NOVEL APPROACH IN FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF ONDANSETRON HYDROCHLORIDE

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ABSTRACT: Mouth dissolving drug delivery systems has number of advantage viz., faster onset of action, elegance, ease of administration, ease of manufacturing, ease of storage and transport. A novel attempt has been made to develop mouth dissolving tablets of Ondansetron hydrochloride by including clove oil as flavor and local anesthetic on taste buds. The tablets were prepared by direct compression technique. The formulated tablets were evaluated for Pre formulation and post formulation parameters and they were found to be saatisfactory. Direct compression method was employed for making mouth dissolving tablets. The formulated mouth dissolving tablets possessed good drug releasing property, good mouth feel and improved drug availability with better patient compliance.

Keywords: Mouth dissolving tablet, Ondansetron hydrochloride, direct compression method, superdisintegrants.

INTRODUCTION

Patients, particularly pediatric and geriatric patients, have difficulty in swallowing solid dosage forms. These patients are unwilling to take these solid preparations due to a fear of choking. In order to assist these patients, several mouth dissolving drug delivery systems has been developed. Mouth dissolving tablets can be prepared by direct compression, wet granulation, moulding, spray drying, freeze drying or sublimation methods (Biradar SS., 2006). Mouth dissolving tablets dissolve rapidly in the saliva without the need for water, releasing the drug (Kaushik D., 2004). Some drugs are absorbed from the oral cavity as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form (Seager H., 1998).

Ondansetron hydrochloride is a 5-HT3-receptor antagonist used as anti-emetic in conditions like motion sickness (K D. Tripathi., 2003). In cancer chemotherapy, drug induced nausea and vomiting may occur so regularly that anticipatory vomiting occurs when patients return for treatment before the chemotherapeutic agent is given. If not controlled, the discomfort associate with drug induced emesis may cause a patient to refuse further chemotherapy. In this condition ondansetron hydrochloride is a drug of choice. The main criteria for mouth dissolving tablets is to disintegrate/dissolve rapidly in oral cavity with saliva in 60 sec, without need of water and should have pleasant mouth feel(Sharma S., 2008). It has been reported that ondansetron hydrochloride possess bitter taste hence the primary objective is to mask the bitter taste and further developing the drug into mouth dissolving tablets.

MATERIALS AND METHODS

Materials

Ondansetron hydrochloride was a gift sample from Alembic Research Ltd, Vadodara, India. Stevia leaf powder was obtained from the medicinal garden of Sri Krishnadevaraya University, Anantapur, India and authenticated by the Botany department of Sri Krishnadevaraya University, Anantapur, India. Mannitol, Clove oil, talc, micro crystalline cellulose, Cross carmellose sodium, Cross Povidone, magnesium stearate and talc were purchased from S.D. Fine Chemicals, Mumbai, India. All other chemicals, solvents and reagents were used of either pharmacopoeial or analytical grade.

Methods:

Preparation of Mouth Dispersible Tablets: (Kuchekar B.S., 2003)

All the ingredients were passed through sieve No. 60. Ondansetron hydrochloride, mannitol, Micro Crystalline Cellulose and stevia leaf powder were triturated in a glass mortar. Superdisintegrants were incorporated in the powder mixture and finally magnesium stearate and talc were added as lubricant. The powder mix was weighed individually and compressed with 10mm flat face surface punches using hydraulic press single tablet punching machine. The formulae of various mouth dissolving tablets were shown in Table 1

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Table 1: Composition of Mouth Dissolving Tablets of Ondansetron hydrochloride

Ingredients (mg)	Formulations				
	F1	F2	F3	F4	F5
Ondansetron hydrochloride	8	8	8	8	8
Mannitol	50	50	50	50	50
Cross carmellose sodium	10	20	30	40	50
Cross povidone	10	20	30	40	50
Stevia leaf Powder	5	5	5	5	5
Micro crystalline cellulose	306	286	266	246	226
Magnesium stearate	3	3	3	3	3
Talc	3	3	3	3	3
Clove oil (Flavoring agent and local anesthetic)	5	5	5	5	5
Total weight of the tablet 400mg					

