Evaluation of Drug Release Kinetics from Mouth Dissolving Cinnarizine Tablets using Mixture of Natural and Synthetic Superdisintegrant

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ABSTRACT

Aim: The aim of current study is to evaluate the drug release kinetics from Mouth dissolving Cinnarizine tablets using natural and synthetic i.e superdisintegrant *Lepidium Sativum* seed mucilage and sodium starch glycolate . Computer-aided optimization technique, using a central composite design (CCD), was employed to investigate the effect of independent variable i.e., amount of *lepidium sativum* seed mucilage and amount of sodium starch glycolate on the various response variables *viz*., disintegration time, wetting time, water absorption ratio and cumulative percentage drug release (12 min).

Study Design: Mouth dissolving tablets of cinnarizine were formulated using different concentrations of superdisintegrant (*Lepidium sativum* seed mucilage as natural superdisintegrant and sodium starch glycolate as synthetic superdisintegrant). Face centered central composite design (FCCCD) was used to optimize the effective concentration of superdisintegrant. The tablets were evaluated for Weight variation, Thickness, Hardness, Friability, Disintegration time ,Wetting time, Drug content, Water absorption time, *in-vitro* dissolution for drug release studies and mathematical modeling with drug release kinetics of optimized batch.

Keywords: Superdisintegrant, *Lepidium sativum*, sodium starch glycolate, Cinnarizine and Face centered central composite design (FCCCD).

Introduction

Oral Drug Delivery Systems

Drugs can be administered via many different routes to produce systemic pharmacological effects. Among all the dosage form that are administered orally, Tablets are popular because of ease of administration, accurate dosing, self-medication, pain avoidance and most importantly the patient compliance[2-4].

Mouth Dissolving Tablets[1]

Mouth dissolving drug delivery systems are a novel drug delivery systems which combine the advantages of both liquid and conventional tablet formulations, and at the same time, offer added advantages over both the traditional dosage forms. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation[5]. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach[6]. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[7]. Mouth dissolving drug delivery system is especially designed for dysphagic, geriatric, pediatric, bed-ridden, travelling and psychotic patients who are unable to swallow or refuse to swallow conventional oral formulations. They simply vanish when placed in the mouth, so cannot be hidden in mouth by psychotic patients[5]. Drug candidates for delivery as MDT dosage form must have ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2), able to permeate oral mucosal tissue, partially non-ionized at the oral cavities pH and have good stability in water and mucosa.

Superdisintegrants

Superdisintegrants are the agents included in tablet formulations to promote moisture penetration and dispersion of the matrix of the dosage form in

dissolution fluids. The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet[8]. Ideally, superdisintegrants should not only produce stronger tablets but also, disintegrate the tablet in the oral cavity in less than 30 seconds[9]. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit[10].

PREPARATION OF MOUTH DISSOLVING TABLETS

Materials Used:

Cinnarizine was obtained from Wallace pharmaceuticals Pvt. Ltd., Goa, *Lepidium Sativum* from Kurukshetra Local Market, Sodium Starch Glycolate from Ranbaxy Laboratories Pvt. Ltd., Gurgaon, Microcrystalline Cellulose from Maple Biotech Pvt. Ltd., Pune, Mannitol from RFCL Ltd., New Delhi and Magnesium Stearate, Talc, Sodium Saccharin, Potassium Dihydrogen Phosphate, Sodium Hydroxide, Hydrochloric Acid, Isopropyl Alcohol, PVP K-30 from S.D. Fine-Chem Ltd., Mumbai.

Direct compression method:

Cinnarizine mouth dissolving tablets were prepared by direct compression method through wet granulation using PVP K-30 in isopropyl alcohol (10% w/w) as a binder. A total number of thirteen formulations were prepared as per the standard experimental design protocol. In these formulations, microcrystalline cellulose was used as directly compressible material, mannitol as diluent and magnesium stearate as lubricant. All ingredients were weighed accurately and passed through 60-mesh sieve separately and collected. They were mixed together and sufficient quantity of alcoholic solution of PVP was added and mixed to form a coherent mass. Wet mass was granulated using sieve no. 12.

Granules were re-granulated after drying in hot air oven at 60^{o}C through sieve no. 16 and evaluated for granular properties. Dried granules were mixed with magnesium stearate and talc and finally compressed into tablets by using 5mm punch using fluid pack 8 station mini rotary tablet punching machine (4D+4B type)[5-7].

In this approach, mouth dissolving tablets of cinnarizine were formulated using different concentrations of mixture of natural superdisintegrant i.e *Lepidium Sativum* seed mucilage and synthetic superdisintegrants i.e Sodium Starch Glycolate.

EXPERIMENTAL DESIGN FOR FORMULATIONS CONTAINING MIXTURE OF NATURAL AND SYNTHETIC SUPERDISINTEGRANT

Two independent variables, the amount of Mucilage (X_1) and Sodium starch glycolate (SSG) (X_2) were studied at 3 levels each. The central points (0, 0) were studied in quintuplicate. All other formulation and processing variables were kept invariant throughout the study. Disintegration time (DT), wetting time (WT), water absorption ratio (WAR) and cumulative % drug release (%CDR) were taken as the response variables. Tables 1 and 2 summarize an account of the 13 experimental runs studied, their factor combinations and the translation of the coded levels to the experimental units employed during the study.

