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Research Article

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Formulation Development and Evaluation of Taste Masked ORO-dispersible tablets of anti emetic drug

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ABSTRACT

Ondansetron hydrochloride is commonly used as anti emetic. But it is a very bitter drug and slightly soluble in water. So in the work under taken an attempt was made to mask the taste and to formulate into a dispersible tablet by complexation with ion exchange resins, which also acts as super disintegrating agents. Since, these tablets can be swallowed in the form of dispersion, it is suitable dosage form for pediatric and geriatric patients. Cationic exchange resins like Indion-204 , Indion-234 and Tulsion-335 were utilized for the sorption of drug. Drug- resinates were prepared in drug to resin ratio of 1:6, 1:5 and 1:6.The prepared tablets were evaluated for general appearance, content uniformity, hardness, friability, taste evaluation, mouth feel, wetting time, *in vitro* and *in vivo* disintegration time, and *in vitro* dissolution studies. Tablets with all the resins have shown quick disintegrating features, i.e., within 20 seconds, which is very characteristic of oro-dispersible tablets. Also, the dispersion not showing any bitter taste, indicate the capability of ion exchange resins used, both as taste masking and super disintegrating agents. Almost more than 90% of drug was released from the formulations within 1 hour. Further formulations were subjected to stability testing for '3 month' at temperatures 25 ºC/60±5%RH&40±5ºC/75±5%RH.All tablet formulations show no appreciable changes with respect to taste, disintegration and dissolution profiles.

Key words: Ondansetron Hcl, drug-resinates, oro-dispersible tablets, ion exchange resins

INTRODUCTION

More than 50% of pharmaceutical products are orally administered for several reasons and undesirable taste is one of the important formulation problem in oral dosage form. Taste of a pharmaceutical product is an important parameter for governing compliance. Thus taste masking of oral pharmaceuticals has become an important tool to improve patient compliance and the quality of treatment especially in pediatrics. There fore formulation of taste masked products is a challenge to the pharmacists[1].

Ondansetron Hcl in most commonly used as anti emetic. It is a very bitter drug and slightly soluble in water[2]. The main objective of the present work is to formulate taste masked dispersible tablets of Ondansetron HCl. The dispersible tablets can be swallowed without water in the form of dispersion. They increase the patient compliance as well as provide quicker onset of action. Ion exchange resins have been increasingly used as taste masking agents[3,4].They are also known to be useful as disintegrating agents superior to other conventional agents. There fore, the study undertaken was aimed to formulate taste masked oro-dispersible tablets of Ondansetron Hcl. Such a tablet may be swallowed in the form of a dispersion, as it is expected to disintegrate quickly when in contact with saliva[5].When it comes in contact with acidic environment of the stomach, the complex will be broken down quickly and releasing the drug, which may then be absorbed in usual way[5].The plan of work was complexing the drug with the resins (Indion-204,Tulsion-335 & Indion-234) to form drug-resinates, evaluation of drug- resinate complexes and compressing drug-resinate complexes into tablets with suitable additives.

EXPERIMENTAL

Preparation of non bitter drug-resinate complex: Ion exchange resins like Indion- 204 Tulsion-335, Indion-234 were pretreated with 1N HCl and1N 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 4 to 8 hours using deionised water. The resinate obtained was separated by filtration and dried. Non bitter complex was yielded at 1:6,1:5 and 1:6 drug to resin ratio using deionised water of pH 7 and also maximum percentage drug loading(96.5, 99.1 & 98.8 %) was determined at the same ratio.

Evaluation of amount of non-complexed drug: The mixtures to be evaluated were kept aside to allow the particles to sediment and then filtered. From this filtrate 1ml is taken transferred in to 100 ml volumetric flask and the volume was made up to 100 ml and absorbance were noted, from which amount of non-complexed drug was calculated.

