American Journal of Multidisciplinary Research & Development (AJMRD)
Volume 04, Issue 03 (March - 2022), PP 61-68
ISSN: 2360-821X
www.ajmrd.com

Research Paper **Open Access**

Formulation and Evaluation of Oro-Dispersible Tablet of Cinnarizine Using Natural Disintegrating Agent

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ABSTRACT: *This study deals with development of oro dispersible tablet of cinnarizine which was prepared using natural disintegrant Lepidiumsativum's mucilage at different concentration using direct compression method. The formulated tablets were evaluated for weight variation, hardness, friability, water absorption ratio, disintegrating time and assay.DryLepidium powder was used in 4%, 6%, 8%, 10%, 12% & 14% of total weight 200 mg of tablets to formulate bateches B1-B6 and other excipients Microcrystalline cellulose, Magnesium stearate & Talc were used accordingly. Also to examine whether lepidium will act as disintegrant or not we formulated another batch B0 in whichlepidium was excluded. In this way the B0 batch was manufactured and disintegration test was performed and compared to first batch B1. B0 batch showed no disintegration within 3 minutes where as B1 batch showed disintegration within 2 minutes, which proved disintegration property of lucidium.Formulation of all batches showed optimumlimitsfor weight variation, hardness, friability of tablet. The tablets disintegrated within 40 to 110 sec. When lepidium was used at 8 percent concentration, disintegration time was least 40 seconds and it fulfilled all the other specification. Therefore, lepidium can be effectively used as disintegrant in cinnarizineoro dispersible tablet.*

Keywords: *Direct compression, Oro-dispersible, Cinnarizine, Disintegrants, Disintegration time.*

I. INTRODUCTION

The most common and preferred route of drug administration is through the oral route. Oro-dispersible tablets are gaining importance among novel oral drug-delivery system as they have improved patient compliance and have some additional advantages compared to other oral formulation [1].

Oro-dispersible tablets (ODT) are solid dosage forms containing drugs that disintegrate in the oral cavity within less than 3 minute leaving an easy-to-swallow residue [2]. The ODT formulation defined by the Food and Drug Administration (FDA) as "a solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds when placed upon the tongue". It is a good choice of drug delivery for pediatric and geriatric patients because it troubleshoots the problem of dysphagia [3].

Cinnarizine is an antihistamine and calcium channel blocker of the diphenylmethylpiperazine group which inhibits contractions of vascular smooth muscle cells by blocking L-type and T-type voltage gated calcium channels. It has also been implicated in binding to dopamine D2 receptors, histamine H1 receptors, and muscarinic acetylcholine receptors. It is prescribed for nausea and vomiting due to motion sicknessor other sources such as chemotherapy, vertigo or Meniere's disease [4].

Vertigo is the sensation that the environment is spinning around relative to oneself (objective vertigo) or vice versa (subjective vertigo). The term is sometimes used erroneously to mean any form of dizziness. True vertigo is described as a rotary sensation of the patient or surroundings, and is often of vestibular origin. This may be associated with nausea, vomiting, sweating, or difficulties walking [5].Meniere's disease (or idiopathic endolymphatic hydrops) is a disorder of the inner ear characterized by hearing loss, tinnitus, and vertigo. It is named after the French Physician Prosper Meniere (1799-1862) who first recognized vertigo as an inner ear disorder [5]Nausea and vomiting are two of the most feared cancer treatment-related side-effects. Ranked over the world, the first and second most severe side-effect of chemotherapy are nausea and vomiting [5].

In geriatric as well as other patients' normal dosage forms such as tablets and capsules are less convenient to administer due to dysphagia and other causes so to eradicate such causes oro-dispersible tablets

plays a very important role. Since oro-dispersible tablets dissolve within mouth and taste masking properties can be included as well it helps in proper administration of drug.

Also when there is a need for immediate drug release to show immediate pharmacological effect, dosage form such as tablet and capsules take significant time whereas oro-dispersible tablet shows immediate action. Since the drug disintegrate rapidly in mouth and it is absorbed rapidly and shows increased bio-availability and immediate pharmacological effect.

The study helps in the selection of optimum concentration of disintegration agent for the formation of mouth dispersible cinnarizine tablet. Study helps to formulate ODTs which increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.

II. MATERIALS AND METHODOLOGY

2.1 Materials

Cinnarizine& MCC of industrial grade were granted to us by Lomus Pharmaceuticals Pvt. Ltd, Nepal. *Lepidiumsativum*linn seeds were obtained from the local market. All of the chemicals used were of analytical grades.Instruments used during this study are listed in table 1.