Evaluation of the prepared tablet: (Avari, N.G., 2004, USP 24/NF 19, 2000))

Pre-compression parameters

Compatibilities study

The compatibility of drug and polymers under experimental condition was conducted using FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

Flow properties

The powdered blend was evaluated for flow properties viz., Angle of repose, loose bulk density (LBD), tapped bulk density (TBD), Carr's compressibility index, and hausner's ratio

Post compression parameters:

Thickness

The thickness of the tablets was determined using a thickness screw gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used and average values were calculated.

Hardness test

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. Three tablets were randomly picked and analyzed for hardness. The mean and standard deviation values were also calculated.

Friability test

The friability of tablets was determined using Roche Friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The % friability was then calculated by eq.1.

$$F = W_{initial} - W_{final} / W_{initial} X\ 100 \quad \ldots\ldots\ldots\ldots\ldots (1)$$

F= friability (%), $W_{initial}$ = initial weight, W_{final} = Final weight

Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX-100, Arvada, Colorado) and the test was performed according to the official method.

Drug content uniformity

Tablet containing 8mg of drug is dissolved in 100ml of 0.1N HCl taken in volumetric flask. The drug is allowed to dissolve in the solvent. The solution was filtered, 1ml of filtrate was taken in 50ml of volumetric flask and diluted up to mark with 0.1N HCl and analysed spectrophotometrically at 310 nm. The concentration of Ondansetron hydrochloride in mg/ml was obtained by using standard calibration curve of the drug. Claimed drug content was 8mg per tablet. Drug content studies were carried out in triplicate for each formulation batch.

Wetting time

The tablet was placed in a petridish of 6.5 cm in diameter, containing 10 ml of water at room temperature, and the time for complete wetting was recorded. To check for reproducibility, the measurements were carried out six times and the mean value calculated.

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish containing 6ml of distilled water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using eq.2

$$R = 10 \times \frac{(Wa - Wb)}{Wb} \quad \ldots\ldots (2)$$

Where, Wb = weight of the tablet before water absorption
Wa = weight of the tablet after water absorption

Three tablets from each formulation were analysed performed and standard deviation was also determined.

In vitro dispersion time

Tablet was placed in 10 ml phosphate buffer solution, pH 6.8±0.5°C. Time required for complete dispersion of a tablet was measured.

In-vitro disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in-vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37±2^{0}C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37±2^{0}C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

Mouth feel

To know mouth feel of the tablets, selected human volunteers were given placebo tablets and the taste sensation felt was evaluated.

In-vitro dissolution studies

In vitro release studies were carried out using tablet dissolution test apparatus USP XXIII. The following procedure was employed throughout the study to determine the *in-vitro* dissolution rate for all the formulations. The parameters *in-vitro* dissolution studies were tabulated in table 5.

Stability studies:

The promising formulations (F4 and F5) were tested stability for a period of 3 months at accelerated conditions of a temperature 40^{0}C and a relative humidity of 75% RH (table-6), for their drug content (Remunan C., 1992)

Table 6: Selected Formulations for Stability Studies F4 & F5 Stored at 40^{0}C/75% RH

Formulation	Tested after time (days)	Hardness (kg/cm^2)	Disintegration time (sec)	Wetting time (sec)	Drug content uniformity (mg)	Friability (%)
F4	0	6.50±0.07	92±8.26	99± 1.47	49.53±0.55	0.34±0.06
	10	6.48±0.45	95±2.65	100± 2.55	49.53±0.52	0.36±0.02
	20	6.44±0.52	96±3.67	99± 1.89	49.53±0.48	0.38±0.03
	30	6.46±0.29	95±6.22	98± 2.29	49.53±0.32	0.37±0.01
F5	0	6.48±0.04	51±4.61	98± 1.58	49.90±0.68	0.67±0.01
	10	6.35±0.31	53±5.48	102± 2.54	49.90±0.51	0.65±0.02
	20	6.39±0.55	54±3.67	101± 3.25	49.90±0.49	0.69±0.05
	30	6.42±0.15	52±4.98	100± 4.52	49.90±0.27	0.68±0.06
Number of trials (n)=3						