Production of tablets: Granules of drug resinate earlier obtained wereMixed with mannitol, followed by 'Microcrystalline cellulose', cros povidone, flavouring agents (mint flavour) and talc(2%). Before compression hardness was adjusted. Drug-resinates equivalent to 10mg of Ondansetron HCl were compressed on cadmach single punch tablet press machine equipped with 6mm flat faced beveled edge punches and same hardness was used for the required number tablets. Prepared tablets were evaluated for post compression param-

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eters like thickness, hardness, weight variation, friability test, drug content uniformity, taste evaluation, wetting time, *in vivo* dispersion time, *in vivo* disintegration time and stability studies.

General appearance, Thickness, Hardness test[7]: Five tablets from both batches were randomly selected and organoleptic properties such as colour, odour, taste, shape, were evaluated. The thickness of five tablets was measured using vernier calipers. The diameter was also determined by using vernier calipers. Hardness of the tablets was tested by using 'Monsanto' hardness tester.

Drug content uniformity: Five tablets taken randomly and crushed individual tablet, added 50ml of 0.1M methanolic HCl. Shaken for 30 minutes and added sufficient 0.1 M methanolic HCl to produce 100ml and filtered. In this 1ml added to100ml volumetric flask, again made up the volume up to the mark with same acid solution. Measure the absorbance spectrophotometrically at 300 nm. The tablets comply with the test if not more than one of the individual values thus obtained is outside the limit 98% to 102% of the average value.

Weight variation test[7] and friability test: Weighed 20 tablets selected at random and calculated the average weight. Then percentage deviation from the average was calculated and then friability of prepared tablets was determined using Roche friabilator.

***In vitro* disintegration test:** This test is performed to ensure disintegration of tablets in water, if it is to be used as a dispersible tablet. To be in compliance with the pharmacopoeial standards, dispersible tablets must disintegrate with in 3 minutes when examined by the disintegration test for tablets.

***In vitro* dispersion time (with simulated salivary fluid)[7]:**This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as a oro-dispersible tablet. *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of simulated salivary fluid of pH 6.8. Five tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

***In vivo* disintegration time:** Six healthy human volunteers were selected and their written consent was obtained. Each volunteer randomly took one tablet and kept on the tongue. The time taken for complete disintegration of the tablet on the tongue was noted. It is expressed in seconds. After the test, mouth was washed with distilled water. Three trials were performed with 2 days intervals.

Wetting time: This method will duplicate the *in vivo* disintegration, as the tablet is motionless on the tongue. Wetting time was measured by placing a tablet on a piece of tissue paper folded twice, and was placed in a small Petri dish containing 6 ml of simulated saliva pH 6.8, and the time for complete wetting was measured. Five tablets from each batch were used and results were compared with commercial product.

Uniformity of dispersion[6]: This test is applicable only to dispersible tablets. In the method, 2 tablets are placed in100 ml of water and stirred gently until completely dispersed. A smooth dispersion must be obtained which passes through a sieve screen with a nominal mesh aperture of 710um (sieve no.22).

Taste evaluation: Taste evaluation was done by a panel of 6 volunteers using time intensity method.1tablet was held in mouth for 10 seconds bitterness levels were recorded instantly and then at the end of 10 seconds, 30seconds, 1 minute and 2 minutes bitterness levels are again noted and recorded and compared with commercial product.

Mouth feel: The same human volunteers participated in taste evaluation test, were asked give their opinion about the feeling of smoothness or grittiness of the dispersion soon after the tablet got disintegrated.

***Invitro* dissolution studies:**The dissolution rate of Ondasetron HCl hydrochloride from the tablets was studied in 0.1 N hydrochloric acid using USP XXIII dissolution test apparatus employing paddle stirrer and assayed spectrophotometrically at 300nm similar test was carried out for a commercial product for comparison.

Stability studies: Stability studies were carried out at 25±5ºC/60±5%RH and 40±5ºC/75±5%RH for a period of 3 months for all F_1, F_2 and F_3 formulations as per ICH guidelines.

