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FORMULATION, DEVELOPMENT AND OPTIMIZATION OF ORODISPERSIBLE TABLETS OF CETIRIZINE HYDROCHLORIDE

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Abstract

Aim: To Formulate, Develop and Optimize Orodispersible Tablets (ODTs) of Cetirizine Hydrochloride. Methodology: Orodispersible Tablets were prepared by direct compression method using different superdisintegrants i.e. Croscarmellose, Crospovidone and Sodium Starch Glycolate. A 3^2 full factorial design was applied to systematically optimize the drug disintegration time. The concentration of Crospovidone (X1) and concentration of Croscarmellose(X2) were selected as independent variables. The Disintegration time (Y1) and Wetting time (Y2) were selected as dependent variables. The prepared tablets were evaluated for hardness, friability, Disintegration time, Wetting time and in vitro drug release. DSC studies were conducted for drug, and drug excipient mixture for interactions if any. Optimized batch was subjected to short term stability study. Results: Cetirizine HCl ODTs prepared were found to be of good quality fulfilling all the necessities for tablets. The results indicated that concentration of Crospovidone (X_1) and concentration of Croscarmellose(X2) significantly affected the Disintegration time (Y1) and Wetting time (Y2).Drug Disintegration & Wetting time were affected by concentration of Crospovidone and concentration Croscarmellose. Disintegration time & Wetting time decreased as the concentration of Croscarmellose & Crospovidone increased. Regression analysis and numerical optimization were performed to identify the best formulation. Formulation F10 prepared with Croscarmellose (3.00) &Crospovidone (3.92) was found to be the best formulation with disintegration time 40.68sec & wetting time 33.66sec. Optimized formulation was found to be stable under accelerated stability studies. Conclusion: Orodispersible tablets of Cetirizine HCl were successfully formulated by direct compression technique with improved patient compliance & immediate onset of action.

INTRODUCTION

Drug delivery through oral route is the most common and preferred route of drug administration both for solid and liquid dosage forms. However, solid dosage forms are popular because of the ease of administration, accurate dosage, self-medication, pain avoidance, and most importantly the patient compliance[1]. Tablets and capsules are the most popular solid dosage forms. However, many people face difficulty in swallowing tablets and hard gelatin capsules. This difficulty in swallowing is called dysphasia[2]. It has been found that this problem has been encountered in all groups of patient, but especially with pediatric and geriatric populations. Thus, these conventional dosage forms result in high incidence of noncompliance and ineffective therapy with respect to swallowing specially in the case of pediatric, geriatric, or any mentally retarded persons.

Orodispersible tablets are also called as orally disintegrating tablets, mouth-dissolving tablets, rapid-dissolving tablets, fast-disintegrating tablets, fast-dissolving tablets. Recently, European Pharmacopoeia has used the term orodispersible tablets. This may be defined as uncoated tablets intended to be placed in the mouth where they disperse readily within 3 min before swallowing[3]. United States Pharmacopoeia has also approved these dosage forms as orodispersible tablets. Thus, orodispersible tablets are solid unit dosage forms like conventional tablets, but are composed of superdisintegrants, which help them to dissolve the tablets within a minute in the mouth in the presence of saliva without any difficulty of swallowing.

It offers several advantages with respect to its stability, administration without water, accurate dosing, easy manufacturing, small packaging size, and handling[4-7]. Its ease of administration in the population especially for pediatric, geriatric, or any mentally retarded persons makes it a very popular dosage form. Due to the presence of superdisintegrants, it gets dissolved quickly, resulting in rapid absorption of drug which in turn provides rapid onset of action[8].Since the absorption is taking place directly from the mouth, so, bioavailability of the drug increases[9]. Drugs present in orodispersible tablets are also not suffering from first pass metabolism. This type of drug delivery is

becoming popular day by day due to its numerous advantages.

Cetirizine HCl is a second-generation histamine H1 receptor antagonist, with a rapid onset, a long duration of activity and is used in the treatment of allergies, hay fever, angioedema and uticaria[10]. Cetirizine HCl preparations available in the market are in the form of tablet and syrup for oral administration.

Regarding liquid dosage form, the major problem is poor stability. Although, the Oral administration is the most popular route, many patients find it difficult to swallow solid unit dosage form and do not take their medication as prescribed. It is estimated that 50% of the population is affected by the problem of difficulty in swallowing, which results in high incidence of patient non-compliance and ineffective therapy[7].

