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Mouth Disintegrating Tablets of Taste-Masked Ondansetron HCl

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Ondansetron HCl is used in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and is bitter drug. The purpose of research work was focused on taste masking of the Ondansetron HCl and further development of the drug in mouth disintegrating tablets. Ion exchange resins, Indion 204 and Indion 234 were used with a view to mask the taste of the drug. Tablet formulations were prepared using wet granulation and direct compression techniques. All formulations were subjected to post compression parameters like uniformity of thickness, hardness, friability test, weight variation and drug content uniformity, all these parameters were within pharmacopoeial limits. Formulations FW 6 and FD 2 showed 102.34 ± 1.34 and 101.94 ± 1.54 % of drug release after 15 min, respectively. Volunteer did not feel bitter taste with these formulations (FW 6 and FD 2). These selected formulations were subjected for stability studies and were found to be stable for 3 month at 45 ± 5ºC/ 75 ± 5 % RH with insignificant changes in all post compression parameters.

Key Words: Ondansetron, Mouth disintegrating tablets.

INTRODUCTION

Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance but one important drawback of these dosage forms for geriatric and pediatric patients, is difficulty to swallow[1,2]. Other categories that experience problems using conventional oral solid dosage forms include the mentally ill, uncooperative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack or coughing. Drinking water plays an important role in swallowing conventional oral dosage forms[3]. Such problems can be resolved by means of mouth disintegrating tablets[4]. The main criteria for mouth disintegrating tablets is to disintegrate or dissolve rapidly in oral

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cavity with saliva in 15 to 60 s, without need of water and should have pleasant mouthfeel[2]. Ondansetron HCl is used in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and is bitter drug. The purpose of research work was focused on taste masking of the Ondansetron HCl and further development of the drug in mouth disintegrating tablets.

EXPERIMENTAL

Preparation of non-bitter complex of drug and resin: Indion 204 and Indion 234 were pretreated with 1N HCl and 1N NaOH in order to remove impurities. Drug and resins were mixed in various ratios 1:1 to 1:6 on weight basis and stirred at magnetic stirrer for a period of 1 to 4 h using deionised water of different pH as the medium. The resinate obtained was separated by filtration and dried at 50 ± 5ºC for 1 h. Non-bitter complex was yielded at 1:2 drug to resin ratio using deionised water of pH 4 and also maximum per cent drug loading (83.41 %) was determined at the same ratio.

Preparation of mouth disintegrating tablets: Two methods were used for formulation of mouth disintegrating tablets of Ondansetron HCl.

Wet granulation technique: Accurately weighed quantities of the resinate, mannitol, sodium saccharin, microcrystalline cellulose (MCC) were mixed thoroughly and passed through sieve no 40. A wet mass was prepared using aqueous granulating agent (carboxy methyl cellulose in water or sodium saccharin in water) and non-aqueous granulating agent (PVP K 30 in ethanol). The above wet mass was passed through sieve no 18 and the prepared granules were dried, passed through sieve no 22. Sodium starch glycolate was added extragranularly and the granules were lubricated with 1 % magnesium stearate. The lubricated granules were compressed to 8 mm tablets of average weight of 100 mg on eight-station tablets machine.

Direct compression technique: A blend of the resinate, mannitol, sodium saccharin, MCC, was lubricated with 1 % magnesium stearate and 2 % talc. The lubricated mass was compressed to tablets of average weight of 100 mg on eight-station tablet machine.

Prepared tablets were evaluated for post compression parameters like uniformity of thickness, hardness, weight variation, friability test, drug content uniformity, *in vitro* dispersion and *in vivo* disintegration time.

Uniformity of thickness, hardness and friability test: Thickness of tablets was determined using screw gauge. The hardness and friability of the prepared tablets were determined using the Monsanto hardness tester and Roche friabilator at 100 rpm, respectively.

Weight variation and drug content uniformity: For weight variation 20 tablets from each batch were weighed individually and average

weight was calculated. For drug content uniformity, 6 tablets from each batch were dissolved in 100 mL of deionized water, filtered and analyzed at 249 nm using UV-visible spectrophotometer.

***In vitro* dispersion time:** 6 Tablets from each formulation were randomly selected and dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 mL of pH 6.8 (simulated saliva fluid).

***In vivo* disintegration time:** 10 Healthy human volunteers, whose informed consent was first obtained, were selected for the study. Each volunteer randomly took one tablet from each formulation and kept on the tongue. The time taken for complete disintegration of tablet on tongue was recorded. The trial was performed in triplicate at different time intervals.

***In vitro* dissolution study:** Dissolution study of Ondansetron HCl mouth disintegrating tablets was carried out using USP XXII dissolution apparatus using 900 mL of distilled water maintained at 37± 0.5ºC at a speed of 100 rpm. After 5 min intervals, 5 mL of sample of dissolution medium were withdrawn, filtered and analyzed at 249 nm spectrophotometrically. The volume of dissolution was adjusted to 900 mL by replacing each 5 mL of aliquot withdrawn with 5 mL of distilled water.