Table 1: Factor combination according to CCD influencing DT, WT, WAR, % CDR

Batch code	Coded factor levels	
	X_1	X_2
C_1	-1	-1
C_2	-1	0
C_3	-1	+1
C_4	0	-1
C_5	0	0
C_6	0	+1
C_7	+1	-1

C_8	+1	0
C_9	+1	+1
C_{10}	0	0
C_{11}	0	0
C_{12}	0	0
C_{13}	0	0

Table 2 : The amount of factors selected for optimization in different levels

Coded level	-1	0	+1
X_1: Mucilage (mg)	1.50	3.75	6.00
X_2: SSG (mg)	1.50	3.75	6.00

Results and Discussion:

Evaluation of Mouth Dissolving Tablets Prepared by Direct Compression Method:
The formulated tablets were evaluated for Weight variation, Thickness, Hardness and Friability and were found in the range prescribed by I.P.

Disintegration time (DT), Wetting time (WT) and Water absorption ratio (WAR)

Batch code	Disintegration Time (sec)	Wetting Time (sec)	Water Absorption Ratio (%)
C_1	116	89	65.02
C_2	112	72	76.32
C_3	72	65	83.24
C_4	105	70	78.36
C_5	71	62	83.51
C_6	69	59	85.45
C_7	70	63	84.21
C_8	67	57	86.21
C_9	65	47	94.48
C_{10}	72	64	83.59
C_{11}	73	62	84.32
C_{12}	74	63	84.23
C_{13}	72	63	84.09

Table 3 : DT, WT and WAR of C_1-C_{13} batches for direct compression method

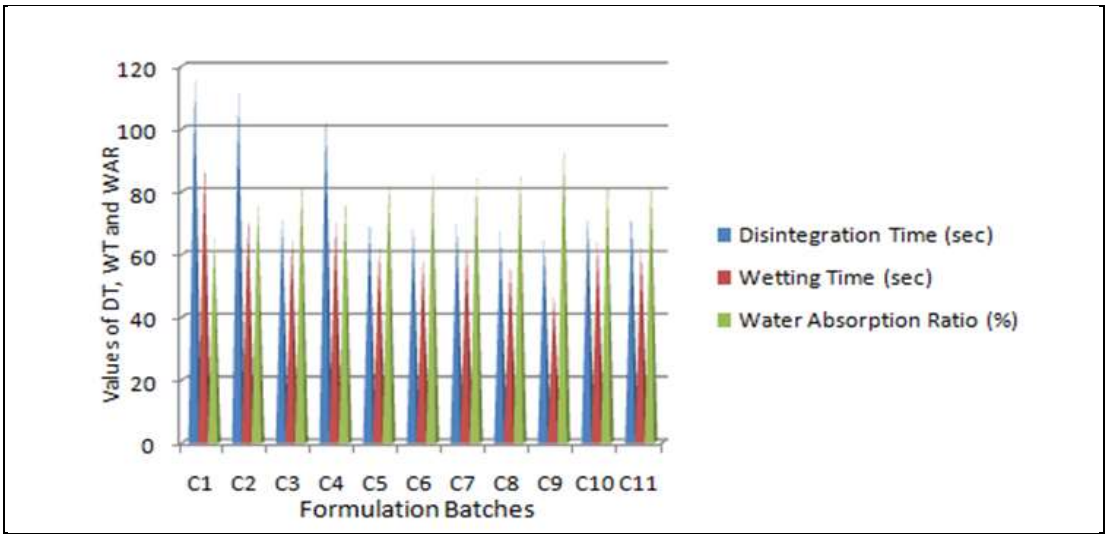

Fig. 1: A column chart comparing DT, WT and WAR of C_1-C_{13} batches for direct compression method.

In-vitro drug release study:

The drug release rate was studied using USP dissolution apparatus II (Paddle type). Phosphate buffer of pH 6.8 was used as medium. The cumulative percent of drug release at different time intervals are shown along with their column chart representation in fig. 2-4.

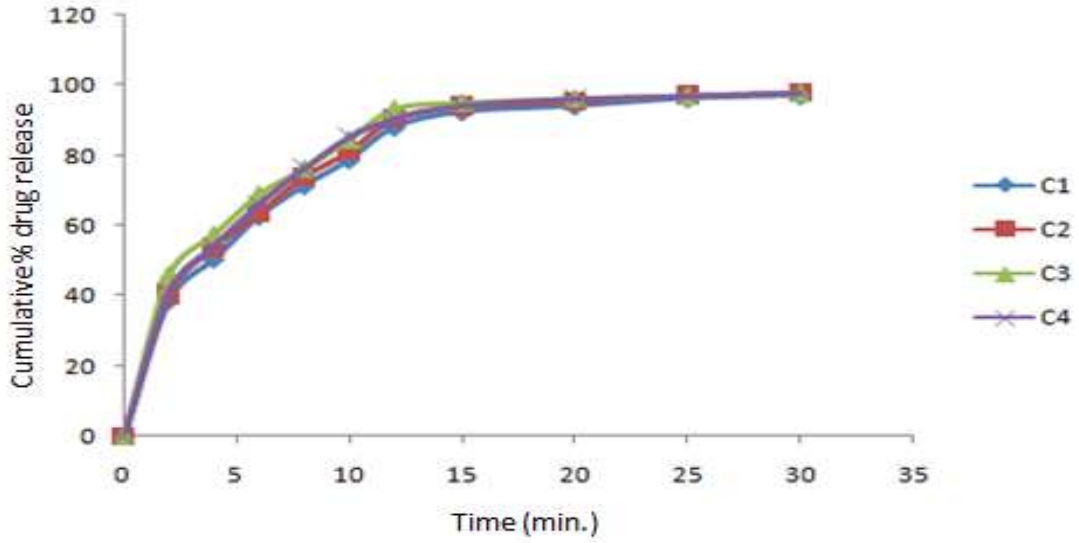

Fig. 2 : Comparative dissolution profile of batches C_1-C_4.

