Research Article

FORMULATION AND EVALUATION OF ORAL DISPERSIBLE TABLETS OF CINNARIZINE USING SUBLIMATION TECHNIQUE

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ABSTRACT

The purpose of the present research was to compare the effect of subliming agents on the oral dispersible property of cinnarizine tablets. The fundamental principle used in the development of the oral dispersible tablets by sublimation technique is to maximize pore structure of the tablets. Compressed tablets prepared using a water soluble material like mannitol, does not rapidly disperse in water since it is difficult for water to penetrate into the tablets due to their low porosity. To increase the porosity of the tablets which are prepared by direct compression using mannitol, subliming agents such as camphor, menthol, ammonium bicarbonate or thymol are to be used. A high porosity was achieved due to the formation of many pores where camphor, menthol, ammonium bicarbonate and thymol particles previously existed in the compressed mannitol tablets prior to sublimation of these subliming materials. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 25 s in the mouth. We developed a direct compression method for the formulation of cinnarizine (an anti emetic drug) tablets with high porosity which dissolves rapidly using mannitol as diluent and camphor, menthol, ammonium bicarbonate or thymol as subliming agents.

Keywords: Oral dispersible tablet; subliming material; High porosity; direct compression.

INTRODUCTION

Over the last few years, a great deal of interest has been directed towards formulating solid oral dosage forms that disintegrate/dissolve rapidly in the mouth without the need for water. These dosage forms are known as rapid disintegrating or oral dispersible tablets[1].

The term 'Oral dispersible Tablet' as appears in European Pharmacopoeia is defined as ''uncovered tablet for buccal cavity, where it disperses before ingestion''[2].

Many patients find difficulty in swallowing tablets and hard gelatin capsules; consequently they do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem which results in a high incidence of incompliance and ineffective therapy. For this reason the development of orally disintegrating or rapidly disintegrating tablets (RDT) have recently interested not only the pharmaceutical industry, but also academia[3, 4]

ODT will avoid missing out of dose even during travelling, busy or other situations where there is no access to water[5].

They undergo disaggregation in the mouth when in contact with the saliva in less than 60 seconds, preferably in less than 40 seconds, forming a suspension which is easy to swallow. The target population for these new fast-dissolving/disintegrating dosage forms have been generally paediatric, geriatric, bedridden or mentally disabled patients[6].

The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market[7].

A major claim of some oral dispersible tablets is increased bioavailability compared to traditional tablets. Because some of the drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, the bioavailability of the drug is significantly increased over those observed in the conventional tablet dosage form[8].

Kei-ichi Koizumi et al., confirmed that a compressed tablet prepared with crystalline cellulose and low-substituted hydroxypropylcellulose (L-HPC) rapidly disintegrated (within 15 s) in saliva (or a small amount of water) in the mouth of humans. However, patients sometimes feel a rough texture in their mouth due to the incomplete solubilisation of this type of tablet in saliva. To eliminate the rough texture in the mouth, we attempted to use a water-soluble material (mannitol) as an excipient instead of crystalline cellulose and L-HPC, in the preparation of this type of tablet. However, the compressed tablet prepared using mannitol did not rapidly dissolve in saliva since it is difficult for water to penetrate into the tablet due to its low porosity. We therefore investigated a new convenient method of preparing compressed tablets with high porosity, which dissolve rapidly in the mouth, using mannitol and a subliming material. We chose camphor, menthol, ammonium bicarbonate and thymol as subliming materials[9].

The basic approach used in the development of the fast-dissolving tablet is the use of superdisintegrants like croscarmellose sodium, sodium starch glycolate, and crospovidone. Another approach used in developing ODT

tablets are maximizing pore structure of the tablets. Freeze-drying and vacuum-drying techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and it yields fragile and hygroscopic product. Therefore, it was decided to adopt the oven-drying technique in the present investigation. Oven drying was adopted after addition of a subliming agent to increase porosity of the tablets. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly[10].

Cinnarizine is a 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 using Sublimation Technique[11].

