

Formulation And Evaluation of Oral Disintegrating Tablets of Cinnarizine

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ABSTRACT : *In the present work, oral dispersible tablets of cinnarizine were prepared by direct compression method with a view to enhance patient's compliance. The aim of the proposed work is to formulate oro dispersible tablets of Cinnarizine for rapid dissolution of drug and absorption, which may produce rapid onset of action in the treatment of motion sickness. Drug and excipient compatibility studies measured by using FTIR studies. These tablets were evaluated for drug content, weight variation, friability, hardness, wetting time and in vitro disintegration time. Among the formulations tablets of batch F1 containing croscarmellose showed superior organoleptic properties along with excellent in-vitro disintegration time and drug release as compared to other formulations.*

Keywords: *Cinnarizine, croscarmellose, crospovidone, FTIR studies, direct compression technique, in-vitro drug release studies.*

I. INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs through various pharmaceutical products of different dosage forms. The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing accurate dosage, and most importantly the patient compliance. However, the most evident drawback of the oral dosage forms, such as tablets and capsules, is difficulty in swallowing, leading to patients in compliance particularly in case of pediatric and geriatric patients.¹ The development of solid dosage form that disintegrates rapidly or dissolves even when taken orally without water are being formulated. This dosage form is known as oral dispersible tablets.^{2,3} Conventional oral dosage forms includes are the mentally ill, uncooperative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack or coughing. Sometimes it may be difficult to swallow conventional products due to unavailability of water. These problems led to the development of novel type of solid oral dosage form called "oro dispersible Tablets". This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva. Produce rapid onset of action. In such a cases Bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.^{3,4,5} Cinnarizine is an H1-receptor antagonist. It is widely used in the treatment of motion sickness, vomiting and vertigo. It is water insoluble and tasteless drug. Hence it was selected as a model drug for the preparation of oral dispersible tablets. Pharmaceutically, it belongs to the biopharmaceutical classification system (BCS) class II, and drug dissolution is the limiting step for its absorption.^{6,7}

II. MATERIALS AND METHODS

Cinnarizine was collected as a gift sample from Hetero labs, Hyderabad and various superdisintegrants and other excipients were purchased from AR chemicals, Hyderabad.

2.1 Methodology

Drug-Excipients Compatibility Studies by FT-IR⁸

A proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of both drug and excipients used in fabrication of the product. Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product. So before producing the actual formulation, compatibility of Cinnarizine with polymers and other excipients were tested using the Fourier Transform Infrared Spectroscopy (FT-IR). For this study, potassium bromide (KBr) pellet method was employed. The samples were thoroughly mixed with dry powdered potassium bromide. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded. The application of infra-red spectroscopy lies more in the qualitative identification of substances either in pure form or in the mixtures and as a tool in establishment of the structure. Since I.R. is related to

covalent bonds, the spectra can provide detailed information about the structure of molecular compounds.

Pre compression parameters^{9,10,11}

Angle of Repose

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. The angle of repose is determined by funnel method. The funnel is fixed at a particular height (2.5cm) on a burette stand. The powder sample was passed through the funnel allowing it to form a pile. No more granules are added as the pile touches the tip of the funnel. This region is encircled to measure radius. The same procedure is done for triplicate, the average value is taken. The angle of repose is calculated by using equation

$$\text{Angle of repose } (\theta) = \tan^{-1} (h/r)$$

Where, h=height of pile r=radius of the base of the pile θ =angle of repose

Bulk Density Determination

Weighed quantity of the powder (W) is taken in a graduated measuring cylinder and volume (V_0) is measured and bulk density is calculated using the formula.

$$\text{Bulk density (BD)} = \text{Weight of the powder} / \text{Volume of powder}$$

Tapped Density Determination

Weighed quantity of powder taken in a graduated cylinder and the volume is measured (V_0). The graduated cylinder was fixed in the 'Tapped Densitometer' and tapped for 500, 750 and 1250 times until the difference in the volume after consecutive tappings was less than 2%. The final reading was denoted by (V_f). The volume of blend was used to calculate the tapped density, Hausner's ratio and Carr's Index.

$$\text{Tapped density (TD)} = W/V_f \text{ g/ml}$$

Carr's Index or Compressibility index

Carr's index is also known as compressibility. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is simple, fast and popular method of predicting powder flow characteristics.

