Research Article

Formulation and *In-Vitro* Evaluation of Mouth Dissolving Tablets of Cinnarizine

V. Mohan, K. Ragavan, V. Venu and R. Sampathkumar

ABSTRACT

Objective of this study was to formulate directly compressible orally 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 varying concentrations of different superdisintegrants such as Agar, gum karaya, platago ovata on disintegration time was studied. Tablets were evaluated for weight variation, thickness, hardness, friability, taste, drug content, in vitro disintegrating time and in vitro drug release. Other parameters such as wetting time, water absorption ratio ('R'), and drug-excipient compatibility were also evaluated. The disintegration time of the optimized D9 batch was 22 sec. Good correlation was observed between disintegration time and water absorption ratio (R) for each of three superdisintegrants at concentrations studied. Considering the 'R' values and disintegration time, platago ovata was significantly superior compared to other two superdisintegrants tested. Release of drug was faster from formulations containing platago ovata compared to the marketed convetional Cinnarizine tablet. Differential scanning calorimetric studies did not indicate any excipient incompatibility, either during mixing or after compression. Finally concluded that directly compressible orally disintegrating tablets of cinnarizine with lower friability, acceptable taste, and shorter disintegration times were obtained using platago ovata at optimized concentrations.

Keywords: Cinnarizine, orally disintegrating tablet, wetting time, water, absorption ratio.

INTRODUCTION

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutics concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. This is possible through administration of conventional dosage form in a particular dose and at a particular frequency. Thus drug may be administered by variety of routes in a variety of dosage forms.

Drugs are more frequently taken by oral administration. Although a few drugs taken orally are intended to be dissolved within the mouth, the vast majority of drugs taken orally are swallowed. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for conventional delivery of drug. It is considered most natural, uncomplicated, convenient, safe means of administering drugs, greater flexibility in dosage form design, ease of production and low cost[2].

Tablets and hard gelatin capsules constitute a major portion of the drug delivery systems that are currently available. However, many patient groups such as elderly, children, and patients mentally retarded, uncooperative, nauseated, or on reduced liquid intake diets have difficulty in swallowing these dosage forms. Many elderly persons face difficulties in administering conventional oral dosage forms because of hand tremors and dysphasia. Swallowing problem is common in children because of their underdeveloped muscular and nervous systems. In some cases like motion sickness, sudden episodes of allergic attack or coughing, and during unavailability of water, swallowing conventional tablets is difficult. To fulfill these medical needs, formulators have devoted considerable efforts for developing a novel type of dosage form for oral administration known as fast water dispersible tablet [3].

The past two decades, there has been enhanced demand for more patient compliant dosage forms. As a result, the

demand for the technologies has been increased 3 fold annually. Since the development cost of a new chemical entity is very high, the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize the side effects.

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly patient compliance. The most popular solid dosage forms are being tablets and capsules one important draw back of these dosage forms is the difficulty to swallow.

Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however hand tremors, dysphasia in case of geriatric patients, the underdeveloped muscular and nervous systems in young individuals and in case of uncooperative patients, the problem of swallowing is common phenomenon which leads to poor patient compliancel.

Dysphagia or difficulty in swallowing is seen to afflict nearly 35% of general population. This disorder is also associated with number of medical conditions including Stroke, Parkinson's disease, AIDS, head and neck radiation therapy and other neurological disorders including cerebral palsy. Many elderly persons will have difficulties in taking conventional dosage forms (Solutions, Suspensions, Tablets, Capsules) because of hand tremors, and dysphagia [3].

Swallowing problems are also common in young individuals because of their under developed muscular and nervous systems. Other groups who may experience problems in swallowing solid dosage forms, mentally ill, the developmentally disabled, un co-operated patient and reduce liquid intake plans or nausea. In some cases such as motion sickness sudden episodes of allergic attack or coughing and unavailability of water, swallowing tablet may become difficult and consequently do not take medications as prescribed which results in high incidence of noncompliance and ineffective therapy.