MATERIALS AND METHODS

Cinnarizine purchased from Seva fine chem, Ahmedabad, Mannitol (pearlitol SD-200) gift sample from Amneal pharmaceutical pvt, Ahmedabad, ammonium bicarbonate purchased from Merck specialities private limited, Mumbai, camphor**,** menthol and thymol purchased from S d fine-chem limited. Mumbai. A schematic representation of tablet preparation is shown in Fig1. For compression of materials, into tablets using tablet machine Rimek mini press-1, Karnavati Engineering Ltd, Mehsana, Gujarat (punches flat-faced, 8 mm diameter) was employed. To prepare 200 mg tablets, mixture of cinnarizine, mannitol and camphor, menthol, ammonium bicarbonate and thymol in various concentrations were compressed. For sublimination of camphor, menthol, ammonium bicarbonate and thymol from the tablets, the tablets are placed in an oven at 60°C until constant weight is obtained. The crushing strength (kg) of tablets was measured using a tablet hardness tester[9].

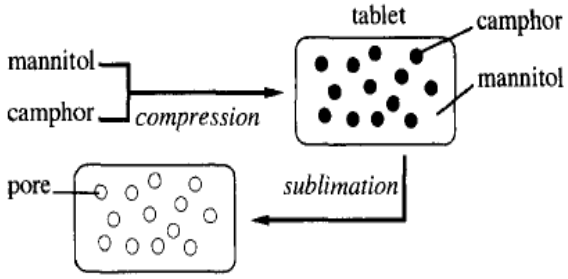


Figure 1: Schematic illustration of the preparation of a high porosity compressed tablet using mannitol and sublimating agent.

Preformulation Studies

Fourier Transform Infrared Spectroscopy:[12] FTIR spectra were obtained on a 8400s spectrophotometer (shimadzu, japan). Samples were prepared in KBr disks (1 mg sample in 100 mg KBr). The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}. FTIR studies confirmed no incompatibility between sublimating agents and the drug.

Evaluation of Powder Blends: The powder blend was evaluated for flow properties as follows and reported in table 2:

Angle of repose:[6] 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. Radius of the heap (r) was measured and the angle of repose was calculated. It is the angle produced between the heap of the pile and base.

Angle of repose, $\tan(\theta) = h / r$

Where,

θ = Angle of repose,

h = Height of heap,

r = Radius of pile.

Carr's index:[13,14] Carr's ''percent compressibility" was calculated using the equation ([ρtap - ρbul]/ρtap) * 100. The bulk and tap densities were determined as follows: A known quantity of each sample (25 g) was poured through a funnel into a 100-mL tarred graduated cylinder. The cylinder was then lightly tapped twice to collect all the powder sticking on the wall of the cylinder. The volume was then read directly from the cylinder and used to calculate the bulk density. For tap density, the cylinder was tapped from a height of 2.5 cm 50 times on a wooden bench top to attain a constant volume reading from the cylinder.

Where,

ρbul= Bulk density=weight of powder / bulk volume of powder

ρtap= Tapped density = weight of powder / tapped volume of powder

Hausner ratio:[6] Hausner ratio is an indirect index of ease of powder flow.

Hausner ratio = ρ_{tap} / ρ_{bul}

Where,

ρ_{tap} = Tapped density

ρ_{bul} = Bulk density

Evaluation of tablets

Uniformity of weight:[15] The test was carried out according to the European pharmacopoeia [9]. Twenty tablets, from each formula, were individually weighed and the mean of tablet weights was calculated. Results are presented as mean value± standard deviation (SD).