Carr's index (%) = [(Tapped Density-Bulk Density) / Tapped Density] X 100 **Hausner's ratio:** It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density.

$$\text{Hausner ratio} = \text{Tapped density} / \text{Bulk density}$$

Formulation development

Table-1: Formulation table

| S.No | Ingredient | F-1 | F-2 | F-3 | F-4 |
|------|----------------|-----|-----|-----|-----|
| 1 | Drug | 15 | 15 | 15 | 15 |
| 2 | Croscarmellose | 20 | 40 | - | - |
| 3 | Crospovidone | - | - | 20 | 40 |

| | | | | | |
|---|--------------------|-----|-----|-----|-----|
| 4 | Aspartamme | 5 | 5 | 5 | 5 |
| 5 | Mannitol | 155 | 135 | 155 | 135 |
| 6 | Magnesium stearate | 3 | 3 | 3 | 3 |
| 7 | Talc | 2 | 2 | 2 | 2 |
| 8 | Total | 200 | 200 | 200 | 200 |

Preparation technique^{12,13}

Direct compression method:

Orodispersible tablets of cinnarizine were prepared by direct compression. All the ingredients were passed through 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 200mg using 8mm round flat punches on 10- station rotary tablet machine (Rimek).

Evaluation parameters

Physical Appearance¹⁴

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odour, taste etc.

Size & Shape¹⁵

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a $\pm 5\%$ variation of standard value.

Weight variation test¹⁶

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form. Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Tablet hardness¹⁷

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The crushing strength of prepared tablets was determined for ten tablets of each batch using Pfizer hardness tester.

Content Uniformity¹⁸

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets and all capsules intended for oral administration where the range of size of the dosage form available include 50mg or smaller sizes. Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Friability¹⁹

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

Wetting time²⁰

Five circular tissue papers of 10-cm diameter were placed in a petridish with a 10-cm diameter. 10 ml of water at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ containing eosin, a water-soluble dye, was added to the petridish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. Six tablets from each formulation batch were tested randomly and the average reading noted.

Disintegration test²¹

The U.S.P. device to test disintegration uses 6 glass tubes that are long open at the top and 10 mesh screens at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at $37 \pm 20^{\circ}\text{C}$ such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets.

Drug release kinetics²²

The drug release from the Cinnarizine fast dissolving tablets was investigated in a USP-II (paddle) apparatus, 900 ml of 6.8 pH Phosphate buffer (50 rpm, 37°C). At predetermined time intervals, 5-ml samples were withdrawn and take 1ml sample and diluted to 10 ml and then analyzed with UV spectrophotometry at λ_{max} 248 nm.

Dissolution study of Cinnarizine of oro disintegrating tablets²³

| | |
|--------------------------------|--------------------------------|
| Bath temperature | : $37 \pm 0.5^{\circ}\text{C}$ |
| Dissolution media | : 6.8 pH buffer |
| Volume of dissolution media | : 900 ml |
| Aliquot withdrawn | : 5 ml |
| Dissolution apparatus | : USP type II (paddle) |
| Revolutions per minute (Speed) | : 50 |

Stability Studies²⁴

Selected Formulation was subjected to stability studies as per ICH guidelines.

Following conditions were used for Stability Testing.

1. $25^{\circ}\text{C}/60\%$ RH analyzed every month for period of 1 month.
2. $30^{\circ}\text{C}/75\%$ RH analyzed every month for period of 1 month.
3. $40^{\circ}\text{C}/75\%$ RH analyzed every month for period of 1 month.

III.RESULTS & DISCUSSION

Fourier Transformation Infra-red (FTIR) analysis:

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan).

