JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Formulation and Optimization of Superdisintegrant using Factorial Design

Nayankumar C. Ratnakar

L. M. College of Pharmacy, Opp. Gujarat University, Navrangpura, Ahmedabad, Gujarat, India

ABSTRACT:

This work approached with 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, tablettose® 70 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 32 full factorial design was applied to investigate the combine effect of 2 formulation variable: directly compressible material, tablettose® 70 andSuperdisintegrant, 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, tablettose® 70, Ac-di-sol

***For Correspondence:**
Nayankumar C. Ratnakar

L. M. College of Pharmacy

Opp. Gujarat University, Navrangpura, Ahmedabad, Gujarat, India

M: 9998690565

(www.jpsbr.org)

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, DuraSolvFlashTab 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. Tablettose® 70 were received as gist sample from megglepharma, Germany. Ac-di-sol was received as gift sample form Torrent Pharma, Ahmedabad. Mg stearate, talc and lactose were purchased from S.D. Fine Chem. Ltd., Mumbai.

Table 1:Formulation of preliminary trial batches:

Batch	N11	N12	N13	N14	N15
Drug(mg)	25	25	25	25	25
Ac-di-sol(%W/W)	3	3	3	3	3
Tablettose® 70 (%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
TotalWt(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: 3^2 full factorial layout

Batchcode	X_1	X_2
D1	-1	-1
D2	-1	0
D3	-1	1
D4	0	-1
D5	0	0
D6	0	1
D7	1	-1
D8	1	0
D9	1	1
Coded	Amount of Direct	Amount of
-1	80	4
0	120	10
1	160	16

X1 code for amount of direct compressible material (tablettose 70)and X2 code for amount of superdisintegrant, Ac-di-sol

Table3:Formulation using32 full factorial design:

Batch	D1	D2	D3	D4	D5	D6	D7	D8	D9
Drug(mg)	25	25	25	25	25	25	25	25	25
Ac-di-sol (mg)	4	10	16	4	10	16	4	10	16
tablettose®	80	80	80	12	12	12	16	16	16
Mgstearate(%	1	1	1	1	1	1	1	1	1
Talc(%W/W)	2	2	2	2	2		2	2	2
Latose	q.	q.	q.s	q.s	q.	q.s	q.	q.	q.
TotalWt(mg)	20	20	20	20	20	20	20	20	20

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 (W0) 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 = $\underline{W_0\text{-}W}$ x 100

$\qquad$ W 0

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 and30min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.45 µ m 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.

Table4:Evaluationofpreliminarytrailbatches

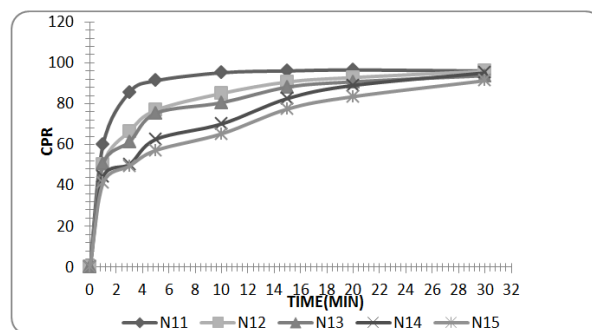| Batch	Disintegration time (sec)	Wetting time (sec)	Hardness kg/cm^2	Friability (In %) (n=10)	Q$_{15}$
N11	18±1.73	30±1	2.5±0.5	1.56±0.08	96.05±0.56
N12	25±3.60	25±3.60	2.5±0.55	1.35±0.06	90.64±1.20
N13	35±2.65	45±3.90	3±0.5	0.76±0.04	88.11±0.78
N14	40±1.7	55±4.5	5±0.43	0.51±0.03	82.53±1.40
N15	70±4.35	90±2.64	6±0.8	0.38±0.02	77.39±0.81

Figure1: 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

Table 5: Effect on dependent variable

Batches	Independent variable		Dependent variables			
	Tablettose 70	**Ac-di-sol**	**D.T. (sec)**	**Wetting time (sec)**	**Friability (in %)**	**Q_{15}**
D_1	-1	-1	50	77	0.92	88.73
D_2	-1	0	45	69	1.02	89.06
D_3	-1	1	53	81	1.07	88.01
D_4	0	-1	42	71	0.83	89.45
D_5	0	0	37	60	0.85	90.52
D_6	0	1	46	73	0.88	87.73
D_7	1	-1	28	38	0.65	92.48
D_8	1	0	24	35	0.73	94.01
D_9	1	1	30	43	0.78	90.14
Independent variable	**Real value**					
	Low (-1)		**Medium (0)**		**High (1)**	
Cellactose (X_1)	80		120		160	
Ac-di-sol (X_2)	4		10		16	
Coefficients	**bo**	**b_1**	**b_2**	**b_{12}**	**b_{11}**	**b_{22}**	**R^2**
Disintegration time	37.88	-11.5	1	5.66	-1	-3.83	0.99
Friability	0.861	-0.1416	0.056	-0.005	0.0083	-0.0116	0.96
Wetting time	61.88	-18.5	1.833	0.25	-10.84	9.16	0.99
Q_{15}	90.41	1.80	-0.79	-1.77	-0.405	1.17	0.95

compressible material (tablettose® 70) were selected as independent variables. The disintegration time and drug release in 15min (Q15), wetting time and friability were selected as dependent variables [15].

