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Formulation and Evaluation of Mouth Dissolving Tablets of Cinnarizine Hydrochloride and Domperidone Maleate

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ABSTRACT

The purpose of this study is to prepare Mouth dissolving tablets of Cinnarizine HCl and Domperidone Maleate by Direct compression method. In the present research study, Crosspovidone (CP) and Sodium Starch Glycolate (SSG) was taken as super disintegrant. Here the Cinnarizine HCl (H_1 anti-histaminics) and Domperidone (anti-emetic) is taken as the model drug for the study and direct compression as a method for preparation of the Mouth Dissolving Tablet. These combination of drugs are ideal for the prevention of symptoms caused by vestibular disorders and vertigo/motion sickness, nausea, dizziness, headache, vomiting, sensation of fullness when there is a delay in gastric emptying. A 3^2 full factorial design was applied to investigate the combine effect of two formulation variable CP(X1) and SSG(X2). Here the concentration of both Superdisintegrants was taken as independent variable, X1 and X2 respectively. I.R. and DSC study revealed that all polymers and excipients used were compatible with the drugs. All the pre and post-compression evaluation parameters shows good results and all batches are within acceptable limits. Mouths feel test gives pleasant sensation on human subjects when tablets are put it on tongue. The effect of Disintegration time (Y1) and % Drug release (Y2) were investigated as dependent parameters. From optimization data results that, among all the formulation F6 Batch was best formulation. The optimized batch obtained from the factorial design was compared with the marketed products. The stability study of the optimized batch is also done at 40ºC and 75%RH.

Keywords: 3^2 Full factorial design, Cinnarizine HCl, Domperidone Maleate, Crosspovidone, Sodium starch glycolate, Disintegration time, and Percentage drug release.

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INTRODUCTION

Many patients especially children and elderly have difficulty in swallowing tablets and capsules and consequently unable to take medicine as prescribed. Almost 50% of the population is affected by such problem, resulting in the high incidence of non compliance and ineffective therapy. Most pharmaceutical forms for oral administration are formulated for direct ingestion, or for chewing, or for prior dispersion and/or dissolution in water; some of them are absorbed in the mouth. To obviate the problems associated with conventional dosage forms, orally Mouth dissolving tablets have been developed, which combine hardness, dosage uniformity, stability and other parameters, with extremely easy administration, since no water is required for swallowing the tablets and they are thus suitable for geriatric, pediatric and traveling patients. MDTs can be prepared by different methods as direct compression, freezedrying, spray drying, sublimation and wet granulation method. The aim of this study was to formulate MDTs with sufficient mechanical integrity and to achieve faster disintegration in the oral cavity without water. To achieve this goal, mannitol used as diluent and Lactose and sodium saccharin as sweetening agent for the formulation of tablets. Attempts were made to enhance dissolution rate along with faster disintegration using superdisintegrants like Cross-povidone and Sodium starch glycolate (SSG) in the formulation of tablets. Two model drugs, with poor aqueous solubility Cinnarizine HCl (H_1 anti-histaminics) and Domperidone (anti-emetic) were selected for the studies. These combination of drugs are ideal for the prevention of symptoms caused by vestibular disorders and vertigo/motion sickness, nausea, dizziness, headache, vomiting, sensation of fullness when there is a delay in gastric emptying.

MATERIALS AND METHOD

Materials

Cinnarizine hydrochloride (Emcure Pharmaceutical Ltd., Pune, India) and Domperidone maleate (Centaur Pharmaceutical Ltd., Pune, India) was kindly supplied as gift samples. Cross-povidone (CP) and Sodium starch glycolate (SSG) was obtained from our laboratory. anhydrous lactose, Mannitol and magnesium stearate (Oxford Chemicals, Pune, India) were purchased. All other chemicals and solvents used were of analytical grade.

Methods

Both the drugs and superdisintegrants are mixed thoroughly along with formulation additives.

12 station rotatory tablet compression machine was used to manufacture the Mouth dissolving tablets in order to get sufficient mechanical strength. All the formulation batches were formulated in accordance with the Optimization technique studies.

Compatibility study

Compatibility study with excipients was carried out by FTIR and DSC. The pure drug and excipients were subjected to FTIR and DSC studies. Then the spectrum obtained after studies were compared with standard spectrum of the drug (11).

Evaluation Parameters

pre-compression parameters

Characteristics of powder mixtures were determined by Angle of repose, Bulk density, Tapped density, Compression index, Hausner's ratio

Angle of repose:

A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph sheet was taken to measure the area of pile, thereby, evaluating the flowability of the powders. Height of the pile is then measured.

Angle of repose for powder mixture is calculated by formula: $\tan \theta = h/r$

$\theta = \tan^{-1} (h/r)$

Where, θ is the angle of repose

h is the height, r is the radius.

Bulk density and Tapped density:

The accurately weighed amount of sample taken in a 25ml measuring cylinder of mixture powder measured/recorded the volume of packing and tapped 100 times on a plane hard wooden surface and tapped volume of packing recorded and LBD and TBD calculated by following formula:

LBD (Loose Bulk Density) = Weight of Powder / Volume of Packing

TBD (Tapped Bulk Density) = Weight of Powder / Tapped Volume of Packing

Percentage Compressibility:

Percent compressibility of powder mix was determined by Carr's compressibility index calculated by following formula.

Carr's Index % = TBD - LBD/ TBD x 100

Hausner's Ratio:

A similar index has been defined by Hausner's, Hausner ratio as an indication of powder flow

Hausner ratio = Tapped density/ Loose density

Experimental design for preparation of tablet

A central composite design was used for optimization procedure. It is suitable for investigating the quadratic response surfaces and for constructing a second-order polynomial model, thus enabling optimization of the tablet. Mathematical modeling and response surface modeling were performed by employing Design-Expert® software Version 8.1. Combination containing drugs for MDT were prepared based on central composite designs. Quantity of CP (X1) and SSG (X2) were selected as two independent variables. Three levels determined from preliminary studies of each variable were selected and nine possible batches were prepared using different levels of variables given in table (18,19,20).