Stability studies: Stability studies were carried out at 25 ± 5ºC/60 ± 5 % RH and 40 ± 5ºC/75 ± 5 % RH for a period of selected formulations (FW6, FW7 and FD2).

RESULTS AND DISCUSSION

10 Formulations were prepared by wet granulation technique and four formulations were prepared by direct compression technique. (Tables 1 and 2). The data obtained of post-compression parameters such as uniformity of thickness, hardness, friability test, weight variation, drug content uniformity, *in vitro* dispersion time and *in vivo* disintegration time are shown in Table 3 and 4. The hardness of tablets, prepared by wet granulation technique or direct compression technique, was found to be in range of 2.8 to 3.2 kg/cm^2 in all formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. Friability was less than 1 % in the all formulations indicating that tablets are mechanically stable. All the tablets passed weight variation as the % weight variation was within the pharmacopoeial limits. The per cent of drug content of all the tablets were found to be between 95.29 ± 1.02 and 102.34 ± 1.34 which was within the acceptance limits.

Results in Table-3 indicate the rapid disintegration in formulations FW6, FW7 and FD2. FW6 and FW7 formulations were prepared using aqueous solution of sodium saccharin as binder while FD2 and FD3 prepared by direct compression technique showed rapid disintegration.

TABLE-1
COMPOSITION OF ONDANSETRON HCl MOUTH-DISINTEGRATING TABLETS PREPARED BY WET GRANULATION TECHNIQUE

Ingredients (% w/w)	Formulation Code									
	FW1	FW2	FW3	FW4	FW5	FW6	FW7	FW8	FW9	FW10
Drug	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.000	4.00	4.000
Mannitol	56.00	55.00	54.00	53.00	64.00	63.00	62.00	86.693	85.00	83.307
Sodium saccharin	1.00	1.00	1.00	1.00	12.00	12.00	12.00	1.000	1.00	1.000
CMC	2.00	2.00	2.00	2.00	–	–	–	–	–	–
PVP K 30	–	–-	–	–	–	–	–	0.307	1.00	1.693
Sod. starch glycolate	4.00	5.00	6.00	7.00	5.00	6.00	7.00	5.000	6.00	7.000
MCC	30.00	30.00	30.00	30.00	12.00	12.00	12.00	–	–	–
Talc	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.000	2.00	2.000
Magnesium stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.000	1.00	1.000

TABLE-2
COMPOSITION OF ONDANSETRON HCl MOUTH-DISINTEGRATING TABLETS PREPARED BY DIRECT COMPRESSION TECHNIQUE

Ingredients (% w/w)	Formulation Code			
	FD1	FD2	FD3	FD4
Drug	4.00	4.00	4.00	4.00
Mannitol	20.00	20.00	20.00	20.00
Sodium saccharin	1.00	1.00	1.00	1.00
Sod. starch glycolate	4.00	5.00	6.00	7.00
MCC	68.00	67.00	66.00	65.00
Talc	2.00	2.00	2.00	2.00
Magnesium stearate	1.00	1.00	1.00	1.00
Total weight	100.00	100.00	100.00	100.00

Fig. 1 showed that rapid dissolution was observed in FW6, FW7, FW8, FD2 and FD3. The rapid drug dissolution might be due to easy breakdown of particles and rapid absorption of drug into the dissolution medium. Formulations FW6, FW7and FW8 were prepared using sodium saccharin as binder and FD2 and FD3 were prepared by direct compression method.

In concern to mouthfeel test of the prepared formulation, volunteers did not feel any bitter taste except with formulations FW1, FW4 and FD2.

Stability studies were conducted for selected formulations (FW6, FW7 and FD2). The selected formulations showed no significant variation in all post-compression parameters.

TABLE-3
RESULTS OF UNIFORMITY OF THICKNESS, HARDNESS, FRIABILITY, WEIGHT VARIATION, DRUG CONTENT UNIFORMITY, *in vitro* DISPERSION TIME AND *in vivo* DISINTEGRATION TIME OF ONDANSETRON HCl MOUTH DISINTEGRATING TABLETS PREPARED BY WET GRANULATION TECHNIQUE