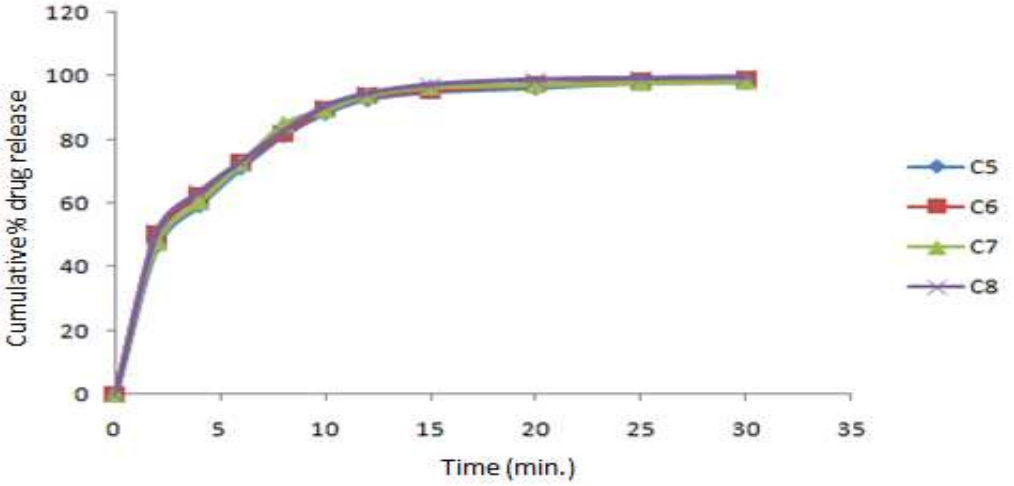

Fig. 3 : Comparative dissolution profile of batches C_5-C_8.

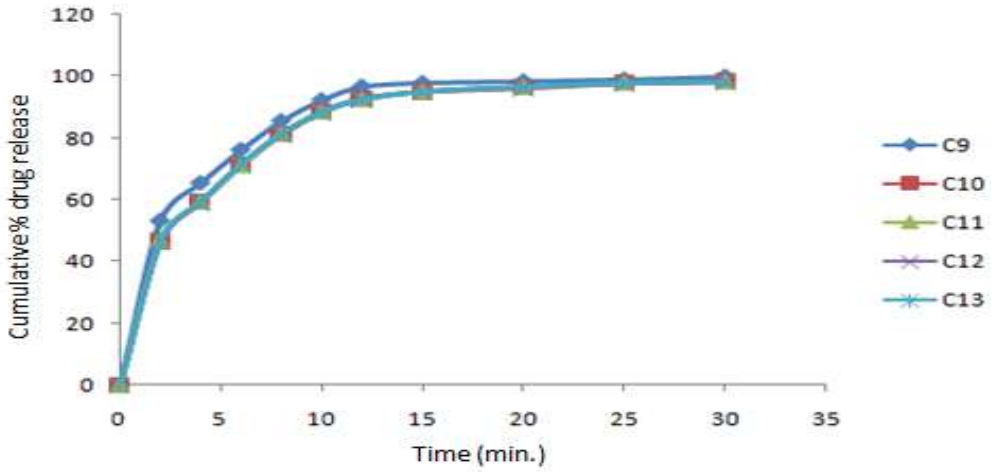

Fig. 4: Comparative dissolution profile of batches C_9-C_{13}.

Optimization of Formulations Using Face Centered Central Composite Design (FCCCD)

Response Surface Methodology (RSM) for Direct Compression Method

Response surface methodology allows understanding of the behavior of the system by demonstrating the contribution of the independent variables is shown in table 4.

Table 4: Response parameters of various mouth dissolving formulations prepared as per the experimental design

Batch code	Mucilage (mg)	SSG (mg)	DT (sec)	WT (sec)	WAR (%)	% CDR
C_1	1.50	1.50	116	89	65.02	87.95

C_2	1.50	3.75	112	72	76.32	90.34
C_3	1.50	6.00	72	65	83.24	93.30
C_4	3.75	1.50	105	70	78.36	90.45
C_5	3.75	3.75	71	62	83.51	92.71
C_6	3.75	6.00	69	59	85.45	93.72
C_7	6.00	1.50	70	63	84.21	94.03
C_8	6.00	3.75	67	57	86.22	94.53
C_9	6.00	6.00	65	47	94.48	96.67
C_{10}	3.75	3.75	72	64	83.59	92.84
C_{11}	3.75	3.75	73	62	84.32	93.06
C_{12}	3.75	3.75	74	63	84.23	92.23
C_{13}	3.75	3.75	72	63	84.09	92.91

ANOVA (Analysis of Variance)

Analysis of variance of the responses indicated that response surface models developed for disintegration time, wetting time, water absorption ratio and cumulative percentage drug release (12 min) were significant and adequate, without significant lack of fit. Influence of formulation variables on the response factors is shown in table 5.