To overcome such problems, Orodispersible tablets can be formulated. The Orodispersible tablets will be intended to meet the requirements of providing fast dissolution and pleasant mouth feeling to the patient. Thus, such a dosage form will not only control allergy, but it will also be convenient and acceptable to use. Such a dosage form will be beneficial to the geriatric and pediatric patients, certain young individuals with underdeveloped muscular and nervous system, mentally ill and developmentally disabled patients, non-co-operative patients, people who are bed ridden, people who do not have access to water (e.g. travelers and army men)[2].

The objective of the present study was to develop orodispersible tablets of Cetirizine HCl using Croscarmellose and Crospovidone as a superdisintegrants, Microcrystalline cellulose and spray dried mannitol as a diluent, Neotame as sweetening agent and Menthol as flavoring agent.

MATERIALS AND METHODS

MATERIALS

Cetirizine Hydrochloride and Croscarmellose were obtained from Azine Healthcare Limited, Ahmedabad, India. Crospovidone was obtained from Torrent Pharmaceuticals, Bhatt. Microcrystalline cellulose was obtained from Intas Pharmaceuticals, Ahmedabad. Spray dried mannitol was obtained from Laser Laboratories. Talc was obtained from J.C Chemicals. Magnesium Stearate was obtained from Laser Laboratories Limited.

Neotame and Spray dried Lactose were obtained from Kawarlal & Co., Chennai. All other solvents and reagents used were of analytical grade.

METHOD

Spectroscopic Analysis of Cetirizine Hydrochloride:

In the present investigation, Cetirizine Hydrochloride has been estimated by UV/Visible Spectrophotometry. The drug release study was carried out using Water as the dissolution medium.

Preparation of Standard Curve:

- For preparation of the stock solution, the drug Cetirizine Hydrochloride (100 mg) was dissolved in 100 ml of Water to obtain a stock solution (1000 µg/ml).
- Aliquots of 0.5, 1.0, 1.5, 2, 3, 4, 5 and 10 ml of solution were serially diluted with Water to 100 ml to get 5, 10, 15, 20, 25,30,35 µg/ml respectively.
- The absorbance of each solution was measured at maxima of 231 nm against Water as blank. Figure 1shows λmax of Cetirizine hydrochloride in distilled water at 231 nm.
- The assay was performed in triplicate and average absorbance was considered.

Formulation of Cetirizine Hydrochloride Tablets:

Preliminary studies were carried out to screen microcrystalline cellulose concentration and selection of superdisintegrants.

In order to investigate the effect of formulation variables on the response variables, and to predict an optimized formulation, a 3^2 factorial design was adopted. List of Independent variables and Dependent variables are mentioned in Table1.

Selection of levels for independent variables

3 levels selected: High, Intermediate and Low for both the independent variables, summarised in Table 2. Concentration of Crospovidone (X1) and Concentration of Croscarmellose(X2) were selected for different levels, based on the preliminary work done on the formulation of orodispersible tablets of Cetirizine Hydrochloride. Nine batches were prepared as per the design layout shown in the Table 3.

Preparation of Orodispersible Tablets

Orodispersible tablets were formulated using Direct Compression method. According to the formula given in Table 3, all the ingredients were passed through #60 mesh separately. The drug and microcrystalline cellulose were mixed by taking small portion of both each time and blending it to get a uniform mixture and kept aside. The above powder was mixed with the superdisintegrants Croscarmellose sodium, Crospovidone, sweetener and the lubricant. Blend was compressed using B-tooling 8 mm round, standard concave shaped punches plain on both the sides and corresponding die to get tablets of 100 mg weight on a single punch tablet machine.

EVALUATION PARAMETERS OF ORODISPERSIBLE TABLETS[11-14]

Drug-Excipient Compatibility Studies

Differential scanning calorimeter (DSC) allows the fast evaluation of possible incompatibilities, because it shows changes in the appearance, shift or disappearance of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug and drug with polymer were recorded. The samples were separately sealed in aluminum cells and set in Perkin Elmer (Pyris 1) DSC (Waltham, MA). The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 50°C to 300°C.

Hardness Testing

The crushing strength of the tablets was measured using Schleuniger hardness tester.

Friability Testing

The crushing strength test may not be the best measure of potential behavior during handling and packaging. The resistance to surface abrasion may be a more relevant parameter. A low friability value represents better tablet strength. Friability of each batch was measured in the Roche Friabilator. Ten pre-weighed tablets were rotated at 25 rpm for 4 min. The tablets were then re-weighed and the percentage of weight loss was calculated.

$$\% \text{ Friability} = \frac{\text{Loss in weight} \times 100}{\text{Initial weight}}$$

Simulated Wetting Time

Wetting time of dosage form is related with the contact angle. Wetting time of the ODT is an important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet.