To fulfill these medical needs pharmaceutical technologists have devoted considerable effort to develop a novel type of dosage form for oral administration, the Fast water dispersible tablet , tablet that disintegrates and dissolves rapidly in saliva without need of drinking water. The orodispersible tablet usually dissolves in the oral cavity in about 10 seconds to 3 minutes. Faster the drug goes into solution, the quicker absorption and onset of clinical effect. Some of the drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down in to the stomach, in such cases bioavailability of the drug of significantly greater than those observed from conventional tablet dosage form. The development of orodispersible also provides line extension in market place, product identity, promotion in the sales in market place. These tablets are not only indicated for the people who have swallowing difficulties, but also ideal for active people [3,4] .

The orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, porous tablets, rapimelts. However of all the above terms, United States Pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term “orodispersible tablet” for tablets that disperse readily and within three minutes before swallowing.

United States Food and Drug Administration (FDA) defined ODT as “A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue”. The disintegration time for ODTs generally ranges from several seconds to about a minute[5].

S. NO.	MATERIALS	SOURCE
1	Cinnarizine	GlaxoSmithKline Pharmaceuticals Ltd., Nashik, Maharashtra
2	Agar	Gifted by Signet Chemical Corp.
3	Gum karya	Gifted by Signet Chemical Corp.
4	Plantago ovata	Gifted by Signet Chemical Corp.
5	PVP K30	Sd Fine Chem Limited, Mumbai
6	MCC	Gifted by Signet Chemical Corp.
7	Mannitol	Strides Arco Labs, Bangalore
8	Magnesium Stearate	Nice Chemicals Laboratory
9	Purified Talc	Sd Fine Chem Limited, Mumbai
10	Aspartame	Medrich Pharmaceuticals, Bangalore
11	Phosphate buffer **pH 6.4**	Nice Chemicals Laboratory

Table 2: Equipment used

S.No.	EQUIPMENT	MODEL/ SOURCE
1	UV-spectrophotometer	1700 Pharmascope, Shimadzu
2	Digital Balance	BL-220H, Shimadzu
3	Digital pH meter	Systronic Electronics, Mumbai
4	Dissolution apparatus	TDT-06 N, Electrolab, Mumbai
5	IR spectroscopy	1615 series, Perkin-Elmer
6	Hot air oven	Tempo Instruments & Equipments, Mumbai
7	Hardness tester	Monsanto Hardness Tester
8	Friability test apparatus	Riche Rich Pharma,Mumbai
9	Tablet punching machine	Clit, Ahmedabad
10	Stability chamber	Osworld JRIC-11, Mumbai

Preparation of Solid Dispersion[60]

Preparation of solid dispersions of cinnarizine

Solid dispersions of Cinnarizine were prepared by solvent evaporation method. Drug was weighed and taken in a china dish, dissolved in methanol and then carrier was added (PVP k30 in ratio of 1:3). The solvent was evaporated at room temperature and dried in hot air oven at 50^0 C for 4 hours. The resultant mass was passed through sieve no. 60 and stored in dessicator.

Physical mixture

Physical mixture (PMs) having the same weight ratio were prepared by thoroughly mixing appropriate amounts of Cinnarizine and pvp k30 in a morter until a homogenous mixture was obtained . the result were sieved through a 60# sieve and denoted as PM.

6.2.4 Characterization of solid dispersions of Cinnarizine with PVP K30

Drug content

An accurately weighed quantity of solid dispersion equivalent to 25mg Cinnarizine was taken into 100 ml of volumetric flask. Dissolved in phosphate buffer pH 6.4 and the volume were made up with the same. An aliquot of the filtrate was diluted and analyzed spectrophotometrically (UV-1700, Shimadzu Corporation, Japan) at 253 nm.

Phase solubility studies

Phase solubility studies were carried out by adding excess of drug (20 mg) in screw-capped vials containing 20ml of aqueous solution of different pvp k30 concentration. Then suspensions were continuously stirred on electromagnetic stirrer at 250 and 37o and 300 rpm for three days (this duration was previously tested to be sufficient to reach

equilibrium). The suspensions were filtered through 0.22µm membrane filter. The filtrate were suitably diluted and analyzed, spectrophotometrically, for the dissolved at 253nm.

Dissolution study

In vitro dissolution studies of CINNARIZINE in powder form, SDs, and PMs were performed by using the USP XXIII type-II dissolution apparatus (Electrolab TDT-06N) employing a paddle stirrer at 50 rpm. 900 ml of pH 6.4 phosphate buffer was used as dissolution medium. The temperature of dissolution medium was maintained at 37 ± 0.5° C throughout the experiment. Samples of dissolution medium (5ml) were withdrawn for 20 min by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 253 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent released was calculated and plotted against time.