Table 5: ANOVA for response surface quadratic model

Response factor	Model F-value	P-value	Lack of fit	Response factor
			F-Value	Prob > F
DT	4.67	0.0589	111.91	0.0005
WT	59.56	< 0.0001	19.60	0.0062
WAR	40.55	< 0.0001	70.32	0.0005
% CDR	8.69	0.0163	2.99	0.1556

Model Summary Statistics

Model summary statistics for the selected quadratic models are recorded in table 6. From this study, it was observed that R^2 value is high for all responses

Table 6 : Model summary statistics for response surface quadratic model

Response factor	Std. Dev.	R^2	Adjusted R^2	Predicted R^2
DT	2.48	0.8130	0.7507	0.6157
WT	2.92	0.9225	0.9071	0.8290
WAR	2.44	0.8902	0.8683	0.7626
% CDR	0.46	0.9660	0.9546	0.8846

Mathematical modeling

Mathematical relationship between dependent and independent variables were analysed by polynomial equations which are as follows –

$$\mathbf{DT = 74.28 - 26.50\ X_1 - 5.0\ X_2 - 0.25\ X_1X_2 + 18.53\ X_1^2 + 0.034\ X_2^2} \quad \mathbf{(1)}$$

$$\mathbf{WT = 64.69 - 16.50\ X_1 - 4.33X_2} \quad \mathbf{(2)}$$

$$\mathbf{WAR = 82.30 + 11.56\ X_1 + 3.29\ X_2} \quad \mathbf{(3)}$$

$$\mathbf{\%\ CDR = 93.32 + 4.33\ X_1 + 1.21\ X_2 + 0.033\ X_1X_2 - 0.36\ X_1^2 - 0.12\ X_2} \quad \mathbf{(4)}$$

From the values obtained for main effects of each factor, it was revealed that *Lepidium sativum* seed mucilage individually has more pronounced effect on the values of disintegration time, wetting time, water absorption ratio and cumulative percentage drug release respectively.

Response surface analysis

Disintegration time and Wetting time

From the (1) and (2) polynomial equations of DT and WT, it was found out that the coefficients of X_1 and X_2 bear a negative sign. Therefore, increasing the concentration of either seed mucilage or SSG decreases the DT and WT. However the effect of seed mucilage seems to be more pronounced as compared with that of SSG in both cases. This was further proved by response surface plots in fig. 5-8.

Water absorption ratio and Percentage cumulative drug release

From the (3) and (4) polynomial equations of WAR and %CDR, it was found out that the coefficients of X_1 and X_2 bear a positive sign. Therefore, concentration of both seed mucilage and SSG has a positive effect on WAR and %CDR. However the effect of seed mucilage seems to be more pronounced as compared with that of SSG in both cases. This was further confirmed by response surface plots in fig. 9-12.

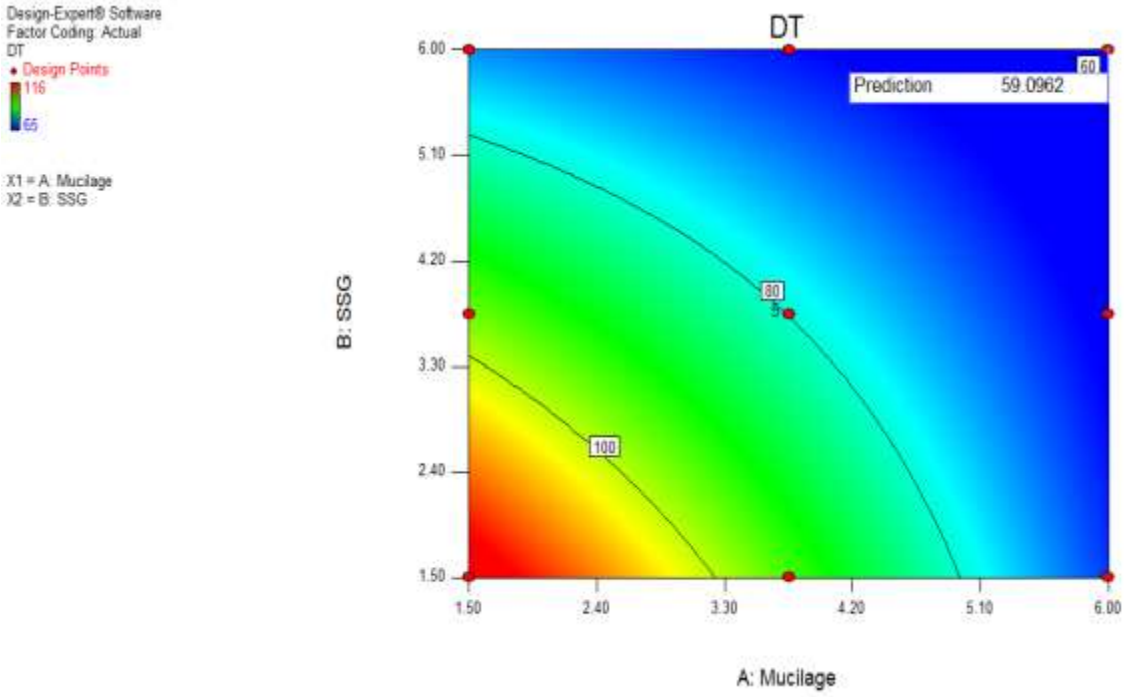

Fig. 5: Contour plot showing the relationship between various levels of two factors on disintegration time.