Lower wetting time implies a quicker disintegration of the tablet. A piece of tissue paper folded twice was placed in a petridish with 10 cm diameter. Ten ml of water (containing water soluble dye Eosin) was added to the petridish. A tablet was placed on the surface of the tissue paper. The time required for complete wetting was measured as the wetting time.

***In Vitro* Disintegration Time**

The assessment of the in vitro disintegration profile of ODT is very important in the evaluation and the development of such formulations. So far neither the US Pharmacopoeia nor the European Pharmacopoeia has defined a specific disintegration test for ODT. Currently, it is only possible to refer to the tests on dispersible or effervescent tablets for the evaluation of ODTs disintegration capacity. The disintegration test for ODT should mimic disintegration in mouth with in salivary contents. One tablet was placed in a beaker/petridish (10 cm diameter) containing 10 ml of pH 6.8 phosphate buffer at 37 ± 0.5 °C. The time required for complete dispersion of the tablet was measured. This method embraces physiological conditions of the oral cavity, as a screening tool for developing ODT products.

***In Vitro* Dissolution Test**

USP dissolution apparatus 1 and 2 can be used for tablet dosage form. But in case of USP 1 Basket apparatus, sometimes tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles.

USP 2 Paddle apparatus is the most suitable and common choice for ODTs, with a paddle speed of 50 rpm. Typically, the dissolution of ODT is very fast when using USP monograph conditions; hence slower paddle speeds may be utilized to obtain a profile. USP Dissolution Test Apparatus Type II (Electrolab) was used with paddle stirred at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37 ± 0.5 °C, as the dissolution medium.

Since the drug absorbance is found very low from the standard curve, a single tablet is not sufficient for dissolution study. Hence, three tablets were used in each dissolution test. Aliquots of dissolution medium were withdrawn at specified intervals of time (2

min.) and analyzed for drug content (i.e. amount of drug dissolved from tablet) by measuring the absorbance at 276 nm. The volume withdrawn at each interval was replaced with fresh quantity of dissolution medium. And then Cumulative % of drug release was calculated.

Short Term Stability Study

Stability study was carried out on optimized formula. The tablets were stored at 40±2°C/75±5% RH. All the tablets were suitably packed in aluminum foil. The tablets to be tested at room conditions were kept outside in a petridish. At the end of every week the sealed tablets were opened and evaluated for different parameters. For tablets to be studied at room temperature with 75 %RH clean and dry desiccators were taken and saturated sodium chloride solution was poured inside the desiccators. The holding plate was placed inside and the desiccators were closed properly. The desiccators were allowed to get saturated for 1-2 hrs. This gave the humidity chamber of 75%RH. Then the desiccators were reopened and the aluminum foil sealed Orodispersible tablets were placed inside and the desiccators were closed. At intervals of every one week, the tablets were evaluated for different parameters for total of 1 month period.

Statistical Analysis

The mean ± standard deviation of the experiment results were analyzed using one-way analysis of variance by using Sigma Plot software, the results were subjected to multiple regression analysis and the equations were evolved.

RESULTS AND DISCUSSION

Spectroscopic Analysis of Cetirizine Hydrochloride:

Equation of the regression line from (Figure 2 & Table 4 & 5):

Absorbance = (0.026* Concentration) + (-0.005)

- R^2 =0.999448
- Slope of the Regression Line = 0.026
- Intercept of the Regression Line = -0.005

Drug-Excipient Interaction Studies:

Cetirizine HCl showed a sharp endothermic peak that corresponds to its melting range as shown in Figure 3. The DSC of the blend of Cetirizine HCl - Superdisintegrants as shown in Figure 4 showed a similar characteristic peak with decreased intensity showing drug in combination with the

excipient. The results of DSC thermograms indicate that there was no interaction between Cetirizine HCl and superdisintegrants and confirmed the drug-excipient compatibility. Hence, DSC studies did not reveal any significant drug-polymer interaction. Cetirizine HCl was found to be compatible with superdisintegrants.

Post – compression parameters

All the prepared tablets showed acceptable pharmaceutical properties as shown in Table 6.

***In Vitro* Dissolution Test**

From the dissolution profile of all the batches it was found that there was fast drug release at initial state of dissolution as shown in Table 7. The initial rise in the drug release was dependent upon the effectively and concentration of superdisintegrants.