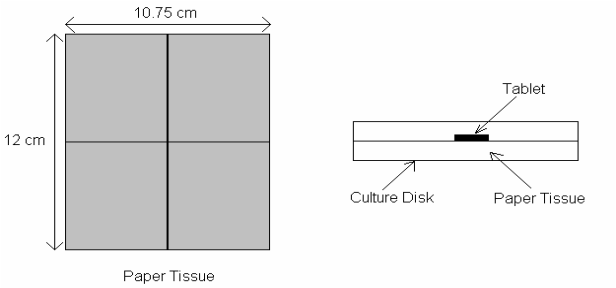
Hardness:[6] The fracture strength, which is defined as the force required to break a tablet by radial compression, was measured with a tablet hardness tester (Monsanto hardness tester)

Friability:[16] The friability of a sample of six tablets was measured using a Roche Friabilator (Electrolab EF-2, USP). Six pre-weighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal

of fine's using 60 mesh screens and the percentage of weight loss was calculated.

% Friability = (Loss in weight / Initial weight) × 100

Wetting time:[17] A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured.



Drug content uniformity:[6] 10 tablets from each formulation were powdered and the blend equivalent to 25 mg of cinnarizine was weighted and dissolved in 100ml of 0.1 N HCl solutions. The solution was filtered, and 1ml of first stock solution was diluted up to 100ml with 0.1N HCl. Drug content was analyzed spectrophotometrically at 253.2 nm. Each sample was analyzed in triplicate.

In vitro disintegration time:[18] In vitro disintegration time was measured by using 200ml distilled water in 250ml beaker at 37± 0.5°C temperature. Time required for disintegration of the tablets was noted

In vitro dissolution studies: ODTs were evaluated for dissolution behaviour. Dissolution tests used the USP apparatus 2, paddle types (Elect lab, Mumbai, India.). Dissolution was carried out with the rotation speed of 50 rpm using 500 ml of 0.1 N HCl as the dissolution medium maintained at a temperature of 37 ± 0.5°C[19]. Samples were withdrawn at predetermined time interval and diluted suitably and analyzed at 253.2 nm for cumulative drug release using Schimadzu UV-Visible spectrophotometer. The dissolution experiments were conducted in triplicate, shown in Fig.2.

Table 1: Formulation of cinnarizine oral dispersible tablets

NAME OF EXCIPIENT	FS1	FS2	FS3	FS4	FS5	FS6	FS7	FS8
	Formula (mg/tablet)							
CINNARIZINE	25	25	25	25	25	25	25	25
CAMPHOR	20	40	----	----	-----	----	----	----
AMMONIUM BICARBONATE	----	----	20	40	----	----	----	----
MENTHOL	----	----	----	----	20	40	----	----
THYMOL	----	----	----	----	----	----	20	40
MANITOL	155	135	155	135	155	135	155	135

Table 2: Physical Characteristics of Powder Blends

FORMULA NO	BULK DENSITY	TAPPED DENSITY	CARR'S INDEX	HAUSNER RATIO	ANGLE OF REPOSE
FS1	0.532	0.632	15.95	1.18	32.62
FS2	0.505	0.588	14.14	1.16	35.86
FS3	0.526	0.617	14.73	1.17	29.28
FS4	0.549	0.641	14.28	1.16	33.69
FS5	0.510	0.602	15.30	1.18	32.27
FS6	0.537	0.617	12.90	1.14	32.27
FS7	0.520	0.595	12.5	1.14	34.59
FS8	0.515	0.609	15.46	1.18	32.59