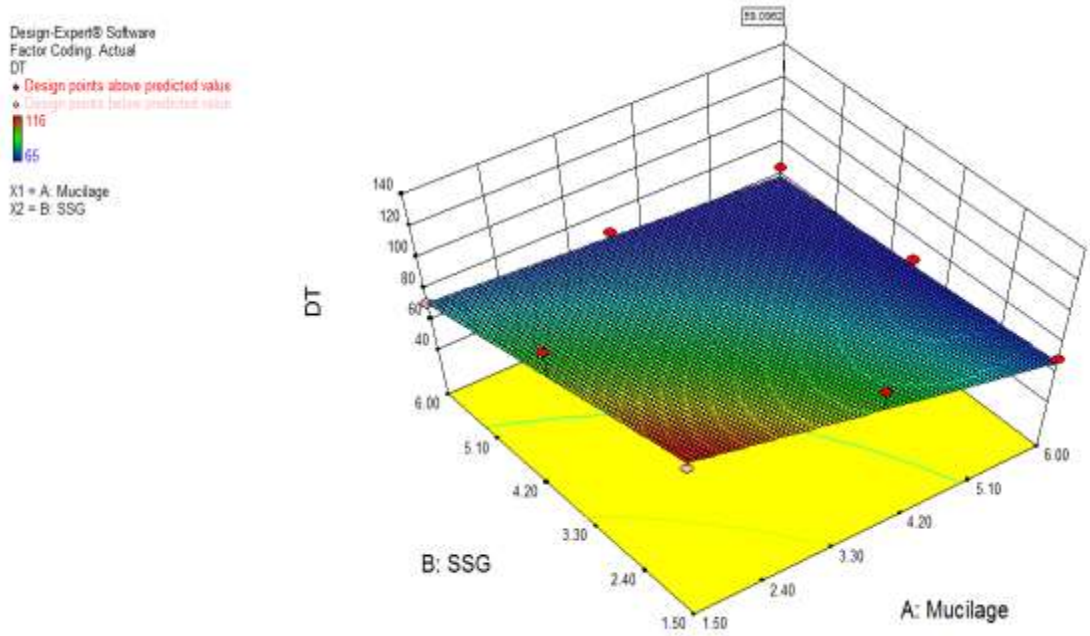

Fig. 6 : Response surface plot showing the influence of two different disintegrants Mucilage and MCC on disintegration time

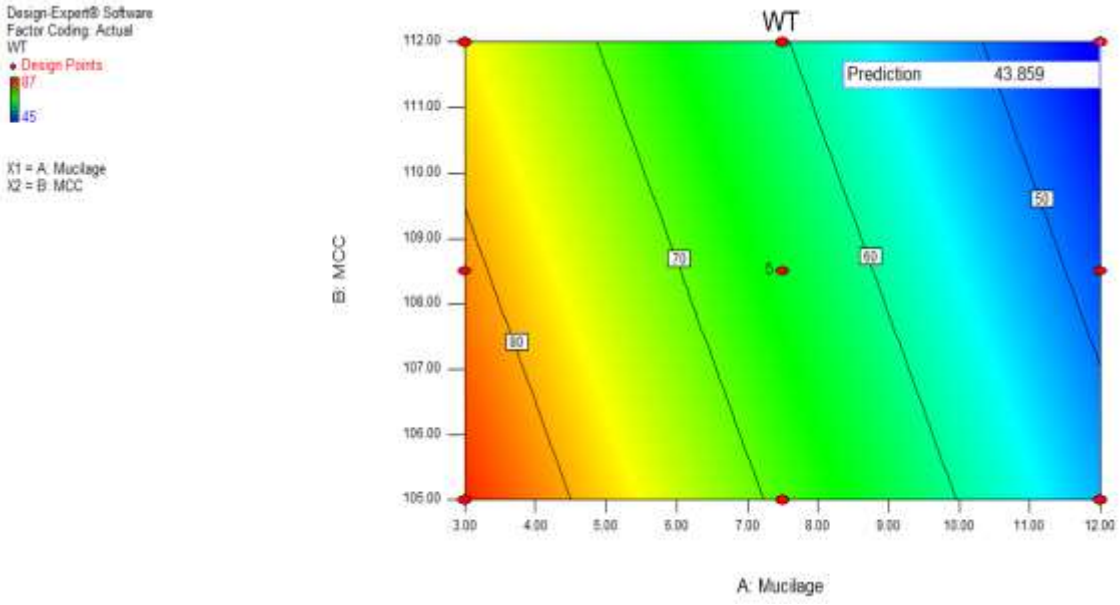

Fig. 7: Contour plot showing the relationship between various levels of two factors on wetting time

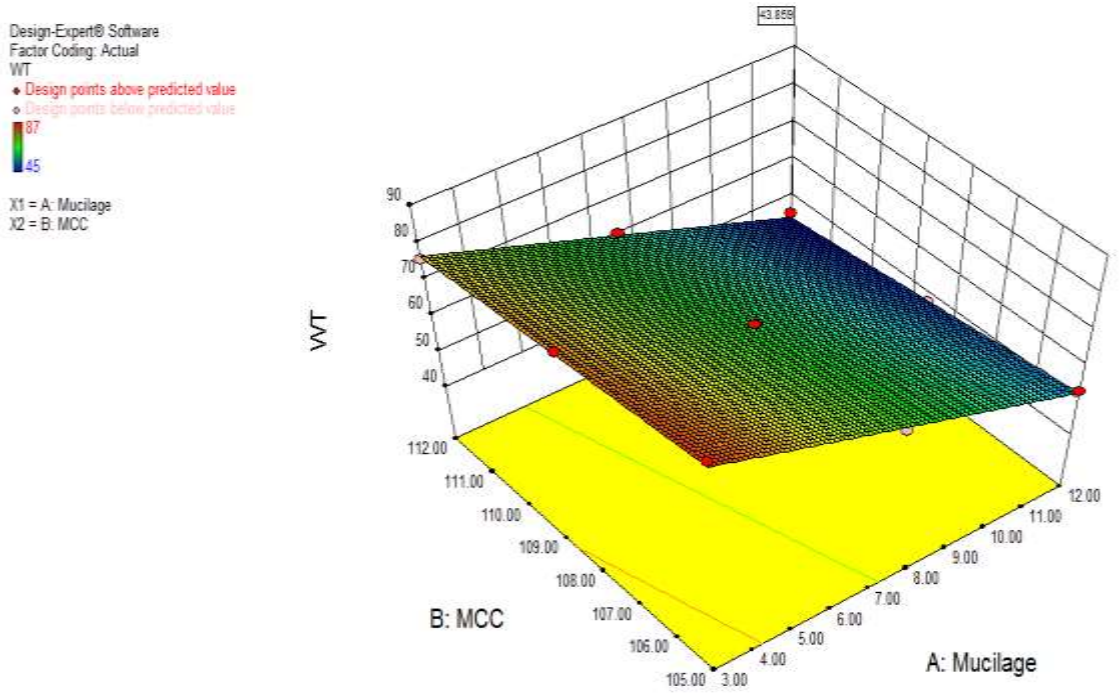

Fig. 8: Response surface plot showing the influence of two different disintegrants Mucilage and MCC on wetting time