Statistical Analysis

Data transformation of a 3^2 Factorial Design is given in Table 8. The data transformation simplifies the calculations for model development. The data generated by the experimental design was utilized for drawing contour plot, to obtain an optimized region within the factorial space, and thereby produce an optimized formulation.

Summary output of regression analysis for effect of X1 and X2 on Y1 is shown in Table 9. Coefficients with one factor represent the effect of that particular factor on responses while the coefficients with more than one factor and those with second order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively. Positive sign in front of the terms indicates synergistic effect while negative sign indicates antagonistic effect upon the responses. For response Y1 reduced mathematical model was evolved omitting the insignificant terms ($p>0.05$) by adopting multiple regression analysis. The main effect X1, X2 & polynomial term X22 and were found significant as P value was less than 0.05. X22

From the eq. of the reduced model as shown, it can be qualitatively concluded that X1 had the largest antagonistic effect on the response of Y1, which indicated that X1 was a more important parameter to regulate Disintegration time, while the

antagonistic effect of the quadratic term of X2 was comparatively smaller.

Summary output of regression analysis for effect of X1 and X2 on Y2 is shown in Table 10. For response Y2 (wetting time) reduced mathematical model was evolved omitting the insignificant terms ($p>0.05$) by adopting multiple regression analysis. The main effect X1 and X2, polynomial term X12 and X22 were found significant as P value was less than 0.05. The interaction term X1X2 was found insignificant as P value was more than 0.05.

Three-Dimensional Response Surface Curve (Contour Plot) for Disintegration time in Figure 5shows the effect of concentration of Crospovidone (X1) and concentration of Croscarmellose on disintegration time (Y1). As concentration of X1 and X2 increases, the value of response Y1 decreases and Three-Dimensional Response Surface Curve (Contour Plot) for wetting time in Figure 6 shows the effect of concentration of Crospovidone (X1) and concentration of Croscarmellose on wetting time (Y2). As concentration of X1 and X2 increases, the value of response Y1 decreases.

Optimization of the Formulation

The optimization was performed by superimposing the contour plots of the response Y_1 and Y_2 and locating the region of optimal surface common to both the plots as shown in Figure 7.

The overlay plot of the responses is shown in Figure 8, generates an optimized area, as per the desired criteria. The disintegration time (X1) was set to less than 40 sec and the wetting time (X2) values less than 35sec.These specifications satisfy the requirements of an Orodispersible tablet for rapid disintegration and sufficient mechanical strength. Based on these requirements a checkpoint batch was formulated and evaluated (Table 11).

Hence, it can be concluded that by adopting a systemic formulation approach, one can reach to an optimum point in the shortest time with minimum efforts.

Short term Stability Studies

The results of stability study as shown in Table 12, indicates no significant change in the tablet properties except a slight increase in disintegration time. Hence it can be concluded that the formulated Orodispersible tablets are stable under appropriate storage conditions.

CONCLUSION

The present work was designed to develop Orodispersible tablets that disintegrate rapidly within the oral cavity hence providing an ease of administration along with rapid onset of action and increased bioavailability. Of the various approaches used to formulate Orodispersible tablets, the simple and cost effective method of disintegrant addition was selected. Croscarmellose sodium, Crospovidone and Sodium Starch Glycolate were chosen as superdisintegrants and also their efficacy was compared.

Cetirizine HCl is an antihistaminic drug. Antihistamines work by preventing the effects of a substance called histamine, which is produced by the body. Cetirizine HCl is used to relieve or prevent the symptoms of hay fever and other types of allergy. Orodispersible tablets were formulated with an aim of reducing the lag time and providing faster onset of action to relieve immediately allergic attacks.

The experiments were designed to produce Orodispersible tablets with hardness of 30-40 N, % friability values less than 0.60% and minimum disintegration time that is less than 60 seconds. The tablet disintegration yields a fine dispersion with pleasant mouth feel.

Orodispersible tablets were prepared following direct compression method. Preliminary studies (with concentration of 1-5 %) indicated the disintegration efficacy in following order: Crospovidone >Croscarmellose >Sodium starch glycolate. A combination of the two best superdisintegrants was tried to provide both the swelling and capillary action for disintegration of tablets and thereby improve the efficacy, to meet the set criteria for tablet properties.