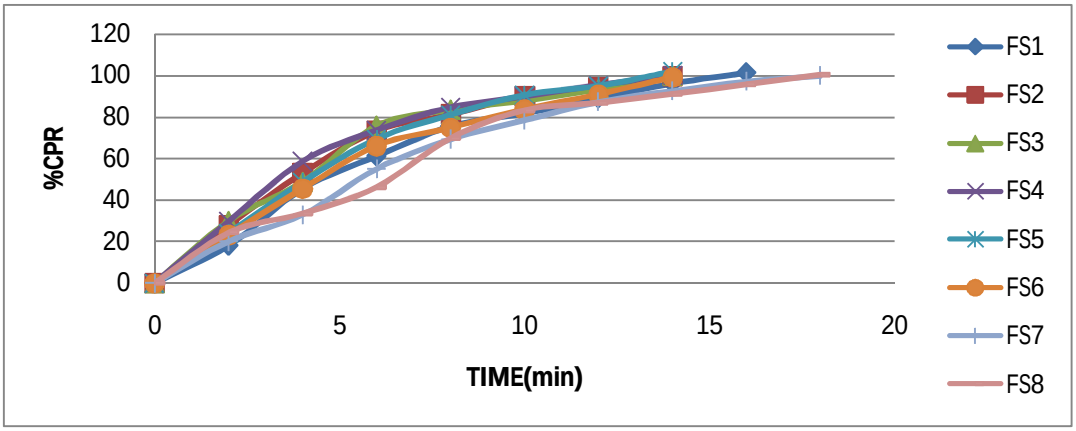


Figure 2: In vitro drug release profile of various cinnarizine formulations.

Table 3: Evaluation of Oral dispersible Tablets

FORMULATION NO	WEIGHT VARIATION (mg) ± S.D	HARDNESS* kg/cm2)±S.D	FRIABILITY (%)	% ASSAY	WETTING TIME* (sce)± S.D	IN-VITRO DISINTEGRATION TIME* (sce)± S.D
FS1	200.8±5.411	2.8±0.273	0.494	98.98	6.56±0.292	6.97±0.347
FS2	197.7±4.738	2.9±0.418	0.558	98.30	6.26±0.058	6.71±0.170
FS3	201.8±8.154	2.9±0.418	0.531	97.62	5.73±0.291	6.1±0.111
FS4	203.2±7.451	2.7±0.273	0.713	99.20	5.37±0.072	5.86±0.105
FS5	198.7±6.084	3.0±0.50	0.474	96.72	5.34±0.120	5.96±0.234
FS6	198.7±7.324	3.1±0.547	0.536	97.62	5.01±0.109	5.67±0.294
FS7	198.2±4.389	2.7±0.447	0.498	98.98	20.26±1.05	33.28±2.01
FS8	195.7±6.149	2.9±0.418	0.661	98.75	19.16±1.18	30.36±0.615

All values are expressed as mean ± SD, n=3

RESULTS AND DISCUSSION

All the formulations were prepared by direct compression followed by sublimation Techniques. The data obtained from pre-compressional parameters such as bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose is given in Table 2 and is found to be within acceptable pharmacopoeia limits. Post-compressional parameters like hardness, friability, weight variation, drug content, wetting time, *in vitro* disintegration time are mentioned in Table 3. The tablets measured hardness was found to be in the range of 2.7±0.273 to 3.1 ± 0.547 kg/cm^2. The percentage friability was less than 1% for all formulations ensuring mechanical stability of the formulated tablets. All formulations are then evaluated for variation in weight and results indicated that for all formulations exhibit very low weight variation and lies within the pharmacopoeial limits i.e. ± 7.5%. The percentage drug content in all formulations was found in the range of 96.72% to 99.20% indicating the compliance with the pharmacopoeial limits. According to the pharmacopoeial standards the dispersible tablet must disintegrate within 3 min. But all formulated batches have shown very low disintegration time 5.67±0.294 to 33.28±2.018 seconds indicating suitability of formulation for fast dissolving tablet. Wetting time is found to be less for the formulation FS6 containing sublimating agent menthol as compared to other formulations. The *in vitro* dissolution profile (Fig. 2) indicated that among the all formulations, faster and maximum drug release was obtained from formulation FS6 due shorter wetting time and formation of porous structure by sublimation of menthol.

CONCLUSION

Oral dispersible tablets (ODT) of Cinnarizine are successfully prepared by using sublimation method. Undoubtedly the availability of various technologies and the manifold advantages of ODT will surely enhance the patient compliance, low dosing, and rapid onset of action, increased bioavailability, low side effect, good stability, and its popularity in the near future. From the study, it can be concluded that sublimation method showed better disintegration and drug release. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the absorption leading to its increased bioavailability. Oven-drying technique would be an effective alternative approach compared with the use of more expensive adjuvant in the formulation of mouth dissolving tablets.

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