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Formulation design and development of Cinnarizine fast disintegrating tablet

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ABSTRACT

Objective of this study was to formulate directly compressible fast disintegrating tablets of Cinnarizine with sufficient mechanical integrity, content uniformity, and acceptable palatability to assist patients of any age group for easy administration. Effect of concentration of superdisintegrant, Ac-di-sol and directly compressible material, cellectose 80 on disintegration time was studied. Tablets were evaluated for weight variation, thickness, hardness, friability, drug content, in vitro disintegrating time, wetting time and in vitro drug release. A 3^2 full factorial design was applied to investigate the combine effect of 2 formulation variable: directly compressible material, cellactose® 80 and Superdisintegrant, Ac-di-sol. Here the concentration of directly compressible material and concentration of superdisintegrant were taken as independent variable, X1 and X2 respectively. The effect of Disintegration time, wetting time, Q15 and friability were investigated as dependent parameters. The results of analysis revealed that for obtaining a rapidly disintegrating dosage form, tablets should be prepared using an optimum concentration of superdisintegrant and a higher percentage of directly compressible material. The systematic formulation approach helped in understanding the effect of formulation processing variables.

Key words: fast disintegrating tablet, Cinnarizine, 32 factorial design, cellactose® 80, Ac-di-sol.

INTRODUCTION

Recent developments in the technology have prompted scientists to develop rapid disintegrating tablets with improved patient compliance and convenience. ODTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water [1]. Orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations

who have difficulty in swallowing conventional tablets and capsules. Additionally, pediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control [2, 3]. Moreover, patients traveling with little or no access to water, limit utility of orally administered conventional tablets or capsules [4]. Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action [5]. Moreover, drug candidates that undergo pre-gastric absorption when formulated as ODTs may show increased oral bioavailability [6]. It provides good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients [7]. On the other hand, techniques like OraSolv, DuraSolv FlashTab and WowTab.Technologies like Zydis, FlashTab have resulted in tablets with a very low disintegration time, but poor mechanical strength [8,9]. On the other hand, techniques like OraSolv, DuraSolv have resulted in products with sufficient mechanical strength but a comparatively longer disintegration time[10]. Motion sickness is the uncomfortable dizziness, nausea, and vomiting that people experience when their sense of balance and equilibrium is disturbed by constant motion. So in case of nausea and vomiting it required to prevent earlier.

In the present research work, fast disintegrating tablets of Cinnarizine is formulated. Cinnarizine is used for the treatment of vertigo/meniere's disease, nausea and vomiting, motion sickness. So in case of motion sickness, vomiting and nausea, it required immediate release of drug from the dosage form, which make Cinnarizine suitable candidate for the fast disintegrating tablets.

MATERIALS AND METHODS

Cinnarizine was purchased from Rakshit Pharma, Mumbai. cellactose® 80 were received as gist sample from meggle pharma, Germany. Ac-di-sol was received as gift sample form DMV-Fonterra Excipients, Gernamy. Mg stearate, talc and lactose were purchased from S.D. Fine Chem. Ltd., Mumbai.

Table 1: Formulation of preliminary trial batches:

Batch	N1	N2	N3	N4	N5
Drug (mg)	25	25	25	25	25
Ac-di-sol (%W/W)	4	4	4	4	4
cellactose® 80 (%W/W)	10	20	30	50	80
Mgstearate(%W/W)	1	1	1	1	1
Talc(%W/W)	2	2	2	2	2
Latose	q.s	q.s	q.s	q.s	q.s
Total Wt(mg)	200	200	200	200	200

Preparation of Cinnarizine fast disintegrating tablets:

Tablets containing 25mg of Cinnarizine were prepared by direct compression method and the various formulation used in the study are shown in Table. The drug, superdisintegrant, directly compressible material, diluents were passed through sieve # 60. All the above ingredients were co-ground and properly mixed together in motor pestle for 5 mins. Talc and magnesium stearate were passed through sieve # 80, mixed, and blended with initial mixture in a poly-bag. The powder blend was compressed into tablets using 8 mm normal concave punches to get tablets of 200 mg weight on a 12-station rotary tablet machine (Rimek Mini Press-1). The formulated

tablets were stored in a tightly closed glass container and evaluated for various characteristics. Formulation of preliminary trail, full factorial layout and composition of factorial batches was shown in table 1, 2 and 3 respectively.