To investigate the effect of formulation variables on the response variables and to predict an optimized formulation, it was decided to apply an experimental design. A 3^2 factorial design was employed for the preparation of the tablets possessing optimal characteristics. The % of Crospovidone (X1) and % of Croscarmellose (X2) were selected as independent variables. The disintegration time (Y1) and wetting time (Y2) were selected as dependent variables. The optimized batch F10 containing 3.00% Croscarmellose and

3.92% Crospovidone, produced tablets with Hardness 39 N, 0.63 % Friability, Wetting time 33.66 and Disintegration time 40 seconds, hence could meet the desired specifications. Determination of drug release from the disintegrated tablets was carried out in a USP-II paddle apparatus containing 900 ml of water as dissolution medium. The sample was taken after 5 min. and absorbance was measured using UV-Visible Spectrophotometer.

Short-term stability studies on the formulation indicated that there are no significant Changes in drug content and in vitro disintegration time.

In conclusion the present study underlines the importance of formulation and processing variables. By using optimum amount of superdisintegrants, it is possible to prepare Orodispersible tablets of Cetirizine HCl with acceptable mechanical strength and rapid disintegration, to provide desired drug release property and pleasant mouth feel.

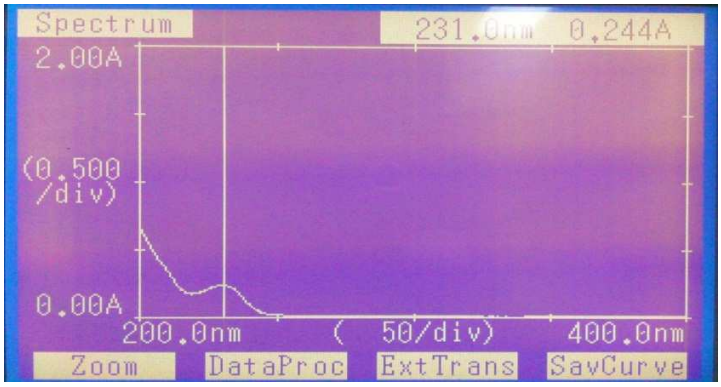

Figure 1 Photographic image showing λ_{max} of Cetirizine hydrochloride in distilled water at 231nm