Table 1 Different batches with their respective compositions as per 3^2 factorial design

Batch code	CP (X1)	SSG (X2)
F1	+1	0
F2	-1	-1
F3	0	0
F4	-1	0
F5	0	+1
F6	-1	+1
F7	0	-1
F8	+1	-1
F9	+1	0

Table 2:3^2 full factorial design layout

Sr. no.	Coded value	Amount of Crosspovidone (X1) in mg	Amount of sodium starch glycolate(X2) in mg
1	-1	12	12
2	0	15	18
3	+1	18	24

Table 3 Composition profile for preparing mouth dissolving tablet by optimization technique

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9
CIN	20	20	20	20	20	20	20	20	20
DOM	15	15	15	15	15	15	15	15	15
CP	18	12	15	12	15	12	15	18	18
SSG	18	12	18	18	24	24	12	12	18
Mannitol	100	100	100	100	100	100	100	100	100
Lactose	69	75	67	85	61	64	73	75	64
Sodium Sacc.	10	10	10	10	10	10	10	10	10
Mg. Stearate	5	5	5	5	5	5	5	5	5

Total(mg)	250	250	250	250	250	250	250	250	250

Post-compression parameters

Prepared mouth dissolving tablets was evaluated for evaluation parameters like thickness and diameter, friability, weight variation, disintegration test, drug content uniformity.

Hardness and thickness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets were determined using Monsanto hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the same tablets from each formulation were determined. The mean and standard deviation values were also calculated.

Friability study:

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

Drug content:

Twenty tablets were weighed and average weight was calculated. The tablets were crushed into fine powder. Tablet powder equivalent to 10mg of CIN and DOM was transferred to 100ml volumetric flask and ultra sonicated for 10min. The volume was made up to the mark with pH6.8 phosphate buffer solution. The resulting solution was then filtered through a Whatmann filter paper and were analyzed at 254.0nm and 284.0nm of CIN and DOM respectively.

Weight variation test:

Twenty tablets were selected randomly from each formulation and weighed individually to check for weight variation. A little variation is allowed in the weight of a tablet by the US Pharmacopoeia.

Wetting time:

The method was applied to measure tablet wetting time. A piece of tissue paper folded twice was placed in a small petridish (i.d. = 6.5 cm) containing 6 ml of water, a tablet was put on the paper, and the time for complete wetting was measured.

Water absorption ratio:

A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using equation -

$R = 10 \times Wa - Wb/Wb$

Where, Wb = weight of the tablet before water absorption

Wa = weight of the tablet after water absorption

In vitro dispersion time:

In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of pH 6.8 (simulated saliva fluid). Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

In vitro disintegration time:

Place three tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at $37\pm^{0C}$ as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at $37.5^{0}\pm0.5C$.

Mouth feel and In vivo Disintegration:

To know mouth feel of the tablets, the human volunteers held the disintegrated particles in the mouth for 30 seconds and the taste sensation felt was recorded and simultaneously the time taken for complete disintegration of the tablet on the tongue was noted.

In vitro Dissolution Studies:

In vitro release studies were carried out using tablet dissolution test apparatus USP XXIII. Dissolution medium: 900 ml of pH6.8 Phosphate Buffer Solution Temperature 37°C ± 5 RPM : 50 Tablet taken: One tablet (As per known drug content) Volume withdrawn: 5 ml every 2.5 min. Dilution factor: 1The drug content was determined by simultaneous equation method by UV spectrophotometer at λ_{max} 254.0nm and 284.0nm taking absorptivity values of standard CIN and DOM as described for the drug content method.

Comparison with Marketed product:

Optimized formulation was compared with marketed product of CIN and DOM tablet preparations. Marketed formulation of CIN and DOM are evaluated for hardness, friability, uniformity of drug content % cumulative drug release study and thickness.

Stability Studies:

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.

In the present study, stability studies were carried out at $40^{\circ}C\pm2^{\circ}C$ / 75% RH for a specific time period up to 30 days for selected formulation.

RESULTS AND DISCUSSION

Both the drugs and superdisintegrants are mixed thoroughly along with formulation additives.

12 station rotatory tablet compression machine was used to manufacture the Mouth dissolving tablets in order to get sufficient mechanical strength. All the formulation batches were formulated in accordance with the Optimization technique studies.

Compatibility studies by

FT-IR Studies:

A comparison between FT-IR spectra of the pure drug and the combination of drug with the polymers, it was observed that all the characteristic peaks of CIN and DOM were present in the combination spectra as well; thus indicating the compatibility of the drug with the polymers used. The individual FT-IR spectra of the pure form of CIN and DOM, combination of drug and polymers were shown in the Figure 1. All the characteristic peaks of CIN and DOM were present in Spectra thus indicating compatibility between drug and excipients.

DSC Studies:

The DSC curve of pure CIN and DOM exhibited an initially flat profile, followed by a single sharp endothermic peak representing the melting of the substance in the range 118 ºC -120 ºC and 137 ºC -139 ºC (Tonset = 231.2, T peak = 233.33 and ǻ Hfusion = -313.51 J/g). There was no shift in the endotherms in the drug-excipient mixtures indicating compatibility of the drug with all the excipients. The comparative DSC thermograms of the drugs, CP and SSG and drug-excipient mixtures are depicted in Figure 2