RESULTANDDISCUSSION

Results of preliminary trail:

For N11 to N15 batch where Tablettose (10%-80%) was used as directly compressible material. Hardness, disintegration time, wetting time and friability of all preliminary batches between 2.5to 6kg/Cm^2, 17to70 sec, 25to90 sec and 0.38to 1.56 % respectively. The release of drug for all the batches was between 76to96%. Very low hardness and higher friability obtained in batch N11 and N12 as compared to other batches because of having low concentration of tablettose in formulation. While N14 and N15 had high hardness and high disintegration time as compare to N13 because of having higher concentration of Tablettose in formulations. There was also high amount of drug release in N13 as compare to other batches in 15 min. So N13 had given best results of hardness of 3 kg/Cm^2, friability of 0.76, disintegration time of 35 sec and wetting time of 45 sec.

On the basis of the preliminary trials in the present study a 3^2full factorial design was employed to study the effect of independent variables, i.e. amount of directly compressible material (tablettose® 70, 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 table5 clearly indicate that all the dependent variables are strongly dependent on the selected independent variables as they show a variation among the nine batches(A1toA9)

Factorial Equation for disintegration and Percentage friability

Concerning disintegration time, the results of multiple linear regression analysis showed that the
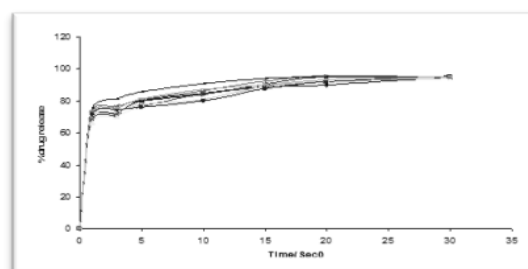

Figure2: cumulative percentage release profile of factorial batches

coefficients b1 bear negative sign and b2 bear a positive 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 not expected to decrease the disintegration time.Disintegration time is increased while increasing the concentration of Ac-di-sol duo to lump formation of superdisintegrants. Ac-di-sol 4% w/w and Tablettose® 70 80% were selected as the optimum concentration that showed minimal disintegration time of 24 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.

When higher percentage of Tablettose® 70 is used, it is expected to tablet became harder so increase in concentration of Tablettose® 70 leads to decrease in friability because of having higher binding between Tablettose® 70 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).
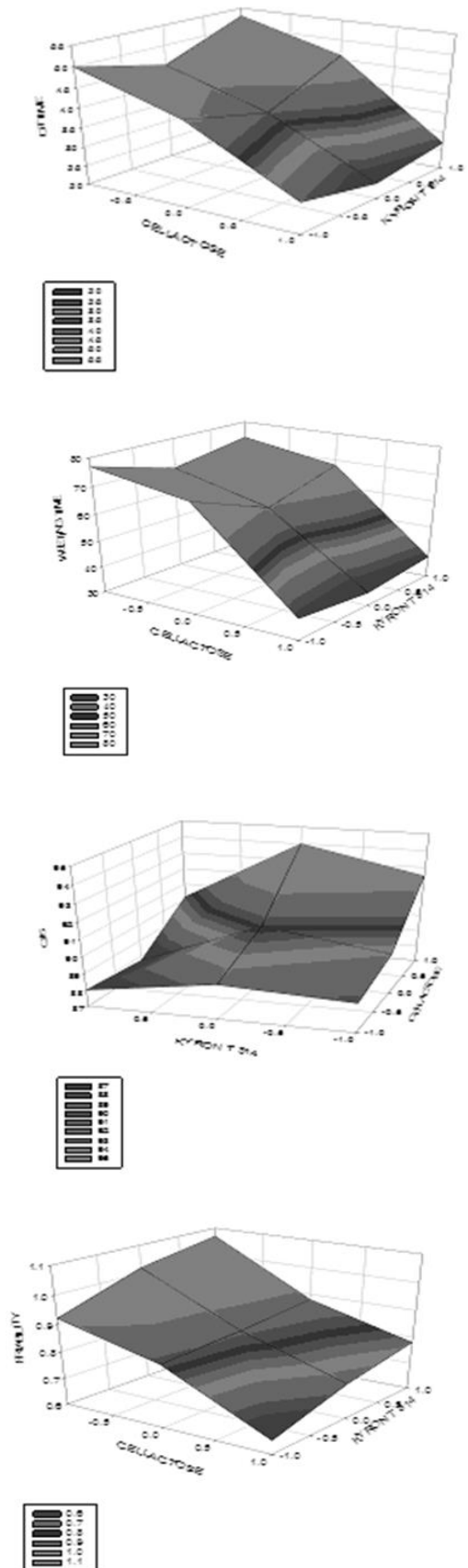
Disintegration time= 37.88-11.5 X_1 +1X2+5.66X1X2-1X_1^2 - 3.83X_2^2

