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Formulation and evaluation of fast dissolving tablets of cinnarizine using various superdisintegrants

Injamamul Haque[1*], KJ Hanumanthachar[2], Chaithanya AN[3], Subhajit Ghosh[4]
[1-4] Sarada Vilas College of Pharmacy, Mysore, Karnataka, India

Abstract
The aim of this study was to develop fast dissolving tablets of cinnarizine by direct compression method. Micro crystalline cellulose (MCC) as diluent and super disintegrants, such as crospovidone (CP), sodium starch glycolate and croscarmellose sodium (CCS) were used. Fast dissolving tablets disintegrates or dissolves rapidly within few seconds due to maximized pore structure in the formulation or by the action of superdisintegrants. Infrared (IR) spectroscopy was performed to identify the physicochemical interaction between drug and polymer. IR spectroscopy showed that there was no interaction of drug with polymer. Various pre-compression parameters such as angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio were carried out to study the flow properties of powder in order to achieve uniformity of tablet weight and the values were found within acceptable limits. The powder mixtures were compressed into tablet using punch tablet machine.
The formulated tablets were evaluated for hardness, thickness, weight variation, friability,% drug content, wetting time, water absorption ratio, *in vitro* disintegration time, *in vitro* dispersion time, *in vitro* drug release and all the values were found within permissible limits. The formulation M12 containing crospovidone (8%) as superdisintegrant and MCC as diluent was found to be the optimized formulation on the basis of wetting time, *in vitro* disintegration time and *in vitro* drug release. Stability studies were carried out at $25^0C \pm 2^0C$ / 60% ± 5% RH and $40^0C \pm 2^0C$ / 75% ± 5% RH for a period of 60 days for the selected formulations.

Keywords: fast dissolving tablets, cinnarizine, superdisintegrants, diluent

Introduction
In the pharmaceutical industry oral delivery is the gold standard because of its convenience in terms of self-administration, compactness, economical and ease in manufacturing having the highest patient compliance [1].
Fast disintegrating or dissolving tablets are novel types of drugs that dissolve/ disintegrate/ disperse within few seconds without water in saliva. The formulation is more useful for the patients who have swallowing problem. The benefits of MDTs is to improve patients compliance, rapid onset of action, increased bioavailability and good stability which make these tablets popular as a dosage form of choice in the current market [2-3].
Fast dissolving tablets (FDT) is defined by US FDA as "A solid dosage form having medicinal substance or active ingredients when placed upon the tongue should disintegrate rapidly within a matter of seconds" [4].
In the present study an attempt was made to formulate directly compressible orally disintegrating tablets of cinnarizine to assist patients of any age group for easy administration. It is used for the treatment of vertigo, nausea, vomiting, and motion sickness with rapid dissolution and absorption of drug which may produce rapid onset of action by the use of different super disintegrants which provides instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva.
Cinnarizine act by inhibiting the contractions of vascular smooth muscle cells by blocking calcium channels. It increases erythrocyte deformability and reduces blood viscosity. It inhibits stimulation of the vestibular system. Peak plasma concentration occurs 2 to 4 hours and its plasma half-life is about is about 3 to 4 hours after an oral dose. It is water insoluble and tasteless. So, it was selected as a model drug for the preparation and evaluation of fast dissolving tablets.

Materials and Method
Materials
Cinnarizine was obtained as a gift sample from Yarrow Chemicals and Pharmaceutical (Mumbai, India). Microcrystalline cellulose, cross carmellose sodium, sodium starch glycolate and crospovidone were obtained as a gift samples from Zydus research centre, Ahmadabad. Sodium saccharin and magnesium stearate were purchased from Fine chemicals. All other chemicals and solvents used were of analytical reagent grade.

Method
Preparation of Cinnarizine fast dissolving tablet by direct compression method
All the raw materials were passed through 80 mesh prior to mixing. Cinnarizine and all excipients were physically mixed using mortar for 15 minutes. The addition of sweetener (Sodium saccharin) impacts satisfying taste to the formulation. Then, the powder mixture was lubricated with 1% magnesium stearate and compressed into tablets using rotary tablet punching machine (Hardik Eng. Pvt. Ltd, Ahmedabad). The composition of formulation is shown in the table 1.