FC	Uniformity of thickness (mm) Mean ± sd n=3	Hardness Kg/cm ^{2} Mean ± sd n=3	Friability (%)	Weight Variation (mg) Mean ± sd n= 20	Drug content uniformity (mg) Mean ± sd n=6	*In vitro* dispersion time (s) Mean ± sd n=6	*In vivo* Disintegration time (s) Mean ± sd n=10	Mouth feel *
FW1	2.9 ± 1.24	3.2 ± 4.12	0.84	11.5 ± 1.41	95.99 ± 2.12	11.54 ± 3.54	94.21 ± 2.65	X
FW2	2.8 ± 2.04	2.8 ± 3.42	0.88	100.3 ± 1.22	11.65 ± 2.12	95.25 ± 2.54	90.21 ± 4.25	O
FW3	2.9 ± 1.45	2.8 ± 1.25	0.84	12.5 ± 3.21	12.58 ± 1.65	80.45 ± 2.12	78.55 ± 3.25	O
FW4	2.9 ± 1.78	2.9 ± 1.29	0.80	99.4 ± 0.95	12.22 ± 0.98	81.45 ± 2.01	79.56 ± 2.01	X
FW5	2.8 ± 1.56	2.8 ± 2.54	0.70	12.3 ± 2.44	96.87 ± 2.45	26.25 ± 1.54	23.65 ± 1.25	O
FW6	2.9 ± 1.35	2.8 ± 2.13	0.92	100.5 ± 1.56	12.34 ± 1.34	22.12 ± 1.01	12.45 ± 1.01	O
FW7	2.9 ± 1.87	2.9 ± 1.45	0.78	99.2 ± 2.50	97.87 ± 2.23	25.45 ± 0.99	15.55 ± 1.35	O
FW8	2.9 ± 1.64	2.8 ± 1.54	0.84	98.2 ± 3.54	96.32 ± 0.92	27.12 ± 1.23	18.56 ± 1.44	O
FW9	2.9 ± 1.88	2.8 ± 1.64	0.84	11.3 ± 3.12	98.25 ± 1.78	52.12 ± 1.25	50.36 ± 1.95	O
FW10	2.9 ± 1.54	2.8 ± 2.01	0.84	99.5 ± 0.09	11.25 ± 1.02	60.54 ± 1.98	59.54 ± 1.56	O

*3 –strong bitter, 2 –moderate bitter, 1 –slight bitter, X –threshold bitter, O –tasteless. FC- formulation code

TABLE-4
RESULTS OF UNIFORMITY OF THICKNESS, HARDNESS, FRIABILITY, WEIGHT VARIATION, DRUG CONTENT UNIFORMITY, *in vitro* DISPERSION TIME AND *in vivo* DISINTEGRATION TIME OF ONDANSETRON HCl MOUTH DISINTEGRATING TABLETS PREPARED BY DIRECT COMPRESSION TECHNIQUE

FC	Uniformity of thickness (mm) Mean± sd n=3	Hardness Kg/cm ^{2} Mean± sd n=3	Friability (%)	Weight Variation (mg) Mean± sd n= 20	Drug content uniformity (mg) Mean± sd n=6	In vitro dispersion time (s) Mean± sd n=6	In vivo Disintegration time (s) Mean± sd n=4	Mouth feel *
FD1	2.9 ± 1.22	2.8 ± 2.21	0.82	12.4 ± 2.45	98.98 ± 0.88	40.42 ± 1.32	30.85 ± 0.99	O
FD2	2.9 ± 1.02	2.8 ± 1.98	0.81	99.54 ± 2.89	11.94 ± 1.54	25.22 ± 0.96	14.42 ± 0.55	O
FD3	2.9 ± 1.55	2.8 ± 1.21	0.81	11.45 ± 1.44	97.92 ± 1.22	28.54 ± 0.25	16.45 ± 0.65	O
FD4	2.9 ± 0.96	2.8 ± 1.05	0.82	11.55 ± 2.45	11.58 ± 1.25	34.55 ± 0.55	29.54 ± 0.35	O

*3 –strong bitter, 2 –moderate bitter, 1 –slight bitter, X –threshold bitter, O –tasteless FC- formulation code

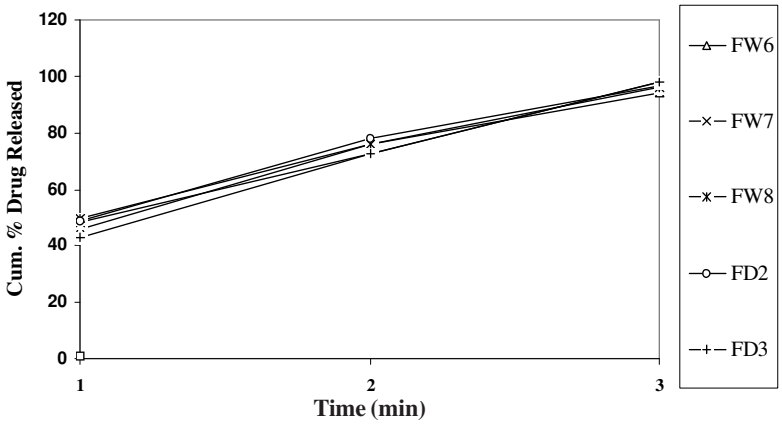

Fig.1. *In vitro* dissolution profile of formulations FW6, FW7, FD8, FD2 and FD3

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