(R^2 = 0.99)

Friability   =   0.861-0.1416X_1 +0.056X_2 -0.005X_1X_2 +0.0083X_1^2-0.0116X_2^2

(R^2= 0.96)

The graphical representation of the response surface plot (figure 3) demonstrate that both X_1 and X_2 affect the friability, wetting time, disintegration time,Q15

(Figure 6.22Surface plots for different factorial batches D1 to D9)

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 (0.96). Concerning dissolution, the results of multiple linear regression analysis showed that both the coefficients b1 and b2 bear a opposite sign. More amount of ac-di-sol were expected to decrease the drug release due to gel formation, While as indicated by positive sign of the coefficient b$_1$, increase in the amount of Tablettose® 70 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 opposite sign for wetting time of tablets. Additions of more amount of Ac-di-sol, wetting period of tablets were increase while the increase the amount of Tablettose® 70 wetting time decreases because of having hydrophilicity of the component lactose and cellulose. That means increasing concentration of superdisintegrant agent increase the wetting time 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= $61.88 - 18.5X_1 + 1.83X_2 + 0.25X_1X_2 - 10.84X_1^2 + 9.16X_2^2$ ($R^2 = 0.99$)

Q15 = $90.41 + 1.80X_1 - 0.79X_2 - 1.77X_1X_2 - 0.405X_1^2 + 1.17X_2^2$

($R^2 = 0.95$)

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 superdisintegrating agent. So here D8 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 D8 batch is concluded as a best formulation for preparing Cinnarizine FDT by direct compression method

REFERENCES

[1.] Lindgren, S., and L. Janzon. "Dysphagia: Prevalence of swallowing complaints and clinical finding." Med Clin North Am 77 (1993): 3-5.

[2.] Chang, R-K., Guo Xiaodi, Beth A. Burnside, and Richard A. Couch. "Fast-dissolving tablets." Pharmaceutical technology 24, no. 6 (2000): 52-58.

[3.] Parakh, S. R., and A. V. Gothoskar. "A review of mouth dissolving tablet technologies." Pharmaceutical technology 27, no. 11 (2003): 92-100.

[4.] Hanawa, T., Watanabe, A., Tsuchiya, T., Ikoma, R., Hidaka, M., & Hidaka, M,Chem. Pharmaceut. Bull., 1995, 43(2), 284–288.

[5.] Sastry S V ,Nyshadham   J R ,Pharm   SciTechnol Today, 2000;3:138-45 [6.] Virely, P., &Yarwood, R.,.Manufac. Chem. 1990, 36–37.

[7.] Seager, H. "Drug-delivery products and the zydis fast-dissolving dosage form*." Journal of pharmacy and pharmacology 50, no. 4 (1998): 375-382

[8.] Patent: Habib W ,   Khankari R K , Hontz   J , Crit Rev Ther Drug Carrier Sys 2000;17:61-72.

[9.] Dobetti L. Fast disintegrating tablets. US Patent, 6:596,311.(2003) [10.] Behnke K et al. indian journal of pharmasci, 2003, 55;245-249

[11.] Indian Pharmacopoeia, 4th edition, Ministry of Health and Family Welfare, Govt. of India. The controller of publications, New Delhi.1996: A-54.

[12.] Lachman.L, Lieberman.A, Kinig.J.L. The Theory and Practice of Industrial Pharmacy, 4th edition, Varghese Publishing House, Bombay.1991: 67-68.

[13] Patel, D. M., R. R. Shah, and P. D. Jogani. "Tablet formulation of piroxicam containing PVP K-30 and sodium lauryl sulphate." Indian journal of pharmaceutical sciences 66, no. 1 (2004): 49-55

[14]British pharmacopoeia, The stationary office of the medicine and healthcare products regulatory agency, Great Briton. Volume-1: 2005. 695-697.

[15] Gohel M, Patel M, Amin A, Agrawal R, Dave R, Bariya N., AAPS Pharm.Sci.Tech. 2004;5: E 36