6.2.5 Preparation of tablets containing solid dispersions of cinnarizine

Different Cinnarizine mouth dissolving tablets were prepared according to the proportion given in table. The raw materials were passed through a screen (40 mesh) prior to mixing. powdered 1:3 ratio solid dispersion, containing amount equivalent to 25 mg Cinnarizine, was mixed with the other excipients and compressed on a rotator tablet punching machine equipped with flat-faced 10-mm punches. The tablet weight was adjusted to ~250 mg

Direct compression method[23]

Fast dissolving tablets of Cinnarizine were prepared by **Direct Compression** method according to the formulae given in the Tables.

All the ingredients were powdered separately and passed through # 60 mesh sieve separately. The solid dispersion and directly compressible excipient were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Then the other ingredients were mixed in geometrical order, in an inflated polyethylene pouch magnesium stearate and talc were added last and the tablets were compressed using 8 mm flat round punches to get tablets of 250 mg weight.

Table 3: Composition of Cinnarizine tablets prepared by direct compression method

INGREDIENTS(mg)	D1	D2	D3	D4	D5	D6	D7	D8	D9
CINNARAZINE solid dispersion PVP K30(1:3)	100	100	100	100	100	100	100	100	100
AGAR	10	15	20	-	-	-	-	-	-
GUM KARAYA	-	-	-	10	15	20	-	-	-
PLANTAGO OVATA	-	-	-	-	-	-	10	15	20
MCC	50	50	50	50	50	50	50	50	50
ASPARTAME	5	5	5	5	5	5	5	5	5
MAGNESIUM STEARATE	2	2	2	2	2	2	2	2	2
TALC	3	3	3	3	3	3	3	3	3
MANNITOL	80	75	70	80	75	70	80	75	70
TOTAL	250	250	250	250	250	250	250	250	250

The quantity of solid dispersions was taken after calculating the dose based on drug content of Cinnarizine**.**

Evaluation of Post Compression Parameters of Cinnarizine Tablets

Weight variation

Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight.

Hardness and Friability

Friability of the tablets was checked by using Roche Friabilator. The device subjects a number of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets from a height of 6 inches with each revolution.

Pre-weighed sample tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed.

Content uniformity test

Ten tablets were weighed and powdered, a quantity of powder equivalent to 10 mg of CINNARIZINE was transferred to a 25 ml volumetric flask and 15 ml water is added. The drug is extracted in water by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the liquid is filtered. The CINNARIZINE content was determined by measuring the absorbance at 220.2 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

Disintegration test

Tablets were taken and introduced in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus was positioned into a 1-liter beaker containing 900 ml of distilled water and the time of disintegration was recorded. To discriminate between the formulations disintegration was done at room temperature and disk was not used for the study.

***In vitro* dispersion time**

Tablet was added to 10 ml of pH 6.4 phosphate buffer solution at 37 ± 0.5° C. Time required for complete dispersion of a tablet was measured.

Wetting time and Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish (internal diameter 5 cm) containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured, the wetted tablet was then weighed.

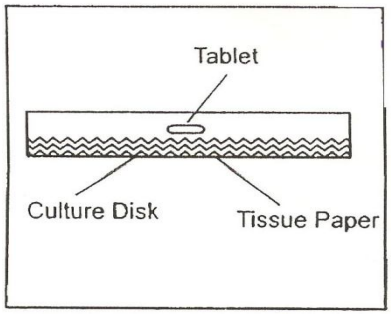


Fig. 2: Schematic representation of wetting time /water absorption determination

Water
using following equation

$$R = 100 \times \left(\frac{W_b - W_a}{W_a} \right)$$

Where, W_a is weight of tablet before water absorption and W_b is weight of tablet after water absorption

Dissolution study

In vitro dissolution of CINNARIZINE mouth dissolving tablets was studied in USP XXIII type-II dissolution apparatus (Electrolab TDT-06N) employing a paddle stirrer at 50 rpm. 900 ml of pH 6.4 phosphate buffer was used as dissolution medium. The temperature of dissolution medium was maintained at 37 ± 0.5° C throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 253 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent CINNARIZINE released was calculated and plotted against time.