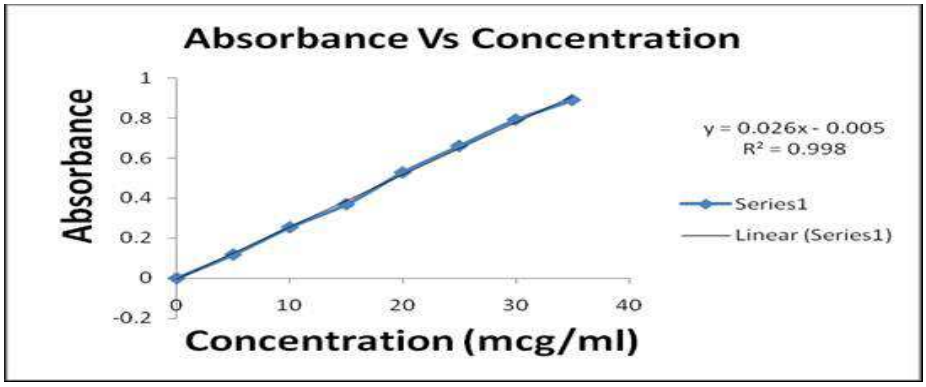

Figure 2 Standard curve of the UV analysis of Cetirizine Hydrochloride

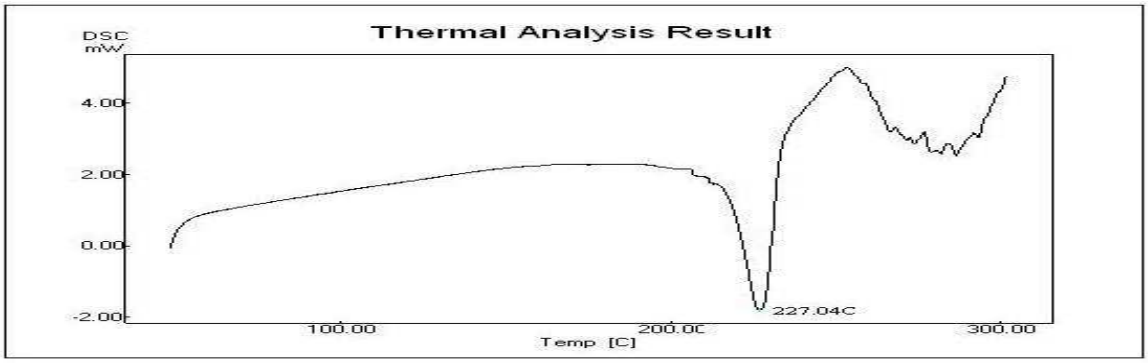

Figure 3 DSC thermogram of Cetirizine Hydrochloride

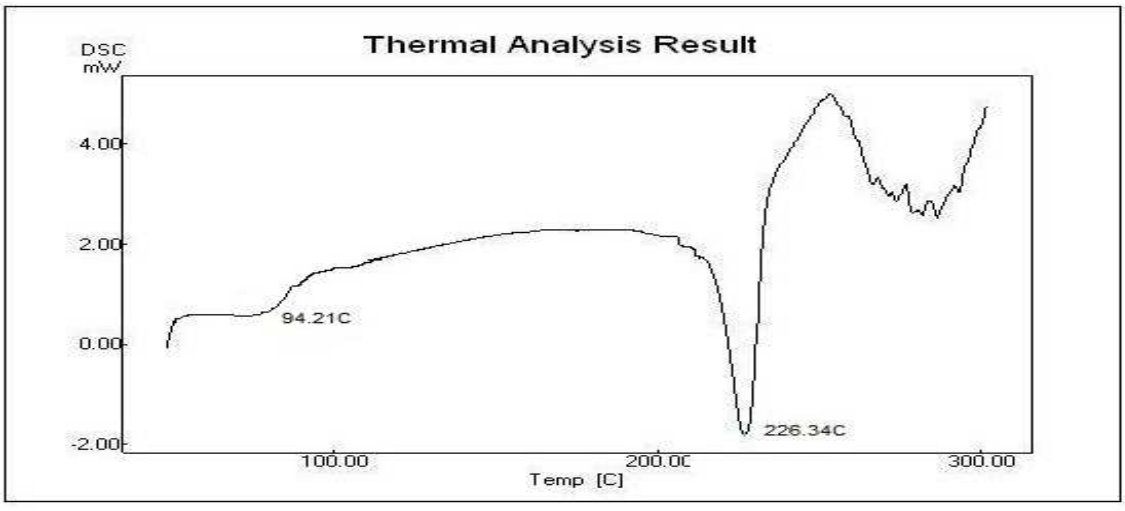

Figure 4 DSC thermogram of a mixture of Cetirizine Hydrochloride and Excipients

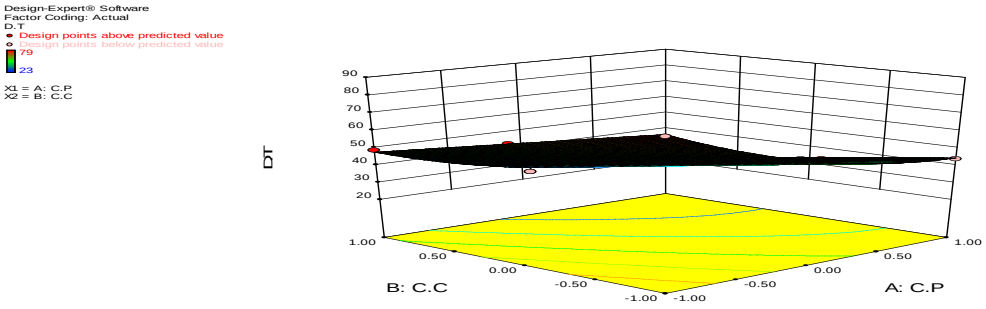

Figure 5 Three-Dimensional Response Surface Curve (Contour Plot) for Disintegration time

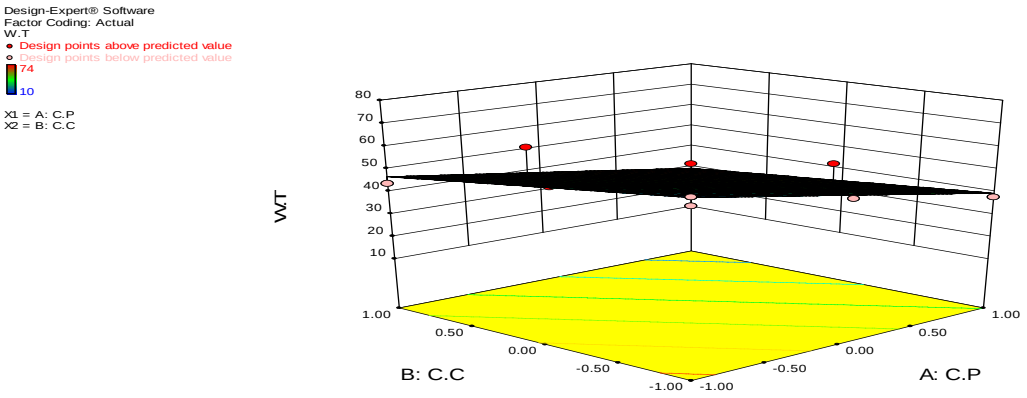

Figure 6 Three-Dimensional Response Surface Curve (Contour Plot) for Wetting time