RESULTS

The SEM photograph of tablet surface was shown in Figure 1 and the FTIR spectrum of the tablet blend (F5) was shown in Figure 2. The results obtained for angle of repose of the powdered blends was less than 30^0, the loose bulk density was ranged from 0.55±0.52 to 0.59±0.66 g/cm^3, the tapped bulk density was ranged from 0.65±0.83 to 0.71±0.51 g/cm^3, the percent compressibility was ranged from 12.12 to 22.50 %. All these values were represented in table 2. The mean thickness values were found in the range from 2.88±0.103 to 3.48±0.074mm, the hardness of formulated tablets were found to be 5.38±0.13 to 7.16±0.07 kg/cm^2, the loss in friability was ranged from 0.34 to 0.93, the weights of tablets were found to be from 298.6±2.509 to 300.2±1.095g. The drug content in the formulations were ranged from 49.53±0.55 to 50.10±0.23 mg and these values were shown in table 3. The wetting time was ranged from 92 ± 1.67 to 100 ± 0.73 sec, the *in-vitro* disintegration time was ranged from 51±4.61 to 92±8.26 sec, the mouth feel was palatable which were shown in table 4. Parameters of the dissolution were shown in table 4.

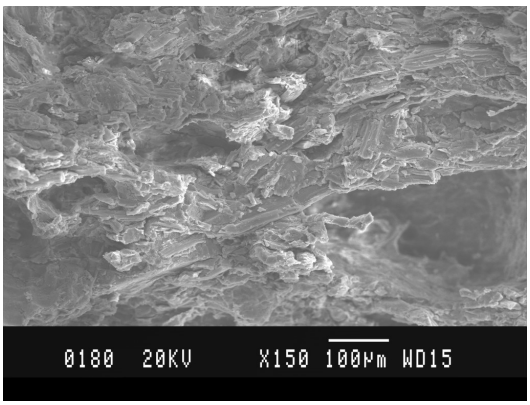

Figure 1: Scanning electron microscopic view of formulated tablet surface (F5)

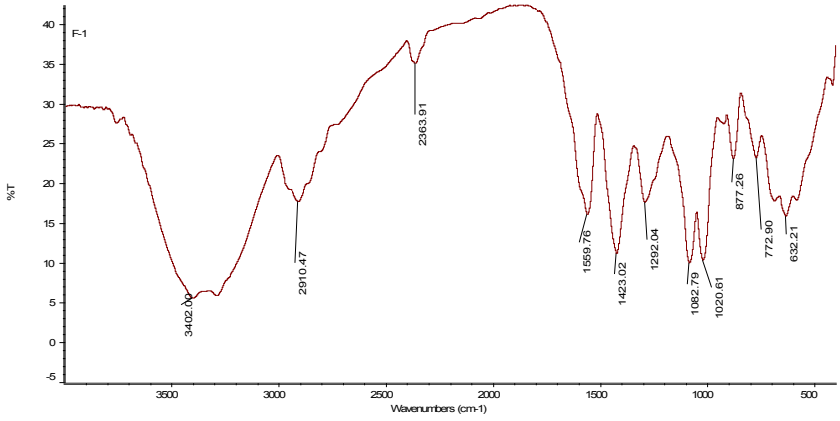

Figure 2: FTIR spectrum of formulation blend (F5)