Table 2: full factorial layout

Batch code	X_1	X_2
A_1	-1	-1
A_2	-1	0
A_3	-1	1
A_4	0	-1
A_5	0	0
A_6	0	1
A_7	1	-1
A_8	1	0
A_9	1	1

Coded value	Amount of Direct compressible material (cellactose® 80) in mg X_1	Amount of Super disintegrant (Ac-di-sol) in mg X_2
-1	80	4
0	120	10
1	160	16

X_1 code for amount of direct compressible material (cellactose 80) and X_2 code for amount of superdisintegrant, Ac-di-sol

Table 3: Formulation using 3^2 full factorial design:

Batch	A1	A2	A3	A4	A5	A6	A7	A8	A9
Drug (mg)	25	25	25	25	25	25	25	25	25
Ac-di-sol (mg)	4	10	16	4	10	16	4	10	16
cellactose® 80 (mg)	80	80	80	120	120	120	160	160	160
Mgstearate(%W/W)	1	1	1	1	1	1	1	1	1
Talc(%W/W)	2	2	2	2	2		2	2	2
Latose	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total Wt(mg)	200	200	200	200	200	200	200	200	200

Evaluation of physical parameters of prepared Cinnarizine FDT.

Uniformity of weigh[11].

The weights were determined to within ±1mg by using Sartorious balance (Model CP- 224 S). Weight control is based on a sample of 20 tablets. Determinations were made in triplicate

Tablet hardness[12].
The hardness of the tablets was determined by diametral compression using a dial type hardness tester (Model no 1101, Shivani Scientific Ind). A tablet hardness of about 4-5 kg is considered adequate for mechanical stability. Determinations were made in triplicate.

Tablet friability[12].
The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\% \, Friability = \frac{W_0 - W}{W_0} \times 100$$

In-vitro disintegration test[12].
The test was carried out on 6 tablets using Tablet disintegration tester ED-20 (Electrolab, Mumbai, India) distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds.

Wetting time[13].
The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Tablet thickness [11].
Tablet thickness can be measured using a simple procedure. 5 tablets were taken and their thickness was measured using Vanier calipers. The thickness was measured by placing tablet between two arms of the Vanier calipers.

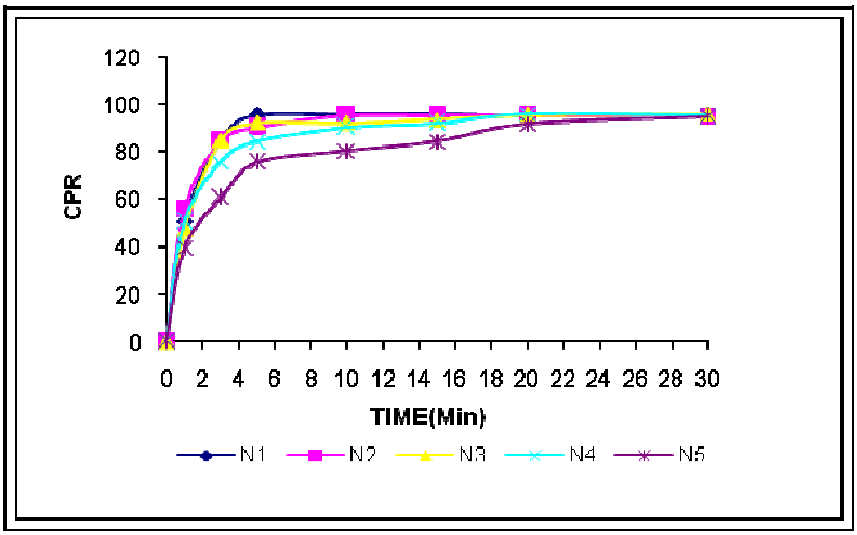
In-vitro dissolution profile of prepared Cinnarizine FDT [14].
The release rate Cinnarizine from fast dissolving tablets was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl (pH=1.2), at 37 ±0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 1, 3, 5, 10, 15, 20 and 30min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.45 µm membrane filter. Absorbance of these solutions was measured at 254 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Table 4: Evaluation of preliminary trail batches

Batch	Disintegration time (sec)	Wetting time (sec)	Hardness kg/cm^2	Friability in % (n=10)	Q_{15}
N1	12±1.73	30±2.64	2±0.43	1.5±0.05	95.84±0.12
N2	15±2	33±1.58	2±0.5	1.45±0.11	95.51±0.61
N3	30±3	45±2.60	3±0.3	0.91±0.12	93.71±0.35
N4	31±3.60	35±2.35	4±0.55	0.55±0.06	92.17±0.93
N5	40±1.73	50±1.73	5.5±0.86	0.38±0.02	84.58±0.42

The value denote the mean±SD(n=3)

Figure 1: cumulative percentage release profile of preliminary trail batches



Full Factorial Design

A 3^2 randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations. The design layout and coded value of independent factor is shown in Table 2 and Table 3 respectively. The factors were selected based on preliminary study. The amount of superdisintegrant, Ac-di-sol and amount of directly compressible material (cellactose® 80) were selected as independent variables. The disintegration time and drug release in 15min (Q_{15}), wetting time and friability were selected as dependent variables [15].