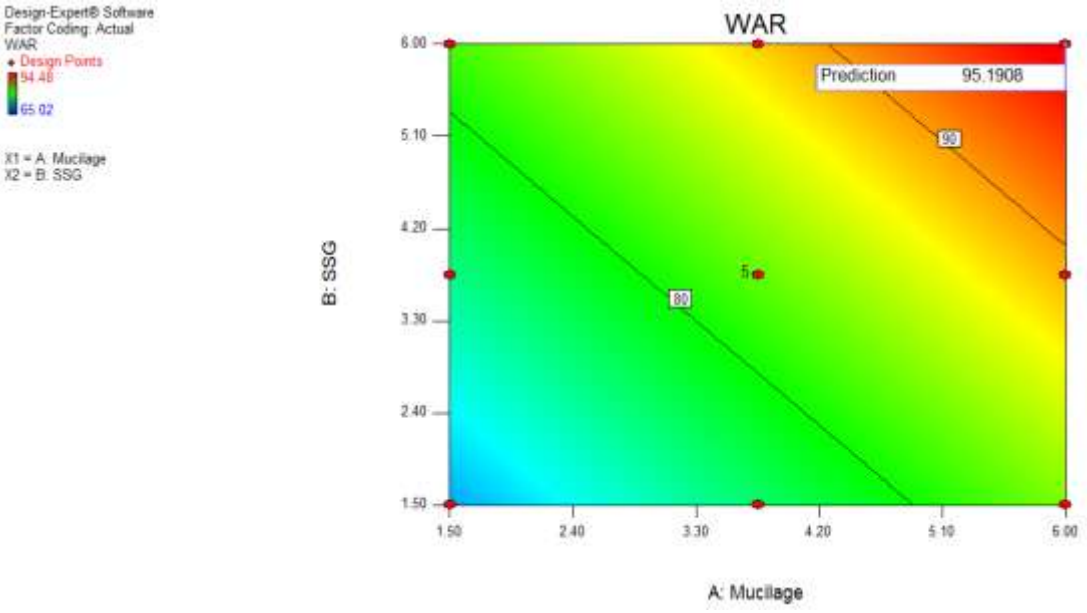

Fig. 9: Contour plot showing the relationship between various levels of two factors on water absorption ratio

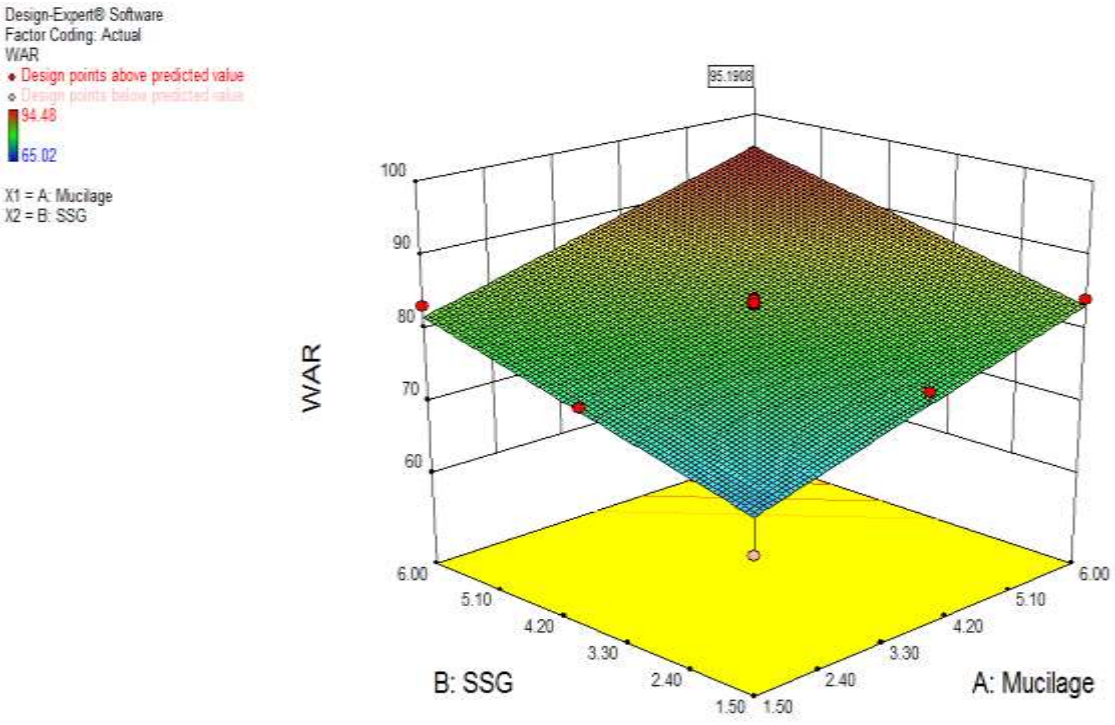

Fig. 10 : Response surface plot showing the influence of two different disintegrants Mucilage and SSG on water absorption ratio