Table 1: List of instruments used

S.N.	Instruments	Manufacturer Company
1	Tablet Compression Machine	(R & D press)
2	Disintegration Apparatus(Single Type)	DICA India
3	Hardness Tester	Electro Lab
4	Friability Test Apparatus	DICA India
5	Thermometer	Victo Lab
6	PH Meter	N/A
7	UV-Visible thermometer	Shimadzu UV-1700 Sharma Spec

1.2 Extraction of Mucilage from *Lepidiumsativum* Seeds [6]

100 gm of seed were soaked for 12 hrs in one liter distilled water and then passed through blender to separate mucilage from seeds. The mass was passed through eight folds of muslin cloth. The mucilage was precipitated from the filtrate by adding 1 liter of acetone. The powder was passed through 70# mesh sieve and weighed to calculate the yield after drying at 55 degrees for 6 hrs.

1.3 Formulation of Oro-Disintegrating Tablets [7]

ODTs of cinnarizine were prepared by direct compression method using natural disintegrant *Lepidium sativum* mucilage. Natural disintegrant in different concentration were used so as to get tablets with good disintegrating properties. All the ingredients were passed through 60 mesh sieves. A weighted quantity of each ingredient was taken, and the powder blend was then compressed on tablet compression machine using flat faced punches.
The composition of each formulation is given in table 2.

Table 2: Formulations B1-B7 by varying percentage of *Lepidium*

SN	Composition	Formulation Code (mg)						
		B1 (0%)	B2 (4%)	B3 (6%)	B4 (8%)	B5 (10%)	B6 (12%)	B7 (14%)
1	Cinnarizine	25	25	25	25	25	25	25
2	Lepidium	Null	8	12	16	20	24	28
3	MCC	162	154	150	146	142	138	134
4	Talc	10	10	10	10	10	10	10
5	Mg. Stearate	3	3	3	3	3	3	3
	Total	200	200	200	200	200	200	200

1.4 Direct Compression Technique [4]

Direct compression is the most straightforward manufacturing option, with the fewest manufacturing steps, making it the easiest to control and least expensive. The direct compression tablet process uses two primary process steps: blending the API with excipients and compressing the finished tablets.

Different tablets were prepared by direct compressing technique. During which diluents, disintegrant and surfactant, magnesium stearate was passed through sieve #70 sieve. Required quantity of drug and surfactant were mixed first than other excipients were mixed thoroughly. The powder was compressed using cad Mach compression machine equipped with one biconvex punch.

1.5 Evaluation of Powder Blends

1.5.1 Bulk density [7]

Bulk density to a measure used describes a packing of particles. It is (gm/ml) and was determine using a balance and measuring cylinder. Initially the weight of the measuring cylinder was taken.

Then, 4gm of pre-sieved bulk drug were poured in to the measuring cylinder using a funnel and weighed (m). Then volume of the power (vb) was taken. Bulk density of the granules was calculated using following formula.

$Bulk\ density = Weight\ of\ Powder\ /\ Volume\ of\ Powder$…..……..(1)

1.5.2 Angle of Repose [7]

Angle of repose was determined by funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (V) was measured and angle of repose was calculated. It is used to determine the flow property of powder.

$$Tan\theta = h/r$$

$$\theta = tan - 1(h/r) \quad \text{…… (2)}$$

Table 3: Angle of Repose

Angle of Repose	Flow Properties
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

1.5.3 Weight Variation [7]

The weight variation test was performed as per the official procedure, 20 tablets were randomly selected and weighted individually and also average and individual was calculated, further percentage of weight variation was also calculated IP limits for weight variation are given below.

Table 4: Weight variation

IP	Limit
80 mg or less	± 10%
More than 80 mg or less than 250 mg	± 7.5%
250 mg or more	± 5%

1.5.4 Friability Test [7]

It is usually performed in the single drum friabilator. 10 tablets were taken randomly and weight of each tablet was taken and their initial total weight (W1) was recorded and after that these tablets were placed in the friabilator. The friabilator was operated for four minutes at 25 rpm speed and after that the tablets were taken out and weighted again (W2) and the percent loss was then calculated by using following formula,

$Percentage\ Friability\ (\%) = [(W1 - W2)/W1]x\ 100$ …..… (3)

The official permissible limit for friability is not more than 1%

1.5.5 Hardness [7]

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Mosanto hardness tester, which applies force to the diametrically with the help of an inbuilt spring.