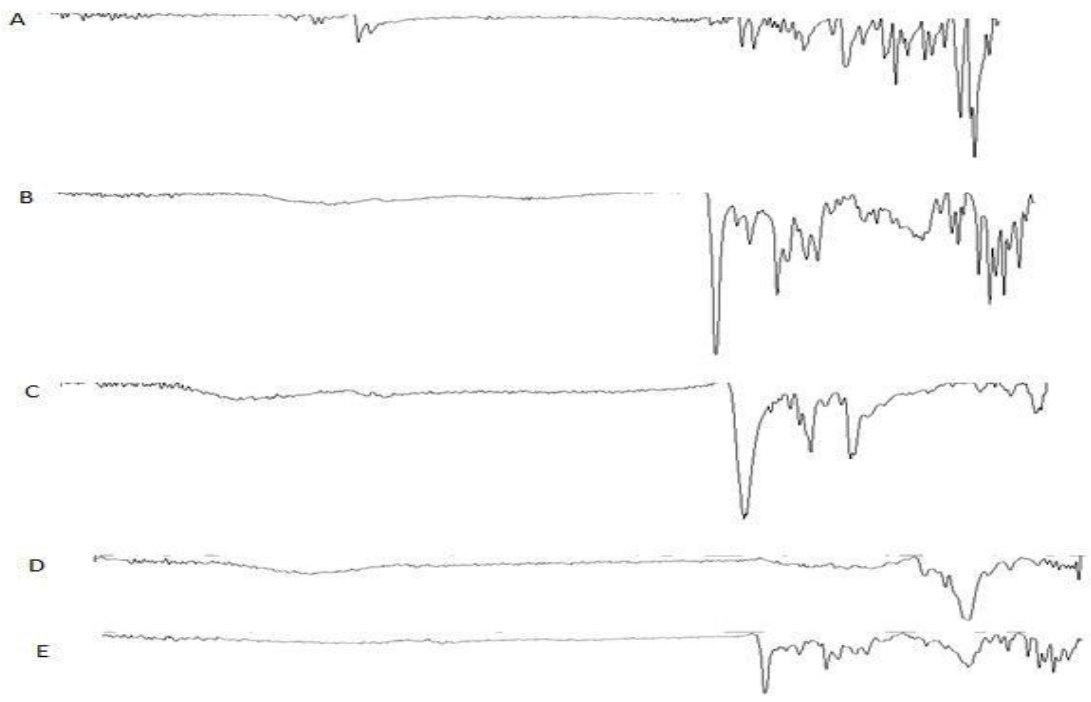

Figure 1. Infrared spectrum of A-CIN B-DOM drugs, C -CP, D-SSG, E-Physical Mixture.

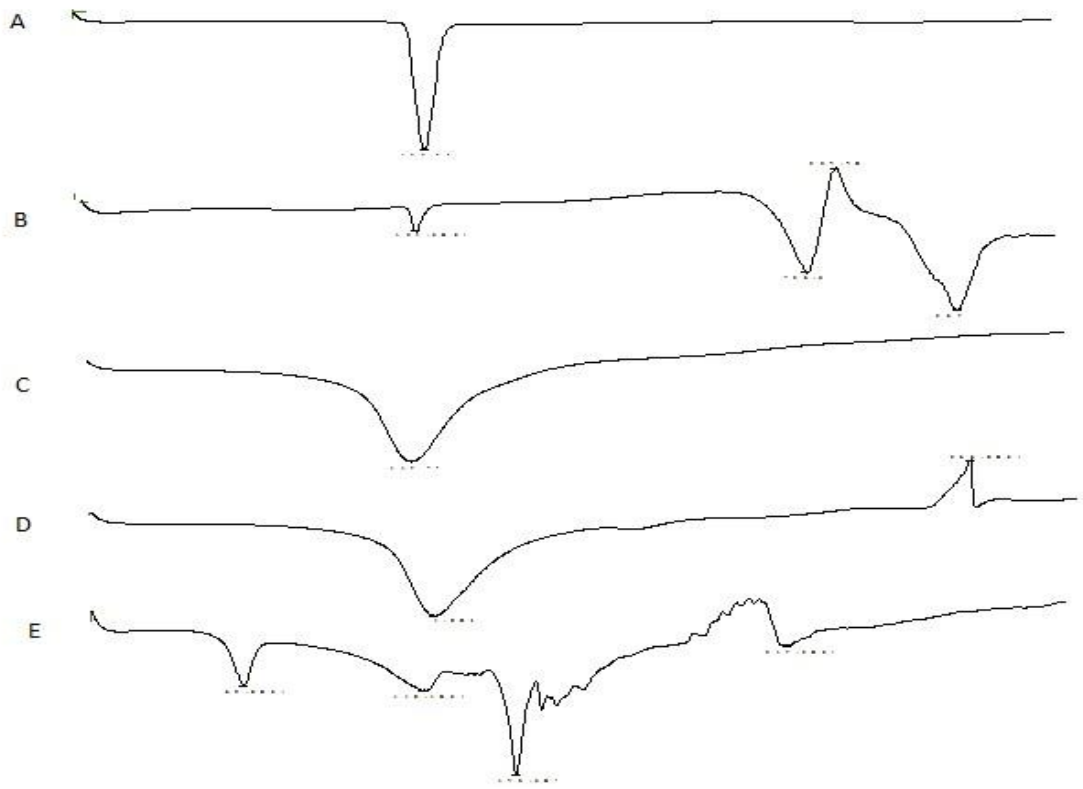

Figure 2. DSC spectrum of A-CIN, B-DOM, C -CP, D-SSG, E-Physical Mixture

Evaluation of pre-Compression Parameters by Angle of repose, bulk density, tapped density, compression index, Hausner's ratio

Results of pre compression parameters of powder mixtures of MDT are shown in table 4 which demonstrates that all the batches have good compressibility. Flow properties of all the batches such as angle of repose and Hausner's ratio were found to be within limits. But batch F6 shows good flow property as compared with other batches. Therefore, batch F6 was selected for further study.

Table 4 Angle of repose, bulk density, tapped density, compression index, Hausner's ratio

Code	Angle of repose	Bulk density(g/cm^3)	Tapped density(g/cm^3)	Compressi-bility index (%)	Hausner's Ratio
F1	28.38±0.12	0. 47±0.01	0.53±0.019	12.78±0.88	1.65±0.025
F2	27.32±0.21	0.52±0.023	0.58±0.022	14.18±0.42	1.68±0.013
F3	28.29±0.18	0.59±0.032	0.68±0.032	13.02±0.32	1.59±0.018
F4	27.21±0.41	0.54±0.029	0.60±0.048	14.25±0.44	1.54±0.015
F5	28.32±0.21	0.57±0.023	0.59±0.022	13.18±0.42	1.71±0.013
F6	28.42±0.32	0.54±0.013	0.55±0.036	14.62±0.41	1.54±0.054
F7	27.42±0.21	0.53±0.023	0.57±0.022	14.18±0.85	1.68±0.025
F8	28.32±0.21	0.42±0.023	0.68±0.022	14.22±0.42	1.69±0.013
F9	27.96±0.82	0.57±0.289	0.55±0.28	14.91±0.78	1.96±0.045

All the values are in mean ±SD, n=3.