Table 1: Composition of mouth dissolving tablets of Cinnarizine with microcrystalline cellulose as diluent

Ingredients	FORMULATIONS (mg)											
	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Cinnarizine	25	25	25	25	25	25	25	25	25	25	25	25
SSG	2	4	6	8	--	--	--	--	--	--	--	--
CCS	--	--	--	--	2	4	6	8	--	--	--	--
CP	--	--	--	--	--	--	--	--	2	4	6	8
MCC	64	62	60	58	64	62	60	58	64	62	60	58
Sodium saccharin	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3
MS	3	3	3	3	3	3	3	3	3	3	3	3
Total weight	100	100	100	100	100	100	100	100	100	100	100	100

SSG- Sodium Starch Glycolate, CCS- Croscarmellose Sodium, CP- Crospovidone, MCC- Microcrystalline Cellulose, MS- Magnesium Stearate

Evaluation of Cinnarizine fast Dissolving Tablets

Pre-compressional studies [5-8]

i) Angle of Repose (Ɵ)

The frictional force in powder can be measured by the angle of repose. It is the maximum angle possible between the surface of pile of powder and the horizontal plane. The blend that has angle of repose between 20^0-30^0 is best for compression as it has good flow property. Angle of repose is calculated by fixed funnel method. In this method funnel was fixed to a stand in such a way that the lower tip of funnel was 2.5 cm above the surface. A graph paper was placed on the flat surface. The blend was allowed to fall freely on the graph paper through the funnel, till the tip of heap formed just touches the funnel. The radius of heap was noted and from this angle of repose was determined using the following equation,

$\tan\theta = h/r$

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

Where, h = height of pile (cm)
r = radius of the base of pile (cm)

ii) Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume. A sample of about 2.5 gm was poured into 10ml-graduated cylinder. The volume was recorded and the bulk density was calculated using the following equation,

Bulk density = weight of sample taken / volume noted

iii) Tapped density

A sample of about 2.5 gm was poured into 10ml-graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wooden surface three times, from a height of one inch. The volume was recorded and the tapped density was calculated using the following equation,

The taped density was calculated by using the following formula

$\rho t = M/Vt$

Where

Vt =minimum volume occupied after tapping (cm3)

M= the weight of blend (gm)

ρt=tapped density

iv) Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it is packed down. The formula for Carr's Index is as below,

$$\text{Carr's Index } (\%) = \frac{[(\text{TBD} - \text{LBD})\ x100]}{\text{TBD}}$$

Where,

LBD = Loose Bulk Density

TBD = Tapped Bulk Density

v) Hausner ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The Hausner ratio of the powder was determined by the following equation:

Hausner ratio = TBD / LBD

Post-Compressional studies [9-11]

i) General appearance

The fast dissolving tablets morphological characterization such as size, shape, colour, presence or absence of odour, taste and surface texture were determined.

ii) Thickness and diameter

Five tablets were picked from each formulation randomly and thickness and diameter was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness and diameter was measured using vernier caliper.

ii) Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm [2]. Five tablets were randomly picked and hardness of the same tablets from each formulation was determined.

iv) Friability test

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche Friabilator was used for the purpose. Pre-weighed sample of ten tablets were placed in the Friabilator, which was then operated at 25 rpm for 4 minutes or ran up to 100 revolutions. After 100 revolutions the tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

The% friability was then calculated by the following formula,

Percentage friability = (Initial weight - Final weight /Initial weight) × 100

v) Weight variation

20 tablets were selected randomly from each formulation and weighed individually to check for weight variation. The US Pharmacopoeia allows a little variation in the weight of a tablet.

vi) Drug content uniformity

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 10 mg was weighed accurately and dissolved in 100ml of pH 6.8 buffer solution. The solution was shaken thoroughly. The undisclosed matter was removed by filtration through what mann filter paper. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 254 nm. The concentration of the drug was computed from the standard curve of the cinnarizine in pH 6.8 buffer solution.

vii) Wetting time and water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish (i.d = 6.5 cm) containing 6 ml of pH 6.8 buffer. A tablet was placed on the paper and the time required for complete wetting was then measured.

The water absorption ratio, R, was determined using the following equation,

$$R = Wa - Wb / Wb \times 100$$

Where,

Wb is the weight of the tablet before water absorption

Wa is the weight of the tablet after water absorption.

viii) *In vitro* dispersion time

In vitro dispersion time was measured by dropping tablets in a measuring cylinder containing 10ml of buffer pH 6.8 at 37±0.5^{0}C. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

ix) *In vitro* disintegration time

The disintegration time was performed by apparatus specified in USP at 50 rpm. 900 ml of buffer pH 6.8 was used as disintegration medium and the temperature of 37± 0.5^{0}C and time in seconds was taken for complete disintegration of the tablet.