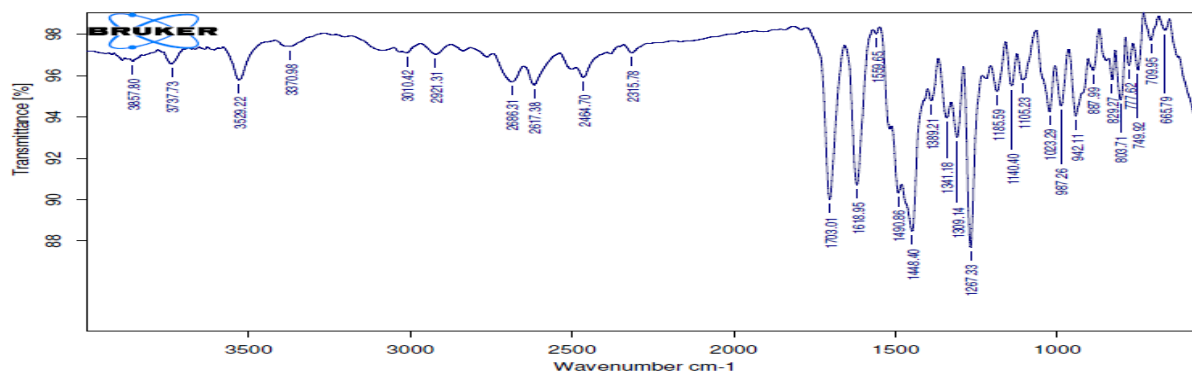


Fig-1: FT-IR Sample for Cinnarizine

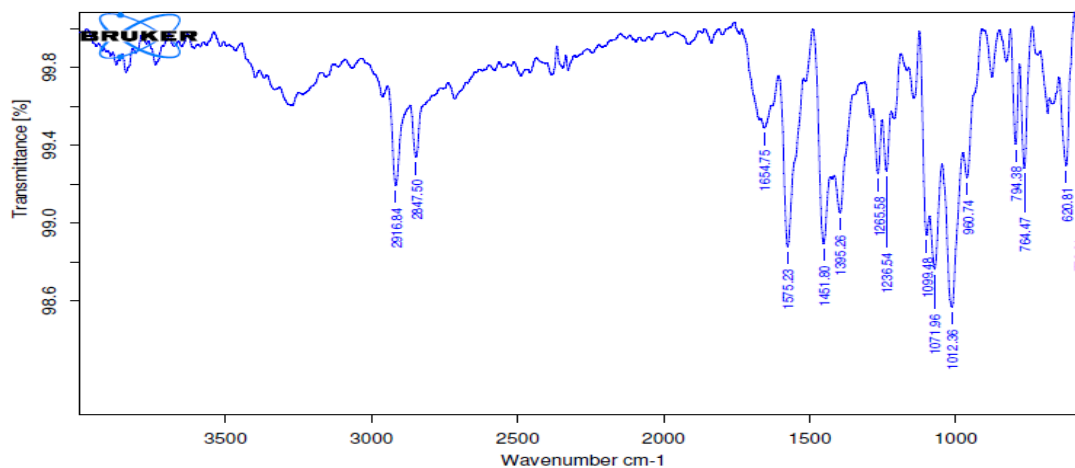


Fig-2: FT-IR Sample for Optimized Formulation

In the present study, it has been observed that there is no chemical interaction between Cinnarizine and the superdisintegrants used. From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. This further confirms the integrity of pure drug and compatibility of them with excipients.

Evaluation parameters

Table-2: Evaluation Parameters for cinnarizine oro dispersible tablets

| Parameter | F1 | F2 | F3 | F4 |
|--------------------------------|-------|-------|-------|-------|
| Weight variation | 200 | 199 | 200 | 199 |
| Thickness (mm) | 2.3 | 2.2 | 1.9 | 2.1 |
| Hardness (kg/cm ²) | 4.35 | 4.39 | 4.20 | 4.52 |
| Friability (%) | 0.56 | 0.60 | 0.59 | 0.58 |
| Disintegration time | 29 | 32 | 38 | 42 |
| Drug content | 91.23 | 86.59 | 90.12 | 89.94 |

Uniformity of weight:

All the prepared fast dissolving tablets of Cinnarizine were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits of $\pm 5\%$.

