parameters	Drugs	Before stability study	After stability study	%Bias
% Drug content	Paracetamol	99.8%	98.4 %	1.40
	Dicyclomine HCl	99.4%	98.1%	1.30

Disintegration time	-	55 sec.	60 sec.	-9.09

Table 19: Comparison of In-vitro drug release study of optimized batch after stability study

Time	Paracetamol		Dicyclomine HCl	
	Before stability study	After stability study	Before stability study	After stability study
0	0	0	0	0
5	58.7	54.1	52.7	47.5
10	85.2	80.2	82.9	80.4
15	94.8	91.4	93.9	91.2
20	99.7	99.1	99.1	98.9

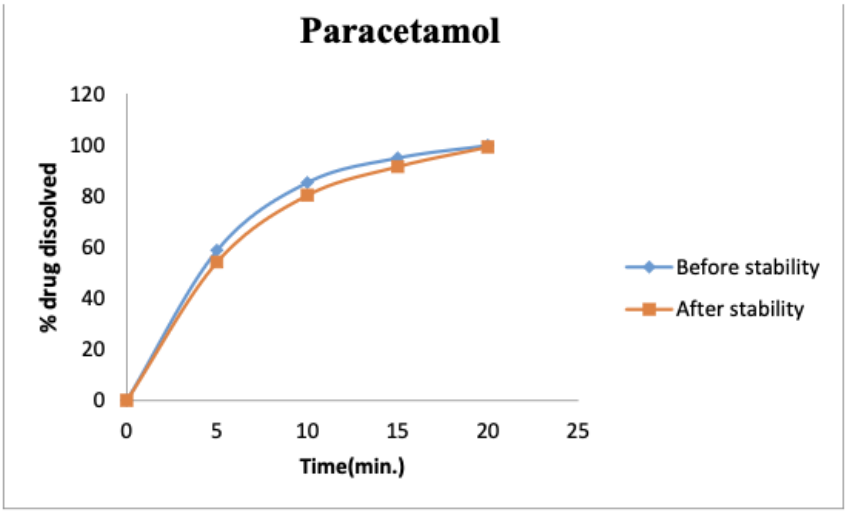

Figure 19: *In-vitro* drug release comparison for stability study (Paracetamol)

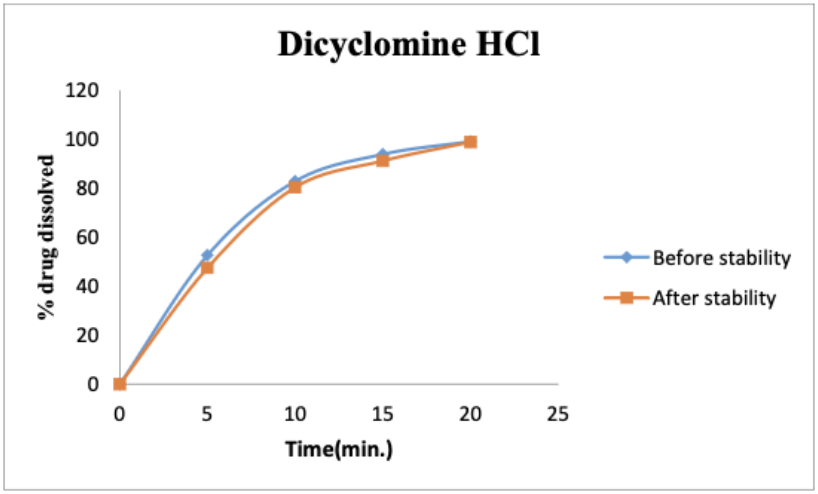

Figure 20: In-vitro drug release comparison for stability study (Dicyclomine HCl)

CONCLUSION

In present investigation, the effervescent tablets were prepared successfully by wet granulation method and taste masking of Dicyclomine HCl was done by Hydroxy Propyl Betacyclodextrin. It was found out that at optimized ratio 1:1 of Dicyclomine HCl to HP-Betacyclodextrin desire taste masking could be obtained. 3^2 full factorial design was selected to study the effect of citric acid ratio

and hardness as independent variables on the response variables % dissolution of Paracetamol and Dicyclomine HCl at 5 min., disintegration time and friability. Optimization was carried out by design expert 10 trial version which showed optimized batch having Paracetamol citric acid ratio and hardness at concentration of 1:0.45 (mg) and 8 (kg/cm^2) respectively.

Result showed optimized formulation having better post compression properties, dissolution profile, disintegration time and friability as well than other design batches.

A final formulation constructed from optimized batch showed better dissolution profile disintegration time and friability.

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