Evaluation of post compression parameters by weight variation, thickness, hardness, friability, drug content

Results of post compression parameters of MDT are shown in table 5 which demonstrates that Weight variation, Thickness, Hardness, Friability, Drug content. All the tablets of the test product compiled with the official requirement. The friability indicates that the tablets are compact and hard. But from above all the results batch F6 shows good post compression property. Therefore, batch F6 was selected for further study.

Table 5 Evaluation of prepared tablets by weight variation, thickness, hardness, friability, drug content

Batch code	Weight variation	Thickness (mm)	Hardness (kg/cm^2)	Friability (mg)	Drug content (%)
F1	249.6±0.42	3.15±0.15	4.16±0.58	0.6633	99.06±0.116
F2	250.8±0.12	3.18±0.46	3.67±0.78	0.6103	98.04±0.114
F3	250.7±0.78	3.13±0.45	3.50±0.42	0.6035	98.44±0.451
F4	250.4±0.56	3.55±0.78	3.54±0.54	0.5336	98.54±0.116
F5	250.6±0.78	2.77±0.56	3.50±0.15	0.8200	99.16±0.145
F6	249.2±0.45	2.67±0.59	3.16±0.65	0.5336	100.06±0.44
F7	249.0±0.74	2.70±0.78	2.50±0.58	0.7496	99.06±0.44
F8	250.2±0.45	2.78±0.98	2.99±0.87	0.7107	99.06±0.674
F9	249.6±0.04	2.65±0.83	2.78±0.73	0.7305	99.99±0.78

All the values are in mean ±SD, n=3.

Wetting time:

Table 6 Wetting time of MDT at various time interval

Sr. no.	Batch code	Wetting time in seconds
1	F1	49±1.95
2	F2	60±0.59
3	F3	75±2.04
4	F4	40±1.45
5	F5	35±0.95
6	F6	25±1.00
7	F7	28±2.45
8	F8	50±1.45
9	F9	41±0.39

All values are in mean ±SD, n=3.

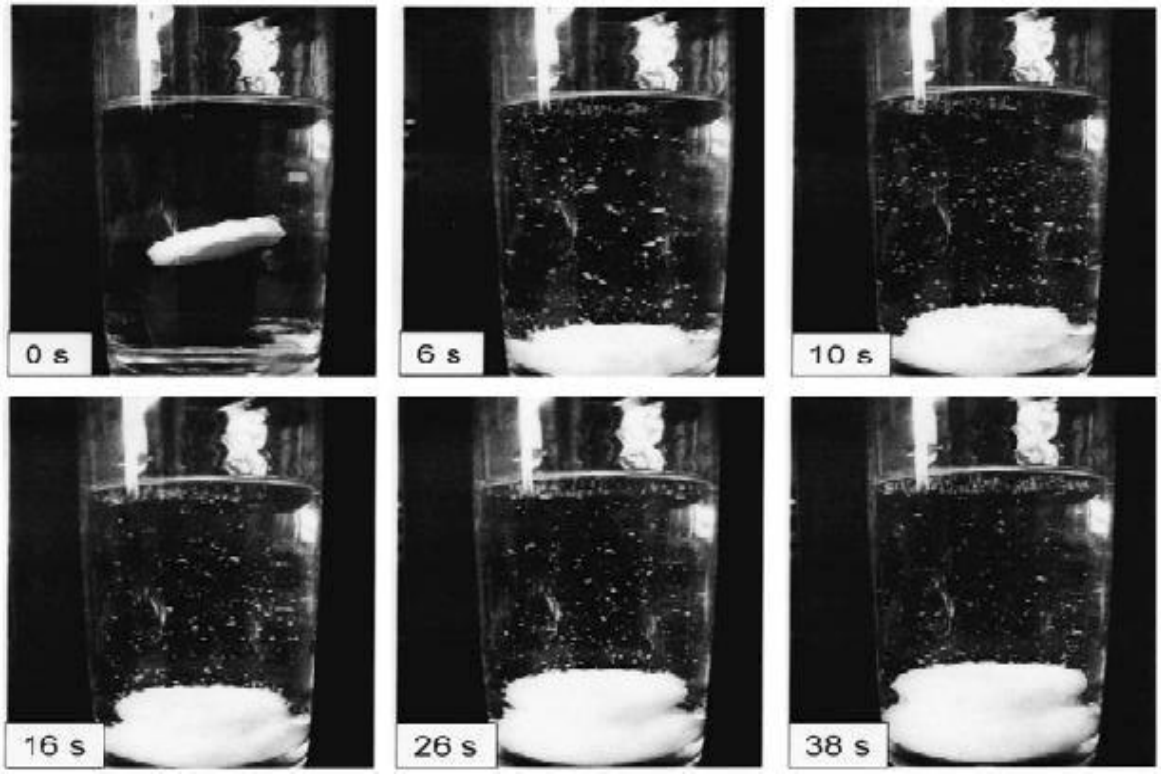

Figure 3. Photographs showing wetting time of an Optimized F6 batch at different time intervals.

Wetting time was determined for all the formulations. Wetting time of all the formulation were more than 25 seconds, due to its rapid water-absorbing nature, involving both capillary and swelling mechanisms of SSG and CP.

Water absorption ratio studies :

Table 8 Water absorption ratio

Sr. no.	Batch code	Water absorption ratio(%)
1	F1	73.57±1.05
2	F2	78.45±0.79
3	F3	81.29±1.56
4	F4	86.78±2.56
5	F5	91.89±0.95
6	F6	95.45±1.00
7	F7	88.45±2.45
8	F8	90.56±2.48
9	F9	41.59±0.39

Results reveals that in Table 8. water absorption ratio also in acceptable limits. Formulation batch F6 containing water absorption shows good absorptive characteristics to as that of other

formulation studies. So, batch F6 was selected for further studies. All values are in mean ± SD, n=3.