Hardness and friability:

The hardness of the tablet formulations was found to be in the range of 4.20 to 4.52 kg/cm². The friability values were found to be in the range of 0.56 to 0.60 %.

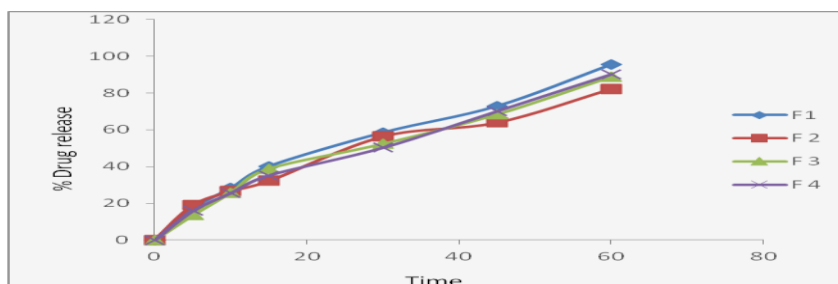
Uniformity of drug content:

The low values of standard deviation indicates uniform drug content within the tablets. The percent drug content of all the tablets was found to be in the range of 86.59 to 91.23 percent (which was within the acceptable limits of $\pm 5\%$).

All Formulations tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeial limits. The results of the tests were tabulated. The drug content of the formulation was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

In vitro Dissolution studies:**Table-3: In-vitro dissolution Profiles of all formulations**

| Time (min) | F1 | F 2 | F 3 | F 4 |
|------------|-------|-------|-------|-------|
| 0 | 0 | 0 | 0 | 0 |
| 5 | 17.39 | 18.95 | 13.56 | 15.89 |
| 10 | 28.25 | 26.55 | 25.86 | 25.58 |
| 15 | 40.18 | 32.21 | 38.88 | 35.17 |
| 30 | 58.56 | 56.38 | 52.45 | 50.26 |
| 45 | 72.93 | 63.96 | 68.49 | 70.12 |
| 60 | 95.50 | 82.24 | 88.93 | 90.21 |

**Fig-3: In-vitro dissolution Profiles for tablets**

Among all formulations, F1 shows better drug release when compared with all other formulations. So formulation F1 selected as optimized formula.

Stability studies**Table-4: Stability Studies of Optimized Formulation**

| S.NO | Time in days | Physical changes | Mean % drug release | | |
|------|--------------|------------------|------------------------|----------|----------|
| | | | Oro dispersible tablet | | |
| | | | 25°C/60% | 30°C/75% | 40°C/75% |
| 1. | 01 | No Change | 95.50 | 95.50 | 95.50 |
| 2. | 30 | No Change | 95.42 | 95.38 | 95.25 |

There was no significant change in physical and chemical properties of the tablets of formulation F1 after 30 days, parameters like % drug release and assay values at various conditions (at 40°C/ 75% RH) as per ICH guidelines quantified at various time intervals were shown in Table and dissolution profile.

IV. CONCLUSION

The aim of the present study was to formulate and evaluate for oro dispersible tablets containing cinnarizine for the management of nausea and vomiting associated with motion sickness, vertigo, Cogan's syndrome. After pre-formulation studies it was decided to prepare oro dispersible tablets prepared by direct compression method. In the formulation of immediate release sodium starch glycolate, were used as super disintegrants. Prior to compression the granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. The compressed tablets were also evaluated for weight variation, hardness, friability, drug content, disintegration time and in vitro drug release. In the above studies F1 formulation showed promising results. It was further supported by FTIR analysis which showed that F1 had no interaction with excipients. The stability studies were carried out for the optimized formulation for 1 months and it showed acceptable results. The kinetic studies of the formulations revealed that dissolution is the predominant mechanism of drug release. So F1 formulation was considered as the optimized formulation.

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