Table 2: The physicochemical properties of granules

Formulations	Angle of Repose (θ)	Loose Bulk Density (g/cm^3)	Tapped Bulk Density (g/cm^3)	Compressibility (%)
F1	29.32±0.21	0.57±0.77	0.68±0.23	16.18
F2	29.98±0.51	0.55±0.52	0.71±0.51	22.50
F3	29.73±0.30	0.59±0.66	0.69±0.65	14.56
F4	28.20±1.54	0.57±0.32	0.65±0.83	12.35
F5	29.30±0.98	0.58±0.75	0.66±0.94	12.12

Table 3: Evaluation parameters of Tablets

Formulation Code	Uniformity of Thickness (mm) (n=3)	Hardness (kg/cm^3) (n=3)	Friability (%) (n=3)	Weight Variation (mg) (n=20)	Drug Content Uniformity (mg) (n=3)
F1	2.98±0.057	5.88±0.08	0.93±0.07	300.2±1.095	49.89±0.44
F2	3.16±0.065	6.50±0.07	0.88±0.08	299.7±2.411	49.65±0.21
F3	2.88±0.103	7.16±0.07	0.71±0.05	298.6±2.509	50.10±0.23
F4	3.05±0.050	5.38±0.13	0.34±0.06	299.1±2.710	49.53±0.55
F5	3.48±0.074	6.48±0.04	0.67±0.01	299.8±2.774	49.90±0.68

Table 4: Wetting Time, Water Absorption time and mouth feel of formulated tablets

Formulation	Wetting Time (sec) (n=3) *Mean ± SD*	Disintegration Time (sec)	Mouth Feel
F1	100 ± 0.73	65±4.25	good palatable
F2	92 ± 1.67	59±2.32	good palatable
F3	95 ± 1.25	62±6.59	good palatable
F4	99± 1.47	92±8.26	good palatable
F5	98± 1.58	51±4.61	good palatable

Table 5: Tablet dissolution apparatus parameters

Parameter	value
Dissolution medium	900 ml of 0.1N HCl
Temperature	$37^0C±1^0C$
RPM	50
Tablet taken	One tablet (Known drug content).
Volume withdrawn	5 ml every 2 minutes
Volume made up to	5 ml
λ_{max}	310 nm
Beer's range	1-10 µg/ml
Dilution factor	10

DISCUSSIONS:

All formulations showed angle of repose within 30^0 which indicates good that showed little higher angle of repose above 30^0 indicating fair flow. The values obtained lies within the acceptable range and not large differences found between loose bulk density and tapped bulk density. This result helps in calculating the % compressibility of the powder. All formulations show good compressibility. The formulated tablets were eligent and almost uniform thickness. All the formulations were almost uniform in specific method and possess good mechanical strength with sufficient hardness. The weight loss after friability test was found well within the approved range (<1%) in all the formulation, indicates the tablets possess good mechanical strength. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5%. All formulations showed quick wetting, this may be due to ability of swelling and also capacity of absorption of water. All superdisintegrants have high water absorption capacity and cause swelling. All formulations showed disintegration time less than 95 seconds, indicates the swelling of disintegration substance suggested mechanism of disintegration. The volunteers felt good taste in all the formulations. As the drug is not bitter and due to presence of stevia leaf powder, which is 400 times sweeter than sucrose and the Euginol in clove oil acts as both flavoring agent and local anesthetic agent to block the bitter taste of the drug on taste buds. In oral disintegration all the formulations showed rapid disintegration in oral cavity. By observing the above results use of cross cormilose sodium and cross Povidone, in direct compression method results in hydrophilicity and swelling which in turn causes rapid disintegration. Thus these disintegrants are suitable in preparing the rapidly disintegrating tablets. This rapid dissolution might be due to fast breakdown of particles of superdisintegrants. In all formulations the drug release was nearer to 100% within 12 minutes. The optimized formulations F4 and F5 were selected for accelerated stability studies and the tablets possessed the same parameters even after the stressed conditions, indicates good stability properties of formulation.

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