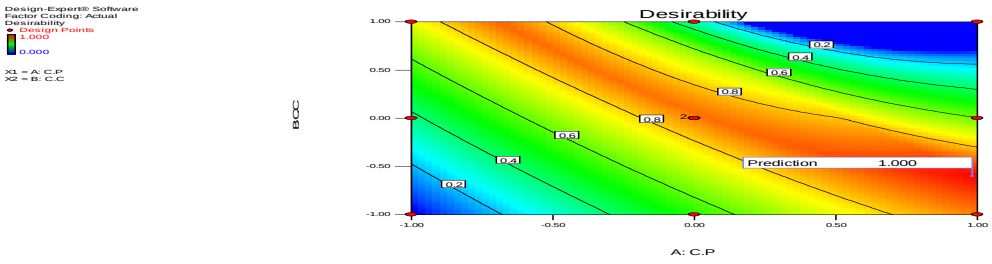

Figure 7 Desirability Plot of Response Variables

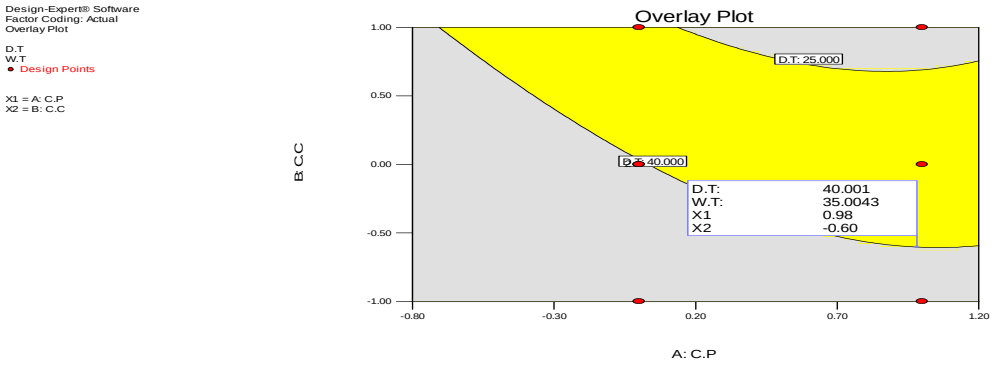

Figure 8 Overlay plot of response variable

Table 1
Selection of Independent variables and Dependent variables

Independent Variables		Dependent Variables	
X1	X2	Y1	Y2
Concentration of Crospovidone	Concentration of Croscarmellose	Disintegration time	Wetting time

Table 2
Selection of levels for independent variables

Independent Variables	Levels		
	Low	**Intermediate**	**High**
	-1	0	1
X1 (%)	0	2	4
X2 (%)	1	3	5

Table 3
Design Layout of factorial design batches

Formulation Ingredients	Formulation Batch Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
CETIRIZINE HCl	10	10	10	10	10	10	10	10	10
Croscarmellose	1	3	5	1	3	5	1	3	5
Crospovidone	0	0	0	2	2	2	4	4	4
Avicel PH 101	10	10	10	10	10	10	10	10	10
Magnesium stearate	1	1	1	1	1	1	1	1	1
Neotame	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Mint Flavor	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Talc	2	2	2	2	2	2	2	2	2
Spray dried mannitol up to…	100	100	100	100	100	100	100	100	100

Note:All quantities are expressed in mg

Table 4
Results of spectrophotometric analysis of Cetirizine Hydrochloride in water

Sr. No.	Concentration (µg/ml)	Absorbance			Average Absorbance
		Set 1	Set 2	Set 3	
1	0	0	0	0	0
2	5	0.118	0.112	0.124	0.118
3	10	0.244	0.264	0.255	0.254
4	15	0.375	0.378	0.344	0.369
5	20	0.534	0.536	0.524	0.528
6	25	0.640	0.680	0.662	0.660
7	30	0.791	0.794	0.791	0.791
8	35	0.886	0.892	0.888	0.889

Table 5
Results of Weighted Regression

Summary Output	
Multiple R	0.999724
R Square	0.999448
Adjusted R Square	0.856591
Standard Error	0.013597
Observations	8