The permissible value of hardness for an ODT is 3-5 kg/cm^2

1.5.6 Disintegration Test [7]
The disintegration time was measured using disintegration test apparatus one tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless steel screen (mesh no 10) was immersed in water bath at 37±2°c. The time required for complete disintegration of the tablet in each tube was noted using a stopwatch which is to be compiled with the pharmacopieal standards of dispersible table.
The permissible limit is within 3 minutes.
1.5.7 Assay of Tablets [7]
Accurately weighted 20 tablets taken at random were powdered, the powder equivalent to 25 mg of cinnarizine was transferred to a 100 ml volumetric flask and dissolved with 0.1 N HCL. The volume was made up to mark using 0.1N HCL.
After dissolving the powdered mixture, it was filtered and 4ml of the filtrate was taken and transferred to 100 ml volumetric flask. The volume was made up to mark using 0.1N HCL. This process produces 10 ppm solution. Similarly, 20 ppm solution was prepared by taking 8, 12, 16 ml of filtrate and diluting to 100 ml in 100 ml volumetric flask using 0.1N HCL. This obtained strength of 10, 20 ppm was later evaluated in UV-Spectrophotometer at 254 nm wavelength [7]. The permissible assay range is 100±5.

III. RESULTS AND DISCUSSION

3.1 Formulations
To formulate oro-dispersible Cinnarizine tablets by direct compression method we used different concentration of super disintegrating agent *Lepidium sativum* mucilage. Formulation code was based on total weight of the tablet and the percentage usage of *Lepidium sativum*. 0%, 4%, 6%, 8%, 10%, 12% & 14% lepidium were used of total weight of tablet and other excipients were used accordingly. We estimated total weight of tablet to be 200 mg. The formulation table is presented in table 2.
3.2 Physiochemical Properties of *Lepidium sativum*[8]
Before the formulation of tablet some criteria for lepidium powder were to be evaluated so that it can be used for formulation of oro-dispersible tablet. This table below shows some physiological properties of the lepidium we extracted. Percentage yield was low because the mucilage produced by the seeds were in small quantity and also there is loss in mucilage while blending in mixture and also at drying. All the other criterias for thelepidium powder to be used in the formulation were met, as shown in table 5.
Table 5: Physiochemical Properties of *Lepidium sativum*

SN	Parameter	Value
1	Percentage Yield	10 %
2	Bulk Density	0.64
3	Tapped Density	0.75
4	Carr's Index	14.6
5	Angle of Repose	28
6	pH (1% W/V)	Neutral

3.3 Flow Properties [7]
Angle of repose of formulation B1 to B6 was calculated and highest and lowest was 29.5 & 27.6 respectively. According to the permissible limit, the powder blend showed good flow property as the value ranges from 25-30. Proper sieving was done for lepidium and as well as mixture of other excipients which also resulted in good flow properties. Angle of repose of *lepidium* was also in the criteria as well as other excipient also had good angle of repose so overall angle of repose was also within the range

Table 6: Pre-Compressibility Test parameters

SN	Batch	Pre-Compressibility Test					
		Bulk Volume	Tapped Volume	Bulk Density	Tapped Density	Compressibility Index	Angle of Repose
1	B1	27.7	24	0.44	0.5	11.2	28.8
2	B2	29.2	25.5	0.41	0.47	12	29.5
3	B3	22.6	22.6	0.53	0.53	10	29.5
4	B4	29.26	20.6	0.41	0.58	9.8	27.62
5	B5	22.64	25.5	0.47	0.53	11.3	28.4
6	B6	25.64	20.6	0.46	0.58	20.6	29.0

3.4 Weight Variation [7]

Limit for weight variation is ± 7.5% for the tablets weighing between 80-250 mg. Tablet shows average weight, standard deviation for 20 tablets of each batch of cinnarizine tablet. The result of weight variation was calculated in which highest and lowest data were 0.95 & 0.125. Total weight of tablet is 200 mg but there is loss while manufacturing of the tablet and as well as while compression so this loss in weight is managed by tooling the compression machine. Over all the weight variation data were within the limit.

Table 7: Weight variation of different batches

SN	Batch	Weight Variation		
		Actual Weight(mg)	Observed Weight(mg)	Variation(%)
1	B1	200	199.7	0.15
2	B2	200	199.75	0.125
3	B3	200	199.25	0.375
4	B4	200	200.8	0.4
5	B5	200	198.1	0.95
6	B6	200	200.5	0.25

3.5 Friability [7]

In the official guideline, it was noted that the percentage of weight loss must be not more than 1%. All the formulation of oro-dispersible tablet compiles the friability test. Friability of tablet of all the batches were within the range. Also, since we used direct compression technique, MCC here acts as strong binder so the loss in friability was very less. This resulted in very low loss in tablet weight as the resistance of tablet towards mechanical stress increased.