Stability testing

Accelerated stability studies on promising CINNARIZINE formulations D1 and D9 were carried out by storing 15 tablets in amber colored rubber stopped vials at elevated temperature of 40 ± 2° C/75±5% RH (Stability chamber, Osworld) over a period of 90 days (3 months). At intervals

of one month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time.

RESULTS AND DISCUSSION

CHARACTERIZATION OF SOLID DISPERSION OF CINNARIZINE

i) Drug content

Drug content in physical mixture and solid dispersions.

Solid dispersion (drug to pvp mass ratio)	Drug content (%)	Physical mixture (deug to pvp mass ratio)	Drug content (%)
SD 1:1	96.61	PM 1:1	95.45
SD 1:2	97.98	PM 1:2	96.34
SD 1:3	99.32	PM 1:3	98.42

ii) Dissolution studies of solid dispersions and physical mixtures

The percentage release of cinnarizine at various time intervals from the physical mixture and solid dispersions made by using various concentrations of PVP K30. It is evident that dissolution of pure drug is very low, about 30.56% of drug being dissolved in 20 min. In the 20 min SD containing 1:3 of drug and PVP K30 showed better drug release 99.45% than other ratios of SD's.

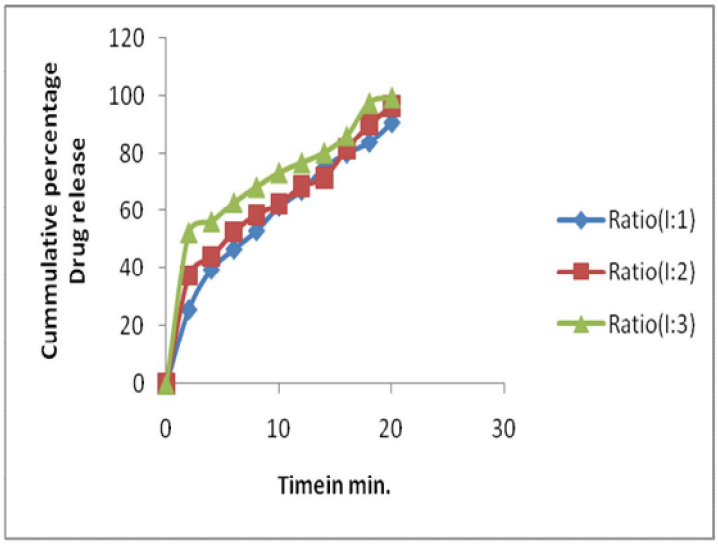
Table 7.3: In vitro dissolution profile of cinnarizine, physical mixture and solid dispersions of cinnarizine in pH 6.4 phosphate buffer

S . No	Formulation	Cumulative % drug release after 20 min.
1	DRUG	30.56 ± 2.45 %
2	PM 1:1	43.45 ± 2.05 %
3	PM 1:2	47.23 ± 1.67 %
4	PM 1:3	54.73 ± 3.41 %
5	SD 1:1	90.74 ± 1.34 %
6	SD 1:2	96.54 ± 1.40 %
7	SD 1:3	99.45 ± 1.60 %

iii) Comparison Study of Solid dispersion

Comparision of solid dispersions

Time (minits)	Ratio(I:1)	Ratio (I:2)	Ratio (I:3)
0	0	0	0
2	25.73	37.5	52.6
4	39.64	44.24	56.39
6	46.75	52.83	63.12
8	53.14	58.88	68.56
10	61.59	62.61	73.4
12	67.33	68.83	76.81
14	74.97	71.77	80.25
16	80.07	81.64	86.16
18	83.80	90.13	97.55
20	90.74	96.54	99.47



PRE-COMPRESSION PARAMETERS OF CINNARIZINE TABLETS

Pre compression parameters of Cinnarizine tablets

Formulation code	Bulk Density (g/cc)	Tapped density (g/cc)	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
D1	0.49	0.57	26.40	14.04	1.16
D2	0.48	0.55	26.06	12.72	1.14
D3	0.46	0.53	23.38	13.20	1.15
D4	0.43	0.49	24.72	12.24	1.14
D5	0.41	0.47	24.94	12.76	1.16
D6	0.39	0.44	25.48	11.36	1.12
D7	0.47	0.64	26.21	14.06	1.16
D8	0.51	0.61	25.74	13.11	1.15
D9	0.46	0.56	23.02	13.79	1.14