x) *In vitro* drug release studies

In vitro release of Cinnarizine tablets were determined by using USP XXIV paddle dissolution apparatus (Electrolab TDT-06P) at 50 rpm using 900 ml of buffer pH 6.8 and temperature was maintained at 37±0.5°C throughout the study. 5 ml sample was collected at regular intervals for 2 min and the same volume of fresh medium was replaced. The samples withdrawn were filtered and drug content in each sample was analyzed after suitable dilution by Shimadzu 1700 UV-Visible spectrophotometer at 254 nm.

xi) Stability Studies

It is the responsibility of the manufacturers to see that the medicine reaches the consumer in an active form. So the stability of pharmaceuticals is an important criterion. 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 present study, stability studies were carried out at 25^{0}C ± 2^{0}C / 60% ± 5% RH and 40^{0}C ± 2^{0}C / 75% ± 5% RH for a period of 60 days for the selected formulations. The formulations were then evaluated for changes in the physicochemical properties, wetting time, *in vitro* disintegration time and *in vitro* drug release.

Results and Discussion

Calibration curve of cinnarizine

Solutions of cinnarizine (2, 4, 6, 8, 10, 12 µg/ml) were prepared using acidic buffer pH 1.2 and absorbance was measured using UV-Visible spectrophotometer (Shimadzu 1700, Japan) at 254 nm.

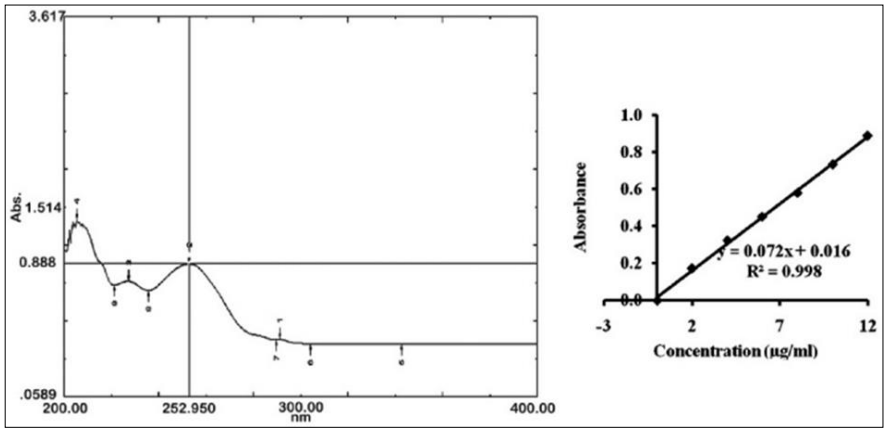

Fig 1: Calibration curve of cinnarizine

Drug- polymer interaction studies

Fourier Transform Infra-Red (FT-IR) spectral analysis

Fourier–Transform Infrared (FT–IR) spectrums of pure cinnarizine and combination of drug and excipients were obtained by a Fourier-Transform Infrared spectrophotometer, (FTIR-8300, Shimadzu, Japan) using the KBr disk method. The scanning range was 400 to 4000 cm^{-1} and the resolution was 1cm^{-1}. This spectral analysis was employed to check the compatibility of drugs with the excipients used.

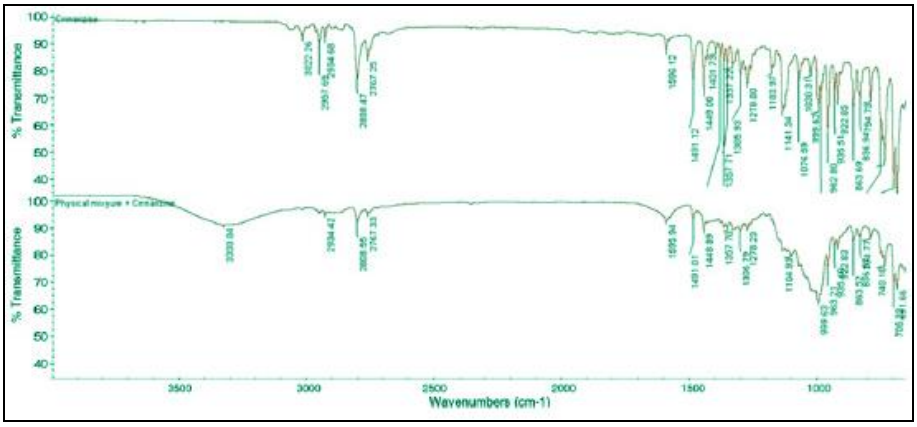

Fig 2: FTIR spectra of pure cinnarizine and physical mixture

Pre compressional Parameters

Powder ready for compression containing drug and various excipients were subjected for various pre compressional evaluation parameters such as bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. Pre-compressional parameters (Micromeritic properties) were studied to determine the flow properties of granules, to achieve uniformity of tablet weight. The results of all the pre formulation parameters are given in table 2.