Table 8: Friability test of different batches

SN	Batch	Friability Test		
		Initial weight	Final weight	Friability %
1	B0	1.992	1.99	0.100402
2	B1	1.99	1.976	0.703518
3	B2	1.998	1.995	0.15015
4	B3	2.003	2.001	0.09985
5	B4	2.001	1.999	0.09995
6	B5	1.991	1.987	0.200904
7	B6	1.996	1.991	0.250501

3.6Hardness [7]

The result of hardness for formulations B1 to B6 were calculated in which highest and lowest data were 3.6 & 3.5 kg/cm^2, which was within the permissible limit. In the beginning hardness of the tablet was significantly low, so it couldn't stand the mechanical stress and showed loss during friability test. Therefore, to overcome this problem we increased the total weight of tablet to 200 mg and increased the amount of MCC used and this resulted in appropriate hardness of the tablet. Thus increasing binder amount increases the hardness of the tablet.

Table 9: Hardness of different batches

SN	Batch	Average hardness (Kg/cm^2)
1	B0	3.7
2	B1	3.5
3	B2	3.6
4	B3	3.5
5	B4	3.6
6	B5	3.6
7	B6	3.5

3.7 Thickness [7]

Thicknesses of different batches of tablet were calculated using 'Vernier Caliber'. The highest and lowest thicknesses were seen as 3.8 & 3 mm and the data is tabulated below in table 10. The thickness of the tablet was managed to appropriate criteria by tooling the compression machine. Increasing pre-compressibility and compressibility value of machine we achieved appropriate thickness of the tablet. Thickness of all the tablets were within the range.

Table 11: Thickness of different batches

SN	Batch	Average Thickness(mm)
1	B0	3.16
2	B1	3.23
3	B2	3.36
4	B3	3.33
5	B4	3.36
6	B5	3.43
7	B6	3.6

3.8 Water Absorption [7]

Water absorption ratios of different batches were calculated and the highest and lowest absorption ratios were found as 72% and 10% respectively. The data is tabulated below in the table 4.7. B1,B2,B3 absorb water in high quantity , where B3 batch absorbs water the highest that is 72%, but after that water absorption decreases. It might be because the amount of lepidium in third batch is 8%, so lepidium here acts as disintegrant but other batches after B3 have lepidium in high concentration that is 10%, 12%, 14%, here lepidium acts as a binder so water absorption is minimum.

Table 12: Water absorption ratio of different batches

SN	Batch	Water Absorption Ratio
1	B1	52%
2	B2	68%
3	B3	72%
4	B4	35%
5	B5	12%
6	B6	10%

3.9 Disintegration Time [9]

The time taken to break each tablet into small particles or granules and pass out through the mesh or no particles or granules left in the tube was recorded. Disintegration time was calculated and highest and lowest was found to be 110 & 40 sec. In the table 13, we can see that with increase in amount of lepidium the disintegration time decreases but eventually after B3 batch the disintegration time increases. This showed that when lepidium is used at 8% of the overall weight it gives optimal disintegration time that is 40 seconds. This might be because after 8% concentration lepidium starts acting as a binder rather than showing disintegration property. Since B1, B2, B3 all contained a binder that is MCC and a disintegrant that is lepidium but after B3 the disintegrant shows its binding property rather than its disintegration property so the disintegration time after B3 increases. Among all the batches, B3 showed best disintegration result. Batch B3 showed optimal result in the entire parametric test with hardness of 3.5, water absorption 72%, assay 101.5%, thus making the batch B3 an optimal oro-dispersible tablet of cinnarizine.

Table 13: Disintegration time different batches

SN	Batch	Disintegration Time (Min:Sec)					
1	B0	> 3mins	> 3mins	> 3mins	> 3mins	> 3mins	> 3mins
2	B1	1:49	1:50	1:35	1:42	1:44	1:53
3	B2	52 sec	55 sec	53 sec	56 sec	56 sec	52 sec
4	B3	43csec	40 sec	48 sec	45 sec	40 sec	43 sec
5	B4	59 sec	50 sec	52 sec	47 sec	49 sec	48 sec
6	B5	55 sec	55 sec	51 sec	60 sec	60 sec	58 sec
7	B6	1:10	1:08	1:15	1:20	1:05	1:22

3.10 Assay [8]

Drug content for each batch were calculated and the assay value with highest assay percentage was found to be of batch B6 and the lowest assay percentage was found to be of batch B4. The data is tabulated below in table 14. All the batches showed permissible assay value. We calculated the equivalent weight of powdered 20 tablets that is equal to 25 mg of cinnarzine and then run it in the UV spectrophotometer after sufficient dilution to 10 ppm. The absorbance values were right around the standard one giving us the data as in Table 14. All the batches were within the assay range.