*Readings are average of 3 determinations

D1 to D9 indicates formulation containing both solid dispersion and super disintegrants

EVALUATION OF CINNARIZINE MOUTH DISSOLVING TABLETS

Post compression parameters

S No	Formulation Code	Hardness* (kg/cm^2) ± SD	Friability (%)	*In vitro* dispersion time (s)* ± SD	Percent drug content* ± SD	Weight variation
1	D1	3.03 ±0.05	0.32	32.96±1.46	81.35±0.63	247.87±0.56
2	D2	2.83±0.05	0.37	33.70±1.45	83.02±2.01	247.70±0.08
3	D3	2.83±0.05	0.38	32.88±0.63	80.45±1.11	248.87±0.76
4	D4	2.7±0.10	0.33	32.16±0.92	89.94±0.20	248.87±0.39
5	D5	2.46±0.05	0.36	30.08±0.75	87.84±0.96	247.17±0.57
6	D6	2.33±0.05	0.31	28.11±0.66	90.41±0.80	247.49±0.11
7	D7	2.34±0.05	0.33	24.56±0.31	93.41±0.80	248.87±0.32
8	D8	2.37±0.05	0.37	24.12±0.91	95.41±0.80	248.71±0.61
9	D9	2.63±0.05	0.32	22.08±0.52	98.41±0.80	248.87±0.53

(± SD SD = standard deviation) ii) Wetting time and water absorption time.

Table 7.6: Data for wetting time and water absorption time of Cinnarizine tablets

S No	Formulation code	Wetting time Sec (± SD)	Water absorption ratio % (± SD)
1	D1	52.48±0.86	59.33±2.89
2	D2	54.15±0.38	57.22±2.46
3	D3	51.86±0.30	57.33±1.12
4	D4	54.69±0.49	54.71±1.51
5	D5	56.54±0.21	63.26±1.86
6	D6	57.47±0.26	60.41±1.93
7	D7	52.33±0.26	61.47±0.26
8	D8	51.67±0.71	63.56±0.31
9	D9	47.47±0.56	67.47±0.26

iii) In-Vitro Disintegration Time of Cinnarizine

In-vitro disintegration data

Formulation	D1	D2	D3	D4	D5	D6	D7	D8	D9
Disintegration time (sec)	33.70	33.65	32.81	30.33	29.65	27.04	25.21	23.59	22.08

Table 7.11 : *In Vitro* dissolution data of formulations (D1-D9)

Time (min)	D1	D2	D3	D4	D5	D6	D7	D8	D9
2	24.31±0.72	28.33±1.16	21.70±0.96	26.94±0.91	28.33±1.16	21.94±0.91	23.70±0.96	23.70±0.96	26.94±0.91
4	29.14±0.68	34.27±0.90	27.55±0.68	32.47±1.12	34.27±0.90	30.47±1.12	26.55±0.68	27.55±0.97	35.47±1.12
6	33.72±0.85	40.52±0.87	32.86±0.85	38.31±0.67	41.52±0.38	36.31±0.17	32.86±0.85	32.86±0.85	42.31±0.67
8	39.47±0.97	47.87±0.73	38.06±0.93	45.05±0.80	47.87±0.73	45.05±0.08	38.06±0.93	31.06±0.73	48.05±0.80
10	45.93±0.63	53.05±0.98	44.83±0.97	52.18±0.76	51.05±0.81	53.18±0.76	44.83±0.97	49.83±0.37	54.18±0.76
12	55.28±1.08	66.49±1.07	53.63±1.37	63.80±0.85	61.49±1.07	64.80±0.85	53.63±1.37	63.63±1.37	67.80±0.85
14	64.85±0.89	77.68±0.67	62.12±0.74	74.52±0.59	74.68±0.67	72.52±0.59	62.12±0.74	67.12±0.74	79.52±0.59
16	72.60±0.75	85.10±0.79	69.19±0.92	85.63±1.20	79.10±0.79	81.63±1.20	69.19±0.92	73.19±0.92	90.63±1.20
18	79.31±0.90	94.75±0.81	78.27±0.98	91.70±0.94	93.75±0.81	93.70±0.94	78.27±0.98	78.67±0.98	98.70±0.94
20	82.73±0.41	97.54±0.11	82.48±0.16	93.65±0.48	95.47±0.42	95.35±0.75	81.75±0.15	81.34±0.38	99.43±0.56