Angle of repose (θ)

The data obtained from angle of repose for Cinnarizine was found to be 23.93^0 to 28.68^0. All the formulations showed the angle of repose less than 31^0, which reveals good flow property.

Bulk density

Bulk density for the blend was performed. The bulk densities of Cinnarizine ranged from 0.43 gm/cc to 0.58gm/cc.

Tapped density

Tapped bulk density (TBD) for the blend was performed. The tapped bulk density of Cinnarizine ranges from 0.49 gm/cc to 0.78 gm/cc respectively.

Carr's consolidation index

The results of Carr's consolidation index or compressibility index (%) of Cinnarizine ranged from 11.53% to 25.64%.

Hausner ratio

Hausner ratio of Cinnarizine was found to be Between 1.13 to 1.31 which indicates better flow properties.

Table 2: Pre compression evaluation of drug/excipient mixture containing microcrystalline cellulose as diluent

Formulation Code	Angle of Repose	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner's Ratio
M1	25.75	0.47	0.54	12.96	1.14
M2	24.89	0.45	0.51	11.76	1.13
M3	27.01	0.53	0.62	14.51	1.16
M4	28.68	0.44	0.50	12	1.13
M5	24.14	0.45	0.52	13.46	1.15
M6	23.93	0.53	0.60	11.66	1.13
M7	26.09	0.46	0.52	11.53	1.13
M8	27.39	0.45	0.51	11.76	1.13
M9	24.8	0.50	0.59	15.25	1.18
M10	25	0.47	0.54	12.96	1.14
M11	27.02	0.43	0.49	12.24	1.13
M12	27.8	0.53	0.62	14.51	1.16

Post-Compressional Parameters

All the tablet formulations were evaluated for parameters such as shape, colour, thickness, hardness, friability, weight variation, drug content, and *in vitro* disintegration time, *in vitro* dispersion time, wetting time, *in vitro* dissolution studies and stability studies.

a) General appearance

All the fast dissolving tablets from each batch were found to be flat, white in colour, circular in shape and having good physical appearance. There was no change in the colour and odour of the tablets from all the batches.

b) Thickness and diameter

The range for tablets of Cinnarizine ranged from 3.12 ± 0.01 to 3.16 ± 0.03mm respectively. The standard deviation values indicated that all the formulations were within the range.

c) Hardness

The hardness of all the tablets prepared by direct compression method was maintained within the range of 3.3 ± 0.23 to 3.9 ± 0.23 kg/cm^2. The obtained results revealed that the tablets were having good mechanical strength and compactness.

d) Friability

The friability found for Cinnarizine was in the range of 0.23 to 0.38%, within the approved range (<1%) which indicates the tablets had good mechanical resistance.

e) Weight variation

The weight variation was found in the range of 99.83±0.36 to 100.92±0.41 mg for Cinnarizine. The weight variation results revealed that average percentage deviation of 20 tablets of each formula was less than ±7.5% i.e. in the pharmacopoeial limits which provide good uniformity in all formulations.

f) Drug content

To evaluate a tablet's potential for efficacy the amount of drug in the tablet need to be monitored from tablet to tablet and batch to batch. The percentage drug content was found to be in the range of 98.3 ± 0.50 to 99.85 ± 0.62%.

g) Wetting time

Wetting time is an important parameter related to water absorption ratio, which needs to be assessed to give an insight to the disintegration properties of the tablets. Water absorption ratio for these formulation batches varied in the following decreasing order:

Crospovidone > Croscarmellose sodium > sodium starch glycolate

Formulation batches of M1-M12 wetting time was found between 26 to 47 seconds.

h) Water Absorption Ratio

Water absorption ratio, which is an important criterion for understanding the capacity of disintegrants to swell in presence of little amount of water, was calculated. The water absorption ratio increased with increase in the concentration of super disintegrant from 2-8%. The water absorption ratio was found in the range between 54.21 ± 0.87 to 79.83 ± 0.91% as MCC as diluent.

i) *In vitro* Disintegration Time

In vitro disintegration time was found to be 32-53 sec with MCC as diluent.

j) *In vitro* Dispersion Time

In vitro dispersion time was measured by the time taken to undergo uniform dispersion. All formulations showed rapid dispersion within seconds. *In vitro* dispersion time found to be 33-60 sec with MCC as diluent.

k) *In vitro* dissolution studies

As the formulation batches M1 to M12 comprised of three different types of superdisintegrants, *in vitro* drug release at 10 minutes was found between 89.2 to 98.9%.