In-vitro Dispersion time studies:

Table 9 In-vitro Dispersion time

Sr. no.	Batch code	In- vitro Dispersion time in seconds
1	F1	37±2.30
2	F2	25±0.57
3	F3	30±2.04
4	F4	18±2.06
5	F5	35±0.56
6	F6	15±1.09
7	F7	29±2.45
8	F8	18±1.45
9	F9	25±0.39
All values are in mean ±SD, n=3.		

The in vitro dispersion time also differs, direct compressed tablet shows decrease in in vitro dispersion time as the concentration of CP and SSG increases. Table 9. shows, F6 shows fastest dispersion time. Probably it may be due formation of dense capillary network structure in directly compressed mouth dissolving tablets. So, batch F6 was selected for further studies.

In-vitro disintegration studies:

Table 10 In-vitro disintegration studies.

Sr.no.	Batch code	In-vitro Disintegration time in seconds
1	F1	58±1.25
2	F2	50±1.00
3	F3	48±1.22
4	F4	56±2.44
5	F5	44±1.24
6	F6	38±1.00
7	F7	40±2.26
8	F8	48±0.58
9	F9	60±0.50
All values are in mean ±SD, n=3.		

When CP and SSG are combined with the water soluble mannitol, it shows the shorter disintegration time than other diluents. This may be attributed to the high water solubility of mannitol which may leaves pores in the tablet. This test reveals that by combination of these superdisintegrants along with lactose powder it gives faster disintegration rate. Result of remaining batches are listed in table 10. Photographs showing of an optimized F6 batch at

different time intervals. Therefore, batch F6 shows fast disintegration time as compared to other batches. So, batch F6 was selected for further studies.

Mouth feel and In-vivo Disintegration

Table 11 Mouth feel and In-vivo Disintegration

Code	Mouth feel	In-vivo Disintegration time(sec)
F1	+	42
F2	-	36
F3	+	32
F4	+	30
F5	+	28
F6	+	24
F7	+	39
F8	+	34
F9	-	40

All values are in mean ±SD, n=3.

'+' sign indicates Good mouth feel '-' sign indicates Poor mouth feel

The result of the mouth feel evaluation by taste panel has been summarized in table 11. All the members of taste evaluation panel reported the formulation from good to poor mouth feel. Except F2 and F9 all remaining batches shows good mouth feel when kept on tongue of subjects for 30 seconds.

The time taken for complete disintegration of the tablet on the tongue was noted for In-vivo disintegration time studies. study reveals that, batch F6 shows faster disintegration time than other batches. After the test, mouth was washed with distilled water.

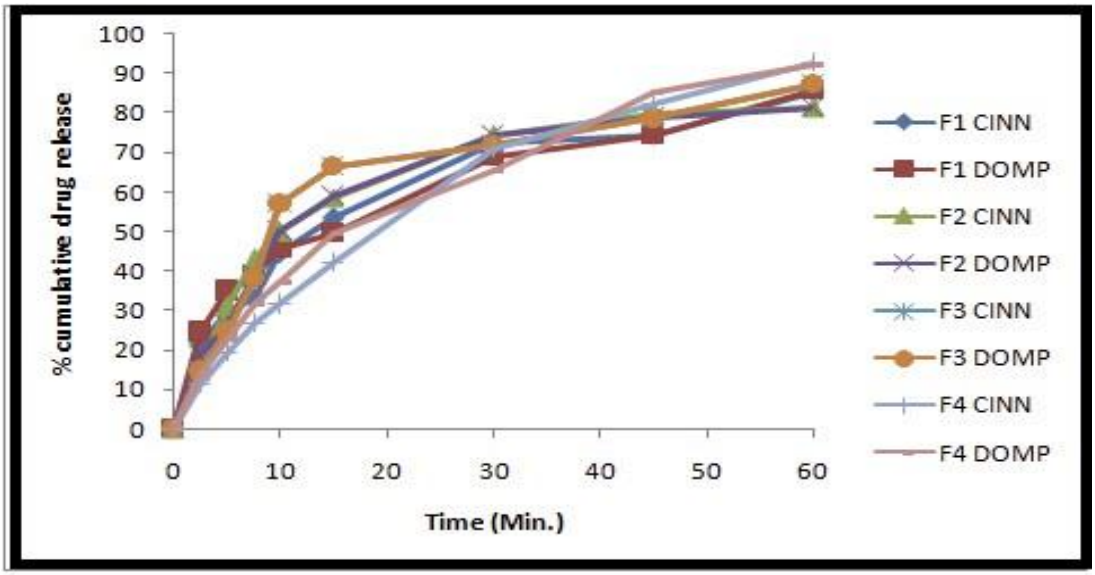

Figure 5. In vitro Dissolution Profile of the Formulations F1, F2, F3, F4

In vitro Drug Dissolution studies:

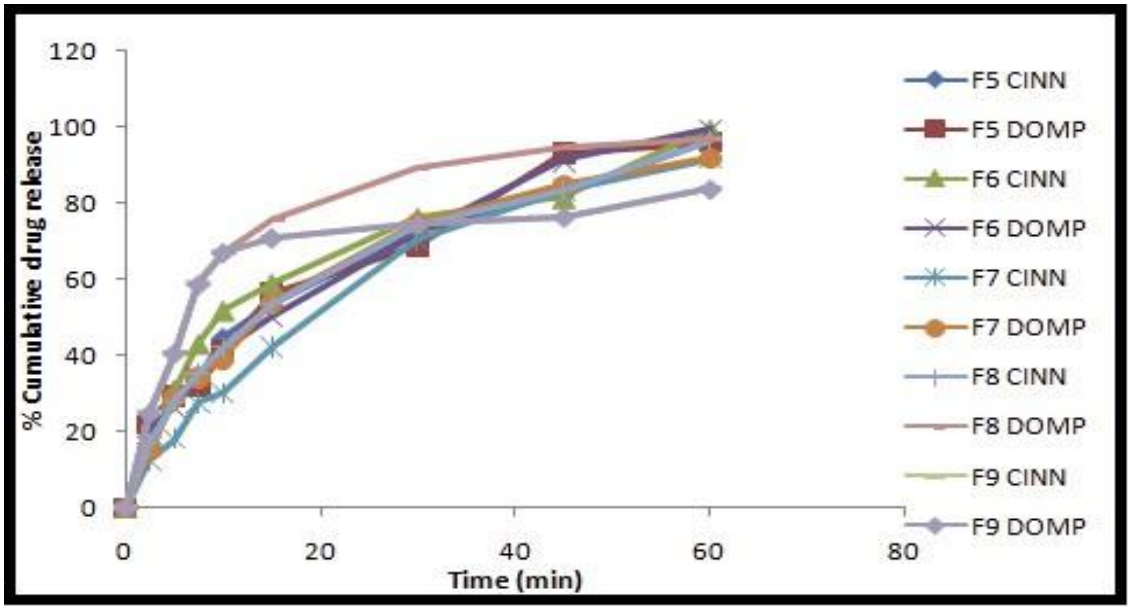

Figure 6. In vitro Dissolution Profile of the Formulations F5, F6, F7, F8, F9

The results of in-vitro dissolution methods was performed in phosphate buffer of pH6.8 for complete drug release having maintained temperature of 37±0.2ºC. All the batches of MDT showed fast disintegration and drug release in phosphate buffer of pH6.8. Although, the drug release in MDT of all batches was quiet rapid one, the composition of MDT shows significant effect on initial drug release. batch F6 showed more than 99% drug release within 60 minutes. F6 was considered as the optimal Mouth dissolving tablet formulation among all of the nine formulations tested in this study.

Experiments of 3^2 full factorial design:

To develop mouth-dissolving tablet, amount of CP and SSG are important parameters affecting the DT and Disso. T. The optimization strategy was carried out with the aim of finding optimu m amount of CP and SSG to achieve mouth-dissolving tablet.

Multiple regression and mathematical model building:

The targeted response parameters were statistically analyzed by applying one-way ANOVA (analysis of variance), at 5% significance level and the significance of the model was estimated using the statistical Design-Expert. The individual parameters were evaluated using F-test and mathematical relationship was generated between the factors X (independent variables) and responses Y (dependent variables) using multiple linear regression analysis, for determining the levels of factors which yield optimum DT and Disso. T. [Table 12].

Table 12. 3^2 Full factorial design of optimization techniques for MDT

CODE	STD	RUN	CP (X1)	SSG (X2)	DT (Sec)	DR (%)
F1	7	1	12	24	48	85
F2	2	2	15	12	34	81
F3	9	3	18	24	28	87
F4	3	4	18	12	59	92
F5	1	5	12	12	32	95
F6	5	6	15	18	23	99
F7	4	7	12	18	52	91
F8	6	8	18	18	25	96
F9	8	9	15	24	42	83

A polynomial equation was used to study the effect of variables on different evaluation responses (Y), where the coefficients in the equation (β0, β1, β2 and β12) were related to the effects and interactions of the factors. A second-order polynomial regression equation that fitted to the data is as follows:

$Y = \beta0 + \beta1X1 + \beta2X2 + \beta1X2\ 1 + \beta2X2\ 2 + \beta12X1X2$

where, β0 is the arithmetic mean response of nine batches, β1 and β2 coefficients of factor X1 and X2 and β12 the coefficient of interaction of X1 and X2. The interaction (X1, X2) shows how the dependent variable changes when two or more factors are simultaneously changed. Design-Expert was used to obtain values of coefficients in the equation and f-statistics were used to identify statistically significant terms. In Table 13, factor effects of 3^2 full factorial design model and associated P-values for the responses Y1 and Y2 are presented. A factor is considered to influence the response if the P-value is less than 0.05. The final equations of the responses are given below:

Table 13 Estimation of regression coefficients for different response variables

Coefficient	Response variables (Y)	
β_0 (Intercept)	51.04	0.9846
B_1	-11.96	0.2489
B_2	0.5	-0.1.925
B12	0.000	0.149
B11	0.000	0.2426
B22	0.000	0.0687
R2	0.9778	0.5708
F*	87.59	0.73
P	0.0071	0.6108

where, β0, arithmetic mean response of nine batches; β1 and β2 coefficients of factor X1 and X2; β12, β11, β22, coefficient of interaction of X1 and X2. *Significant level is set at 5%. A bold value has P-value less than 0.05, hence the corresponding factors are considered to significantly influence the response.

Disso (Y1) = 51.04 - 0.03* X1 + 0.025* X2 - 0.000030* X1*X2 +0.07*X22+ 0.001133*X10

D. T. (Y2) = 0.9846 + 2.50*X1 - 1.25*X2 - 3.75*X1*X2 -0.73*X1.5- 1.09*X22

The equations represent the quantitative effect of factors (X1 and X2) upon the responses (Y1 and Y2). Coefficients with one factor represent the effect of that particular factor 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 of the factors.

Response surface analysis:

The quadratic models generated by regression analysis were used to construct 3D response surface plots in which response parameter Y was represented by a curvature surface as a function of X.

A linear synergistic relationship between the two independent variables on response Y1 as was also evident from the P-value listed in Table 17. and it depicts curvilinear relationship for response Y2 with 'a region of maxima' lying between the lower to higher levels of the factors. A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses.

For Disintegration time-R1Conc.of SSG, X1 = 18 mg

For % Drug release-R2 Conc. of CP, X2 = 99.33%

Validation of response surface methodology:

In order to assess the reliability of the developed mathematical model and dissolution test of the formulated pellets corresponding to the predicted optimum CP and SSG was performed. For each of these test run, responses were estimated by use of the generated mathematical model and by the experimental procedures. For the optimized batch predicted values for DT Y1 is 37.35 s while the experimental values for responses Y1 is 36.53 s, respectively. The tablets prepared according to optimum formulation achieved Disso. T Y2 1.081mm while the experimental values for response Y2 is 1.080 mm. The release profile of optimized tablet formulation.