RESULT AND DISCUSSION

Results of preliminary trail:

In preliminary study, N1 to N5 batch where cellactose® 80 (10%-80%) was used as directly compressible material. Hardness, disintegration time, wetting time and friability of all preliminary batches between 2to 6kg/Cm^2, 12to40 sec, 30to50 sec and 0.38to 1.5 % respectively. The release of drug for all the batches was between 85to95%. Release profile of all the preliminary batches were shown in Figure 1 Very low hardness and higher friability obtained in batch N1, N2 and N3 as compared to other batches because of low concentration of cellactose® 80 in formulation. So N4 had given best results of hardness of 4 kg/Cm^2 ,friability of

0.55, disintegration time of 31 sec and wetting time of 35 sec. Considering all the formulation of N1 to N5 batches, N4 formulation having 50% cellactose® 80 gave best results among different concentration of cellactose® 80 so it can be used as directly compressible materials.

On the basis of the preliminary trials in the present study a 3^2 full factorial design was employed to study the effect of independent variables, i.e. amount of directly compressible material (cellactose® 80, X1) and the amount of superdisintegrant (Ac-di-sol,X2) on dependent variables like disintegration time, wetting time, friability and Q15. The results as summarized in table 5 clearly indicate that all the dependent variables are strongly dependent on the selected independent variables as they show a variation among the nine batches (A1 to A9)

Table 5: Effect on dependent variable

Batches	Independent variable		Dependent variables			
	cellactose® 80	Ac-di-sol	D.T. (sec)	Wetting time (sec)	Friability (in %)	Q_{15}
A1	-1	-1	60	85	0.85	88.72
A2	-1	0	55	75	0.94	91.47
A3	-1	1	40	70	1.07	93.65
A4	0	-1	50	67	0.74	90.73
A5	0	0	38	56	0.86	93.76
A6	0	1	30	45	0.89	93.25
A7	1	-1	39	47	0.54	92.51
A8	1	0	21	30	0.6	95.21
A9	1	1	30	40	0.57	93.35

Independent variable	Real value		
	Low (-1)	Medium (0)	High (1)
cellactose® 80 (X_1)	80	120	160
Ac-di-sol(X_2)	4	10	16

Summery output for regression analysis of Cinnarizine FDT

Coefficients	bo	b_1	b_2	b_{12}	b_{11}	b_{22}	R^2
Disintegration time	40.11	-11	-9.83	0.25	1.33	-1.16	0.98
Friability	0.8355	-0.1916	0.071	-0.04	-0.068	-0.008	0.98
Wetting time	55.77	-18.83	-9	-0.5	1.83	0.33	0.99
Q_{15}	92.92	1.20	1.69	-0.55	-0.095	-0.515	0.93

Factorial Equation for disintegration and Percentage friability

Concerning disintegration time, the results of multiple linear regression analysis showed that the coefficients b1 bear negative sign and b2 bear also a negative sign. Therefore, increasing the concentration of directly compressible materials is expected to decrease the disintegration time while increasing the concentration of superdisintegrant (Ac-di-sol) is also expected to decrease the disintegration time. Ac-di-sol 5% w/w and cellactose® 80 80% were selected as the optimum concentration that showed minimal disintegration time of 30 seconds. It was observed that further increase in concentration of directly compressible material led to the fell in disintegration time because of the having macropore volume at hardness of 4 kg/cm^2 means at low punch pressure. So ultimately water uptake is increased by hydrophilicity of component lactose and cellulose leads to quick water uptake resulting in disintegration in primary particles. The water uptake by the tablet is facilitated by the cellactose® 80, while the tablet disintegration