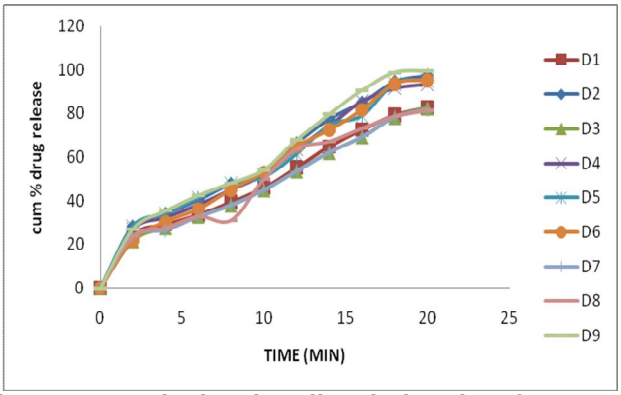


Fig. 7.13: graph showing dissolution data for D1- D9

The in vitro dissolution study of all formulations (D1-D9) gives maximum drug release of 99.43% W/V for formulation D9 at the end of 20 min. all the formulations were within the limits for various post compression parameters like hardness, friability, weight variation and drug content.

Here, D9 given less disintegration time and better drug release after 20 min.

Hence, D9 having Plantago Ovata as disintegrant was selected as the best formulation.

7.8 STABILITY STUDY

Optimized formulation D9 was subjected to stability studies 40 ± 2^0C / 75 ± 5% RH for 90 days. The product was evaluated for description, drug content and in vitro disintegration time. Drug release studies were conducted as per the procedure.

Descriptions

Storage condition	Taste	Observation	inference
RT	Descriptions	No changes of colour in all formulations	Complies with stability condition
40 ± 2^0C / 75 ± 5% RH	Descriptions	No changes of colour in all formulations	Complies with stability condition

8. SUMMARY AND CONCLUSION

Cinnarizine is a histamine H_1-receptor antagonist is the most frequently prescribed drug in treatment of motion sickness, vomiting, allergic reaction, vertigo and insomnia. Conventional Cinnarizine tablets available in market are not suitable where quick onset of action is required. To overcome these problems, there is a need to develop a rapidly disintegrating dosage form, particularly one that would rapidly disintegrate in saliva and could be administered without water anywhere anytime. No such mouth dissolving tablet of Cinnarizine is available in the market.

In the present work, Mouth dissolving tablets were prepared by Effervescent, Superdisintegrant addition and evaluated for disintegration time, hardness and friability.

The Mouth dissolving tablets of Cinnarizine were prepared by superdisintegrants addition method using agar ,gum karaya and plantago ovate in different concentration like 4%, 6% and 10%. There are total nine formulations were prepared and evaluated for Weight variation, Thickness, Friability, Hardness, Disintegration time, Wetting time, Assay and In-vitro dissolution study.

The results of all formulations for Weight variation, Friability, Hardness and Assay were found to be within the IP limit and no significant variation. The Dispersion time for all formulations was found to be 22 to 33.70 seconds and wetting time was between 47.47 to 56.54 seconds. Based on the In-vitro dissolution studies, it was found that the drug release for all the formulations were within 30 minutes.

Formulation D9 containing plantago ovata in concentration of 10% showed minimum disintegration time, wetting time as compare to other formulations. Dissolution studies conclude that the total drug was released within 6 minutes. The results shown that disintegration time was increased in the following manners

Plantago Ovata < Gum Karaya < Agar.

The stability studies were performed for formulation D9 as per I.C.H guidelines, for its in-vitro disintegration time, wetting time and in-vitro drug release pattern. The formulation showed no significant variations for the above mentioned parameters and it was stable for the specified time period.

It was concluded that the mouth dissolving tablet of Cinnarizine can be formulated by superdisintegrant addition technique using Plantago ovate, Gum Karaya and agar in different concentrations.

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