Design-Expert® Software

Factor Coding: Actual R1 DT

59

23

60

X1 = A: A Cross-povidone X2 = B: B SSG

50

Actual Factor

C: C Mannitol = 120.00 40

30

20

24.00

21.00

18.00

B: B Sodium starch glycolate

15.00

18.00

17.00

16.00

15.00

14.00

13.00

12.00 12.00

A: A Cross-povidone

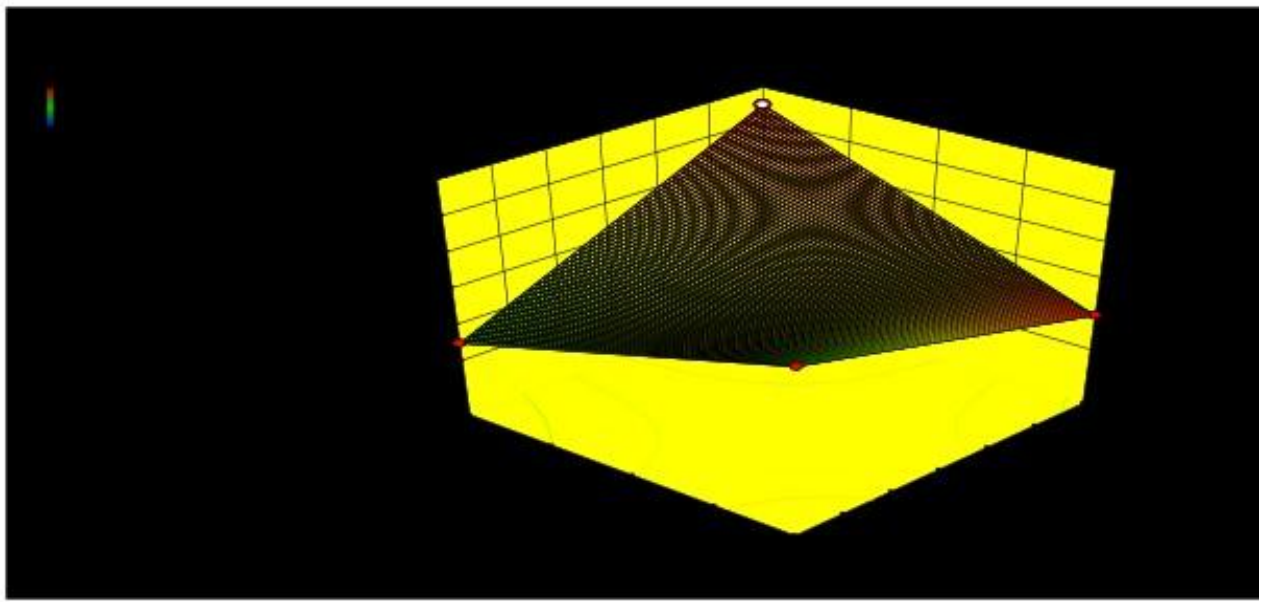

Figure 7. Surface response plot showing the influence of varying concentration of CP and SSG levels of an optimized F6 batch for Disintegration time.

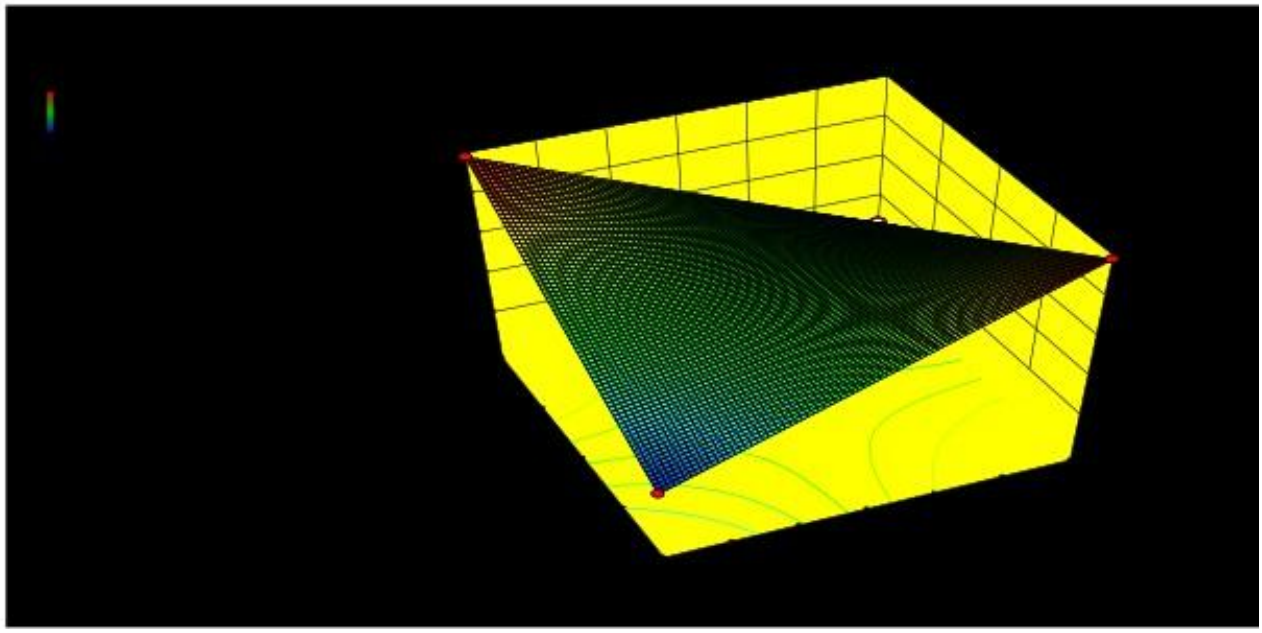

Figure 8. Surface response plot showing the influence of varying concentration of CP and SSG levels of an optimized F6 batch for % Drug release.