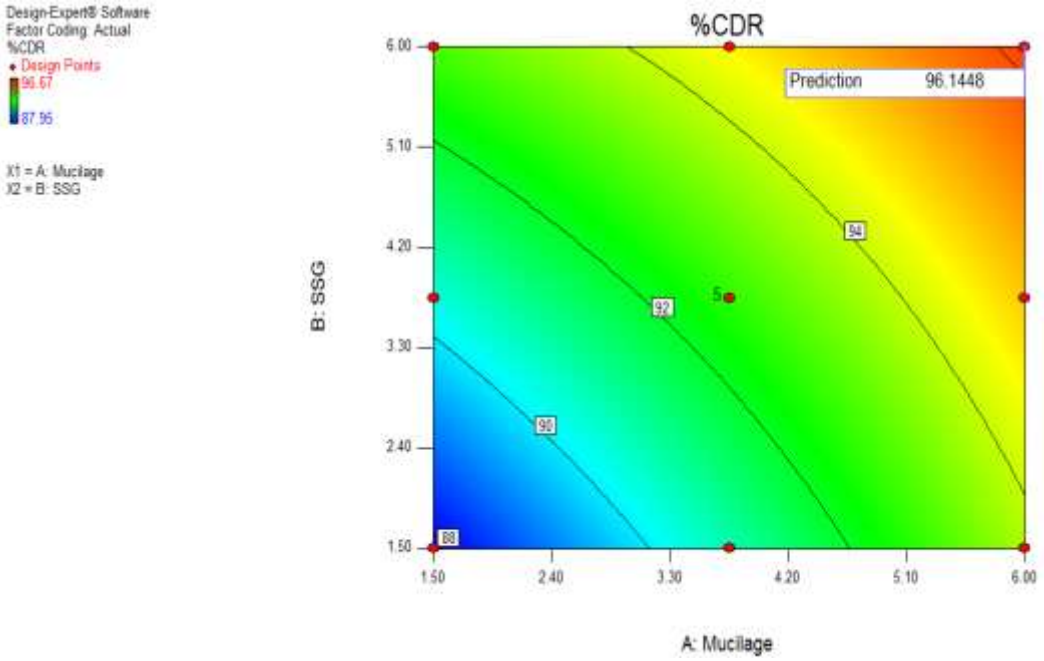

Fig. 11 : Contour plot showing the relationship between various levels of two factors on cumulative % drug release

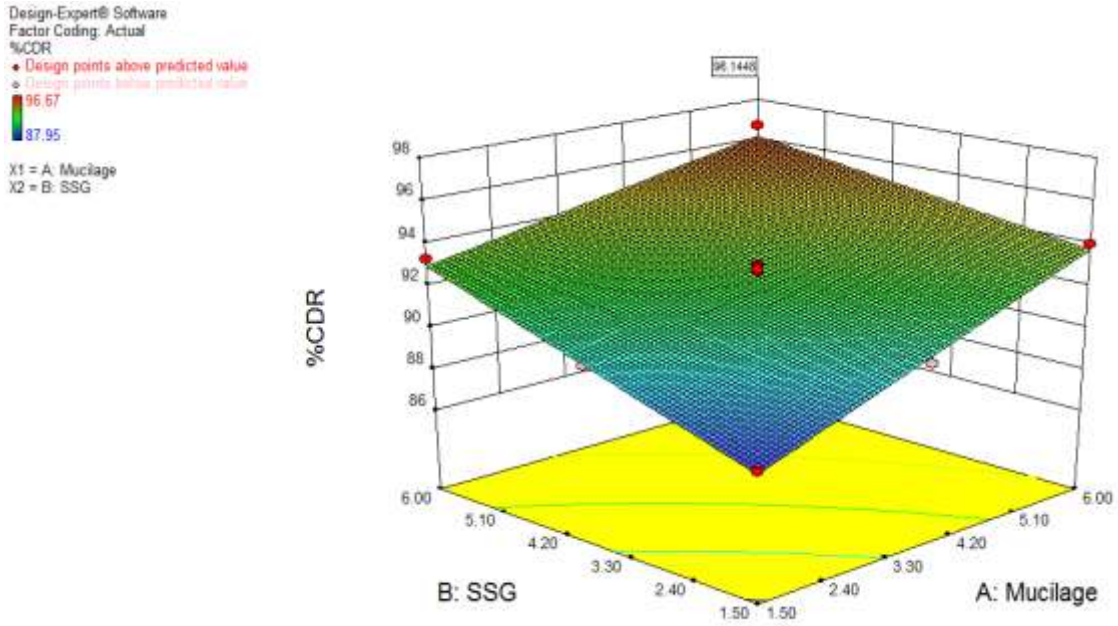

Fig. 12: Response surface plot showing the influence of two different disintegrants Mucilage and SSG on cumulative % drug release

Numerical Optimization

A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. This study revealed that the formulation C_9 fulfilled maximum requisites of an optimum formulation because of better regulation of release rate and water absorption ratio and less disintegration time and wetting time. The solution provided by FCCCD is reported in table 7.

Table 7: Solution provided by face centered central composite design

Constraints						
Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
Mucilage	is in range	1.50	6.00	1	1	3
SGG	is in range	1.50	6.00	1	1	3
DT	minimize	65	116	1	1	5
WT	minimize	47	89	1	1	5
WAR	maximize	65.02	94.48	1	1	5
%CDR	maximize	87.95	96.67	1	1	5

Solutions								
Number	Mucilage	SSG	DT	WT	WAR	%CDR	Desirability	Result
1	6.00	6.00	59.10	45.97	95.19	96.14	0.986	Selected

A new optimized formulation was prepared using 6 mg of mucilage and 6 mg of sodium starch glycolate, and all other factors were remain constant.