Table 14: Assay of different batches

SN	Batch	Absorbance	Assay Percentage
1	B1	0.398	99.59
2	B2	0.408	102.2
3	B3	0.406	101.5
4	B4	0.392	98.18
5	B5	0.403	100.8
6	B6	0.419	104.8

Calibration curve as shown in Fig. 1 prepared using standard drug was used to carry out the assay of tablets of different batches.

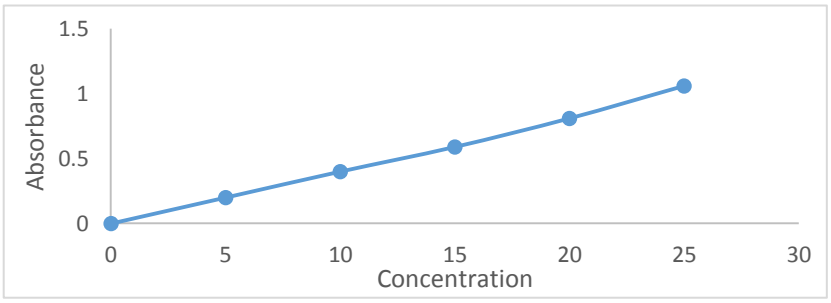

Figure 1: Plot of concentration vs. absorbance

IV. CONCLUSION

Attempt was made in the present investigation to make an oro-dispersible tablet of cinnarizine by direct compression method. Formulations was carried out using different concentration of *Lepidiumsativum* as disintegrant and optimize this concentration, hardness of the tablets to give the minimum disintegrations time and maximum drugs release.

In this study, the effects of different concentration of natural disintegrants on ODTs of Cinnarizine were studied. It was found that cinnarizine tablet passes for hardness, friability, disintegration time and content of drugs. It was observed that when *Lepidium sativum* mucilage powder was used at 8 % concentration of total weight, disintegration time was lowest*i.e.,*40 seconds, which was the best formulation among all six batches. Hence, *Lepidium sativum* mucilage can be used to formulate oro-dispersible tablet of cinnarizine.

REFERENCES

[1]. P. Dey and S. Maiti,Orodispersible Tablets: A New Trend in Drug Delivery,*Journal of natural science, biology, and medicine*, 1(1), 2010, 2-5.

[2]. A. Roy,Orodispersible tablets: A review, *Asian J Pharm Clin Res*,2(1), 2016, 19–26.

[3]. D. Sivadasan, M.H. Sultan, O. Madkhali, S. Javed, and A. Jabeen, Formulation and in vitro evaluation of orodispersible tablets of fexofenadine hydrochloride,*Tropical Journal of Pharmaceutical Research,* 19(5), 2020, 919-925.

[4]. R. K. Dhahir, and M. Y. Al-Kotaji, Formulation of orally disintegrating tablets of cinnarizine by using direct compression method, *Int J Appl Pharm*, 11(1), 2019, 117-123.

[5]. S. Rosen, MÉNIÈRE'S DISEASE: Successful Treatment by Chorda Tympanectomy, *AMA Arch Neurol Psychiatry*, 72(6), 1954, 682.

[6]. A. Pahadia, R. Gawde, S. Agrawal, and N. Manocha, Utilization of Natural Superdisintegrants in Orodispersible Tablets: A Review, *International Journal of Pharmacy Research & Technology*, 3(2), 2019, 312-317.

[7]. P. Nagar, K. Singh, I. Chauhan, M. Verma, M. Yasir, A. Khan, R. Sharma, and N. Gupta,orally disintegrating tablets: formulation, preparation techniques and evaluation,*J Appl Pharm Sci*, 1(4), 2011, 35-45.

[8]. R. Hajiboland, S. Bahrami-Rad, N. Zeinalzade, E. Atazadeh, H Akhani, and C. Poschenrieder, Differential functional traits underlying the contrasting salt tolerance in Lepidium species,*Plant and Soil*, 448(1-2), 2020, 315-334.