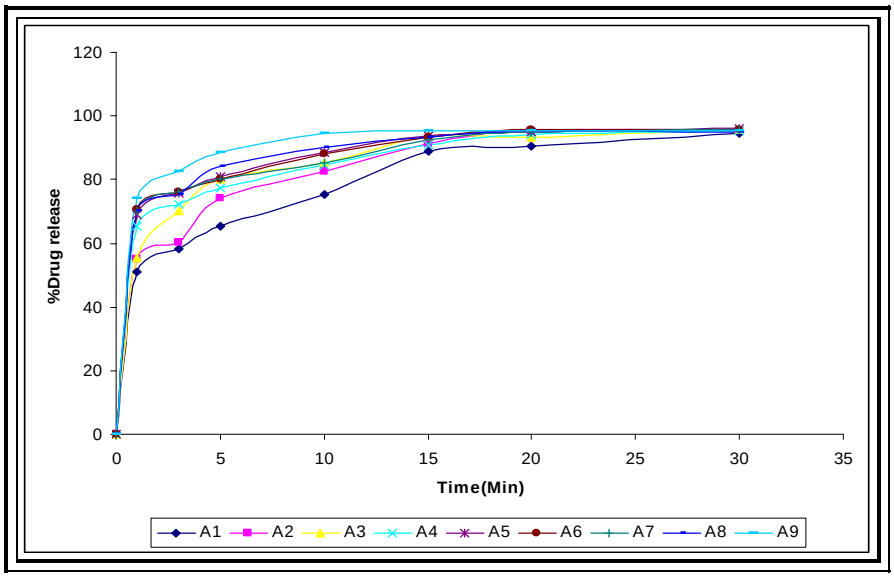
is facilitated by the wicking and swelling action exhibited by ac-di-sol at their optimum concentration. When higher percentage of cellactose® 80 is used, it is expected to tablet became harder so increase in concentration of cellactose 80 leads to decrease in friability because of having higher binding between cellactose 80 particles. This was confirmed by the negative sign of the coefficient b1. As indicated by positive sign of the coefficient b2, the increase in the incorporated amounts of Ac-di-sol resulted in increase in the friability due to its less compressibility which ultimately results in weak tablets. In case of depended variable disintegration time and Friability, X_1 and X_2 factors showed significant effect on formulation ($P < 0.05$).

Disintegration time = $40.11-11.01\ X_1 -9.83X2+0.25X1X2 +1.33X_1^2 -1.16X_2^2$
($R^2 = 0.98$)
Friability = $0.8355-0.1916X_1 +0.071X_2 -0.04X_1X_2 -0.068X_1^2 +0.008X_2^2$
($R^2= 0.98$)

Factorial Equation for wetting time and Q_{15}

The in vitro dissolution after 15 min varied from 88 to 97 and showed good correlation coefficient (0.93). Concerning dissolution, the results of multiple linear regression analysis showed that both the coefficients b1 and b2 bear a positive sign. More amount of Ac-di-sol were expected to increase the drug release due to the faster disintegration of the tablets, therefore increasing the concentration of Ac-di-sol is expected to increase the drug release after 15 min. While as indicated by positive sign of the coefficient b_1, increase in the amount of cellactose 80 also increase the release of the drug after 15min due to itself having disintegrating properties. From the multiple regression analysis, both the coefficients b1 and b2 bear a negative sign for wetting time of tablets.

Figure 2: cumulative percentage release profile of factorial batches:



Additions of more amount of ac-di-sol, wetting period of tablets were decrease while the increase the amount of cellactose® 80 wetting time decreases because of having hydrophilicity of the component lactose and cellulose. That means increasing concentration of superdisintegrant agent and directly compressible materials decrease the wetting time. In case of depended variable wetting time and Q_{15}, X_1 and X_2 factors showed significant effect on formulation ($P < 0.05$).

Wetting time = $55.77-18.83X_1 -9X_2 -.05X_1X_2 +1.83X_1^2 +0.33X_2^2$

($R^2 = 0.99$)

$Q15 = 92.92+1.20X_1 +1.69X_2 -0.55X_1X_2 -0.095X_1^2 -0.515X_2^2$

($R^2 = 0.93$)

CONCLUSION

Based on results of multi linear regression analysis, it was concluded that lower disintegration time of tablet could be obtained when X_1 is kept at higher level and X_2 is kept at optimum level when Ac-di-sol is used as super disintegrating agent.

So here A8 batch exhibited lower disintegration time and also had better drug dissolution at 15 min. It was concluded that by adopting a systematic formulation approach, an optimum point could be reached in the shortest time with minimum efforts so A8 batch is concluded as a best formulation for preparing Cinnarizine FDT by direct compression method

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