Evaluation of tablets of optimized batch

Table 8 : Evaluation parameters of tablets of optimized batch

Batch code	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	DT (sec)	WT (sec)	WAR (%)	% CDR
C_9	150.8± 0.41	3.2± 0.20	0.125	3.0± 0.05	60.21	47.02	94.48	96.67

In vitro dissolution profile of optimized batch

Dissolution study of final optimized batch was performed in triplicate manner in 6.8 pH phosphate buffer and the results are shown in table 6.12(b).

Table 9: *In vitro* dissolution data of final optimized batch

Time (min)	0	2	4	6	8	10	12	15	20	25	30
% CDR	0	53.21 ± 0.51	65.43 ± 0.78	76.19 ± 0.24	85.54 ± 1.35	92.30 ± 1.64	96.67 ± 0.31	97.85 ± 0.51	98.39 ± 0.36	98.95 ± 0.21	99.89 ± 0.11

Drug Content of the Drug for optimized batches

Table 10: Drug content for optimized batches

Batch code	Absorbance at 272 nm	Drug content (%) ±SD
Direct compression method		
C_9	0.762, 0.764, 0.762	99.31± 0.18

Kinetic study of drug release

Data obtained from *in-vitro* dissolution studies were fitted in different models viz. zero order model, first order model, Higuchi model, Hixson-Crowell model and Korsmeyer peppas model. Results are shown below:

Table 11: *In-vitro* release data of optimized formulations for zero order kinetics

Time (min.)	% Cumulative Drug Release
	0
0	53.21± 0.51
2	65.43± 0.78
4	76.19± 0.24
6	85.54± 1.35
8	92.30± 1.64
10	96.67± 0.31
12	97.85± 0.51
15	98.39± 0.36
20	98.95± 0.21
25	99.89± 0.11
30	0

Table 13: *In-vitro* release data of optimized formulations for first order kinetics

Time (min.)	Cumulative % drug retained	Log of cumulative % drug retained
	C_9	A_9
0	100	2
2	46.79	1.67
4	34.57	1.54
6	23.81	1.38
8	14.16	1.15
10	7.70	0.89
12	3.33	0.52
15	2.15	0.33
20	1.61	0.21
25	1.05	0.02
30	0.11	-0.96

Table 14: *In-vitro* release data of optimized formulations for Higuchi kinetics

Time (min.)	Square root of time (min.)	Cumulative % drug release
		C_9
0	0	0
2	1.41	53.21
4	2	65.43
6	2.45	76.19
8	2.83	85.54
10	3.16	92.3
12	3.46	96.67
15	3.87	97.85
20	4.47	98.398
25	5	98.95
30	5.48	99.89

Table 15 : *In-vitro* release data of optimized formulations for Hixson-Crowell kinetics

Time (min.)	Cumulative % drug retained	Cube root of cumulative % drug retained
	C_9	C_9
0	100	4.64
2	46.79	3.60
4	34.57	3.26
6	23.81	2.88
8	14.16	2.42
10	7.70	1.97
12	3.33	1.49
15	2.15	1.29
20	1.61	1.17
25	1.05	1.02
30	0.11	0.48

Table 16 : *In-vitro* release data of optimized formulations for Korsmeyer peppas model

Time (min.)	Log of time (min.)	Cumulative % drug release	Log of cumulative % drug release
		C_9	C_9
0	-	0	-
2	0.301	53.21	1.73
4	0.602	65.43	1.82
6	0.778	76.19	1.88
8	0.903	85.54	1.93
10	1.000	92.3	1.97
12	1.079	96.67	1.98
15	1.176	97.85	1.99
20	1.301	98.398	1.99
25	1.397	98.95	1.99
30	1.477	99.89	1.99

Table 17 : Value of R^2 obtained from different kinetics models

Kinetic models	Value of R^2
	Direct compression method
Zero order model	0.528
First order model	**0.927**
Higuchi model	0.806
Hixson-Crowell model	0.847
Korsmeyer peppas model	0.879
Best suited model	**First order model**

CONCLUSION:

The objective of present study was to formulate, evaluate and optimize mouth dissolving tablets of cinnarizine by using combination of natural superdisintegrant (*lepidium sativum* seed mucilage), synthetic superdisintegrant (sodium starch glycolate). In direct compression method, the batch C_9 was found optimized according to the face centered central composite design. Batch C_9 showed least disintegration time (60.21sec), least wetting time (47.02 sec), maximum water absorption ratio (94.48%) and maximum *in-vitro* drug release 99.89% in 30 min. From the results, it was concluded that natural superdisintegrant *lepidium sativum* seed mucilage powder with sodium starch glycolate showed excellent disintegrating property. Additionally, natural superdisintegrants are cheap, biocompatible, devoid of toxicity, biodegradable and easily available. Therefore, they can be used as superdisintegrants in addition of currently marketed synthetic superdisintegrants. The optimized batches were further subjected to kinetic modeling studies. In kinetic modeling studies, on the basis of R^2 values obtained for different models, it was concluded that batch C_9 showed First order model (R^2 = **0.927**) as drug release model.

It is noteworthy to envisage that this natural superdisintegrant could be considered for developing a future disintegrating system alone and in combination of synthetic superdisintegrant for MDTs. Further *in-vivo* investigations are required to correlate *in-vitro* drug release studies for the development of suitable rapid release system of cinnarizine.

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