Table 3: Post compression evaluation of formulated Cinnarizine fast dissolving tablets containing microcrystalline cellulose as diluent

Formulation Code	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	Friability (%) (n=10)	Weight variation test (mg) (n=20)	Drug content (%) (n=3)
M1	3.12 ± 0.01	3.5 ± 0.24	0.36	99.91±0.22	98.70 ± 0.72
M2	3.15 ± 0.03	3.6 ± 0.25	0.32	99.83±0.36	98.55 ± 0.09
M3	3.16 ± 0.03	3.4 ± 0.27	0.38	100.21±0.49	99.30 ± 0.55
M4	3.14 ± 0.02	3.6 ± 0.23	0.23	100.92±0.41	99.56 ± 0.29
M5	3.14 ± 0.01	3.8 ± 0.25	0.26	100.16±0.32	98.65 ± 0.50
M6	3.15 ± 0.04	3.7 ± 0.26	0.33	99.95±0.91	98.58 ± 0.45
M7	3.12 ± 0.01	3.3 ± 0.24	0.28	100.51±0.99	98.28 ± 0.75
M8	3.14 ± 0.04	3.9 ± 0.23	0.34	100.60±0.60	98.90 ± 0.65
M9	3.14 ± 0.01	3.8 ± 0.24	0.31	100.01±0.58	99.46 ± 0.48
M10	3.15 ± 0.01	3.6 ± 0.25	0.23	100.51±.82	99.35 ± 0.53
M11	3.14 ± 0.01	3.3 ± 0.23	0.28	100.03±0.59	99.65 ± 0.62
M12	3.13 ± 0.01	3.6 ± 0.24	0.34	100.01±0.50	99.85 ± 0.71

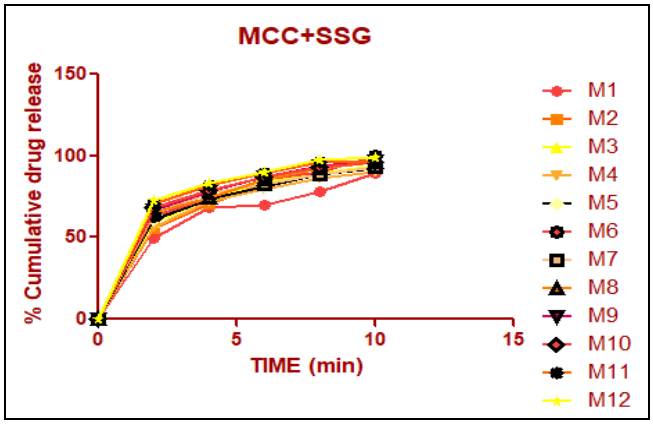

Fig 3: Plots of cumulative% drug release as a function of time for formulated Cinnerizine fast dissolving tablets containing MCC (M1-M12)

Stability Studies

Stability studies of formulation M12 was performed at 25^{0}C ±2^{0}C/60% ± 5% RH and 40^{0}C ± 2^{0}C/75% ± 5% RH for a period up to 60 days. The formulations were selected for stability studies on the basis of their high percentage cumulative drug release and also results of *in vitro* disintegration time, wetting time and *in vitro* dispersion studies.

There was no change in colour and shape of the tablets when stored at 25^{0}C ± 2^{0}C /60% ± 5% RH and 40^0 ±2^{0}C/75% ±5% RH and observed every 20 days interval, up to 60 days. Formulations M12 showed not much variation in any parameter. From these results it was concluded that formulations were stable and retained its original properties.

Conclusion

From the study conducted and from the observations and the

results obtained thereof, following conclusions were drawn:

- The fast dissolving tablets of cinnarizine was successfully developed and evaluated. FTIR studies concluded that drug and excipients were compatible with each other.
- The formulated tablets were satisfactory in terms of hardness, thickness, friability, weight variation, drug content, wetting time, water absorption ratio, *in vitro* disintegration time, *in vitro* dispersion time and *in vitro* drug release.
- Formulation containing superdisintegrant crospovidone showed least wetting time and *in vitro* disintegration time as compare to croscarmellose sodium and sodium starch glycolate.
- As the superdisintegrant concentration increases, the wetting time and *in vitro* disintegration time on tablets decreases.
- The formulation M12 was found to be the best on the basis of wetting time, *in vitro* disintegration time and *in vitro* drug release.

The formulation M12 containing Crospovidone (8%) as superdisintegrant and microcrystalline cellulose as diluent was found to be the optimized formulation.

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