Table 6
Evaluation Parameters

Test Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness (N)	36	38	35	39	41	40	36	35	39
Friability (%)	0.53	0.47	0.58	0.52	0.48	0.45	0.54	0.51	0.36
Wetting time (sec)	74	70	44	49	38	31	38	42	12
Disintegration time (sec)	79	64	49	56	41	24	44	32	21

Table 7
***In Vitro* Dissolution**

Batch Code	Time	Absorbance	conc. (µg/ml)	conc. (µg/5ml)	conc. (µg/900ml)	% drug released after 5min
F1	5min	0.234	9.915254237	49.57627119	8923.728814	89.23729
F2	5min	0.248	10.50847458	52.54237288	9457.627119	94.57627
F3	5min	0.259	10.97457627	54.87288136	9877.118644	98.77119
F4	5min	0.222	9.406779661	47.03389831	8466.101695	84.66102
F5	5min	0.231	9.788135593	48.94067797	8809.322034	88.09322
F6	5min	0.239	10.12711864	50.63559322	9114.40678	91.14407
F7	5min	0.215	9.110169492	45.55084746	8199.152542	81.99153
F8	5min	0.219	9.279661017	46.39830508	8351.694915	83.51695
F9	5min	0.221	9.36440678	46.8220339	8427.966102	84.27966

Table 8
Data transformation of a 3^2 Factorial Design

Batches	Real Values		Transformed Values		Response	
	% Crospovidone	% Croscarmellose	X1	X2	DT	WT
F1	0	1	-1	-1	79	74
F2	0	3	-1	0	64	70
F3	0	5	-1	1	49	44
F4	2	1	0	-1	56	49
F5	2	3	0	0	41	38
F6	2	5	0	1	24	31
F7	4	1	1	-1	44	38
F8	4	3	1	0	32	42
F9	4	5	1	1	21	12

Note: DT= Disintegration time, %F= % Friability

Table 9
Summary output of regression analysis for effect of X1 and X2 on Y1

Regression statistics		
Multiple R	0.997013	
R Square	0.994035	
Adjusted R square	0.986579	
Standard error	2.036132	
Observations	9	
	Coefficients	
Coefficient	**Coefficient value**	**P-value**
b_0	88.125	9.33E-06
b_1	-17.4375	0.000394
b_2	-8.04167	0.0018764
b_{11}	2	0.003879
b_{22}	-7.1E-16	1
b_{12}	0.5625	0.091619
Equation		
Full Model		
$Y_1 = 88.13–17.44X_1 -8.04 X_2 + 2.00X_1^2 +0X_2^2 + 0.56 X_1X_2$		
Reduced Model		
$Y_1 = = 88.13–17.44X_1 -8.04 X_2 +2.00X_1^2$		

Table 10
Summary output of regression analysis for effect of X1 and X2 on Y2

Regression statistics		
Multiple R	0.964394	
R Square	0.930056	
Adjusted R square	0.842626	
Standard error	7.284197	
Observations	9	
Coefficients		
Coefficient	Coefficient value	P-value
b_0	43.40	0.003181
b_1	-16.33	0.03971
b_2	-12.67	0.04123
b_{11}	2.142857	0.146671
b_{22}	-1.85714	0.194278
b_{12}	0.125	0.89744
Equation		
Full Model		
$Y_2 = 43.40–16.33X_1 -12.67 X_2$		
Reduced Model		
$Y_2 =43.40–16.33X_1 -12.67 X_2$		

Table 11
Formulation and Evaluation of checkpoint batch F10

FORMULATION INGREDIENT	FORMULATION BATCH F10
CETIRIZINE HCl	10
Croscarmellose	3.00
Crospovidone	3.92
Avicel PH 101	30
Neotame	0.75
Magnesium stearate	1
Talc	2
Spray dried mannitol……to……	100
EVALUATION	
Hardness (N)	39
Weight variation	99.8±0.50
Content uniformity	100.43%
Friability (%)	0.63
Wetting time (sec)	33.66
Disintegration time (sec)	40.68
Drug release (%) in 5min	91.72

Table 12
Results of short term stability study

No. of weeks	Hardness (N)	Friability (%)	Disintegration time (sec)	% Drug Content
0	**36**	**0.49**	**39.33**	**97.10**
1	**36**	**0.45**	**40.08**	**97.10**
2	**38**	**0.43**	**40.32**	**97.10**
3	**41**	**0.43**	**41.43**	**97.10**
4	**41**	**0.39**	**42.58**	**97.10**

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