Design-Expert® Software

Factor Coding: Actual R2 %DR

99

81

X1 = A: A Cross-povidone

X2 = B: B SSG

Actual Factor C: C Mannitol = 120.00

100

98

96

94

92

90

24.00

21.00

18.00

15.00

B: B Sodium starch glycolat18.00

17.00

16.00

15.00

14.00

13.00 A: A Cross-povidone

12.00 12.00

The results of a 3^2 full factorial design revealed that the amount of CP and SSG significantly affect the dependent variables, Disintegration time, and Drug release.

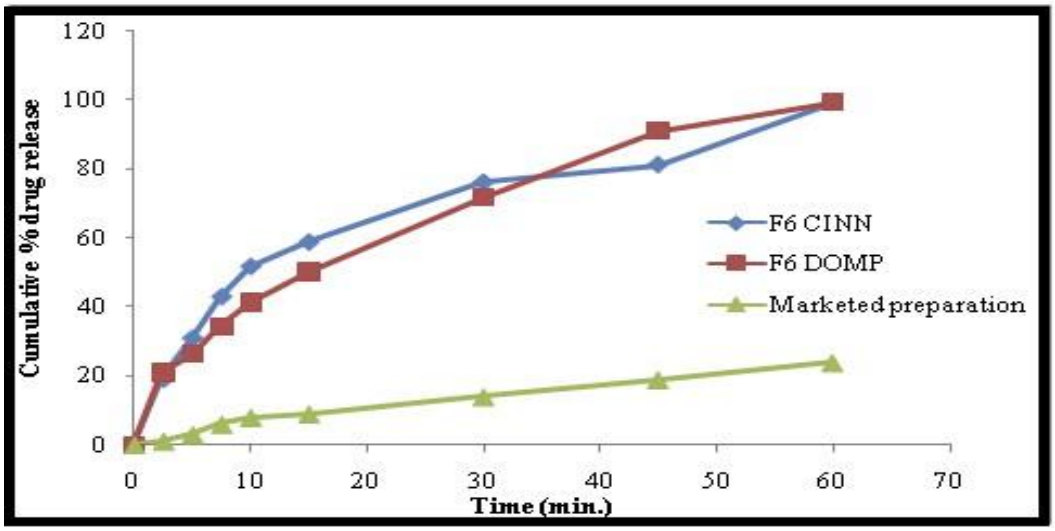

Figure 9. Comparison of optimized F6 batch with conventional marketed tablet

It is thus concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts. Direct compression method would be an effective alternative approach compared with the use of more expensive adjuvants in the formulation of MDT.

Comparison of optimized formulation with conventional marketed tablet

Table 13. Comparison of optimized formulation with conventional marketed tablet

Sr.no.	Time (min.)	Cumulative % drug release from conventional marketed tablet	Cumulative % drug release from optimized F6 batch	
		STUGIL CIN+DOM	CIN	DOM
1	2.5	1.81±3.84	19.1 ±2.8	21.05±1.5
2	5	3.45±1.69	31.00±3.8	26.35±2.9
3	7.5	6.29±0.67	42.97±2.1	34.26±2.4
4	10	8.93±1.45	51.73±3.1	41.36±1.9
5	15	9.81±3.25	58.78±1.9	50.11±2.6
6	30	14.33±2.88	76.12±1.3	71.68±2.1
7	45	19.54±1.89	81.22±1.5	90.86±2.7
8	60	24.70±3.78	99.89±2.3	99.67±2.8

In-vitro dissolution studies for batch F6 was carried out using tablet dissolution test apparatus USP XXIII at 50rpm, which shows that the drug release was more than 90% within 45 min which is better than conventional marketed tablet. The results are shown in Table 13 and a plot of comparison is shown in figure 9.

Stability studies

Table 14. Stability studies of an optimized batch

Code	Hardness (kg/cm^2)	Friability (%)	Disintegration (sec)	Wetting time (sec)	Drug content(%)
F6	3.16±0.65	0.5336	35	26	99.96±0.445
All the values are in mean ± SD, n=3.					

Selected Formulations batch F6 Stored at 40°C /75% RH Hardness (kg/cm2), Disintegration time (sec), Wetting time(sec) Formulation Code Tested after time (in days) Mean ± SD (n=3) Drug content uniformity(n=3) Friability %

The factorial design batches were subjected to short term stability studies at 40°C and 75% RH for one months. Studies indicated that no significant change in appearance of the tablets, Disintegration time, wetting time, Drug content was observed.

SUMMARY AND CONCLUSION

Summary

The aim of this research work was to develop the mouth dissolving tablets of Cinnarizine and Domperidone. Mouth dissolving tablets were formulated to give quick onset of action by rapidly disintegrating in a matter of seconds without the need of water and also to achieve better patient compliance. After performing compatibility studies by IR spectrophotometry along with DSC thermogram analysis and conforming no interaction of drugs with polymers. Mouth dissolving tablets of cinnarizine and Domperidone were formulated by using

3^2 full factorial optimization technique

By Direct Compression method

Conclusion

The mouth dissolving tablets of cinnarizine and Domperidone can be formulated by direct compression method and also by 3^2 full factorial optimization study. The FT-IR spectras and DSC Thermogram revealed that, superdisintegrants and formulation additives used were compatible with drugs. Hardness and friability of all the formulations indicated tablets were mechanically stable and percentage weight variation and drug content uniformity found within limits.

Sodium starch glycolate, cross-povidone and Mannitol in combination (in direct compression technique) acts as super disintegrants, which is revealed by in vitro disintegration time, in vivo disintegration time, in vitro dispersion time and wetting time results. Water absorption ratio indicates well absorptivity in all formulations. In vitro release studies revealed that 99% of drug release formulations F6 batch was within 60 mins. Best selected formulations F6 batch found to be stable.

The results of optimization study showed that all two independent variables had significant effect on the selected responses.

Overall, Optimization study reveals that as the concentration of Crosspovidone and sodium starch glycolate increases, bioavailability increases, which is more beneficial for better patient compliance. formulations F6 tablets disintegrated rapidly with good results. Direct compression methods can be utilized in preparing mouth dissolving tablets.

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