RESULTS AND DISCUSSION

Formulations were prepared by direct compression technique [table1]. The data obtained for post-compression parameters such as uniformity of thickness, hardness, weight variation, friability test, drug content uniformity, taste evaluation, wetting time, *in vivo* dispersion and *in vivo* disintegration time are shown in the [table 2]. The tablets diameters were almost uniform in F_1, F_2 and F_3 formulations and thickness range was very well within ± 5% of the standard value in both batches.The measured average hardness of the tablets of was 3.5,4.0 & 3.0 Kg/cm^2 respectively for all three formulations, this ensures good handling characteristics of all formulations. The percentage drug content of all tablets formulations was found to be between 92 to 99%, which complied with the limits established in the pharmacopoeia.The percentage friability was less than 1% in all three formulations, ensuring that the tablets were mechanically stable.

All the tablets passed weight variation test, as percentage weight variation was with in the pharmacopoeial limits i.e.±7.5%. To be complied with the pharmacopoeial standards, dispersible tablets must disintegrate within 3 minutes. But formulated products have exhibited very less disintegrating time (i.e.14, 21 and 20 seconds), indicating that all three formulations were suitable for oro-dispersible tablets.

The *in vivo* disintegration time, wetting time was observed to be very fast in F_1 formulation when compared to F_2, F_3 & marketed product.Panel of healthy human volunteers for taste masking evaluation using time intensity method, whi ch shows satisfactory masking of taste as shown in the [table 3]. All F_1 and F_2 & F_3 formulations did not show any bitter taste when tablets are held in the mouth by using time intensity method, which shows excellent taste masking effect of the resins. In case of marketed formulation, bitterness was felt by all the volunteers.

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Table 1: Formulation of tablets formulated with resins Indion-204 (F_1), Indion-234 (F_2) & Tulsion-335(F_3)

Ingredients	Formula for 100 tablets(F_1)	Formula for 100 tablets(F_2)	Formula for 100 tablets(F_3)
Drug resinates equivalent to 8 mg of Ondasetron HCl	4.8g	4.0g	4.8g
Crosspovidone	2.5g	3.3g	3.5g
Micro crystalline cellulose	2.1g	2.1g	1.1g
Mannitol	2.8g	2.8g	2.8g
Talc (2 %)	0.2g	0.2g	0.2g
Magnesium stearate	0.1g	0.1	0.1
Mint flavour	q.s	q.s	q.s

q.s = quantity sufficient to produce

Table 2: Results of post compression parameters

Batches	Diameter* (mm) ±SD	Thickness*(mm) ±SD	Hardness* Kg/sq.cm2 ±SD	Friability(%)	Weightvariation (mg)Mean ± SD n=20	Drug content uniformity (%)
F_1	6 ± 0.020	2.9 ± 0.050	3.5 ± 0.1	0.59	228.2 ± 1.45	96.5
F_2	6 ± 0.050	2.9 ± 0.020	4.0 ± 0.2	0.71	274.4 ± 2.89	99.1
F3	6± 0.045	2.9 ± 0.020	3.0± 0.1	0.60	274.4 ± 2.89	98.8

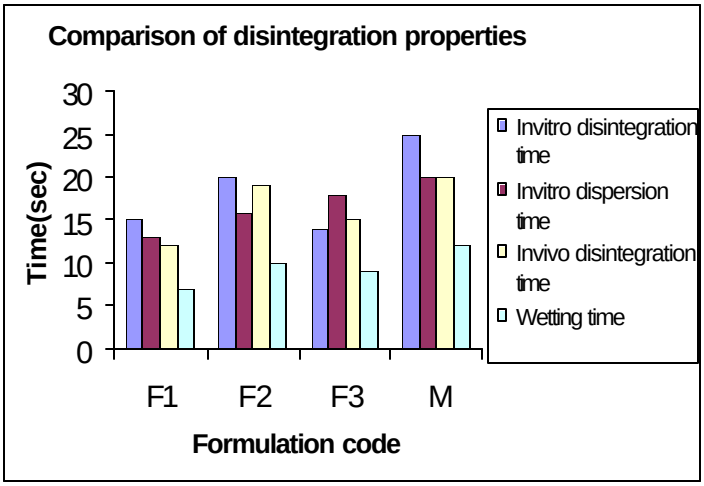

Fig 1 : Bar graph comparison of disintegration properties with rank order

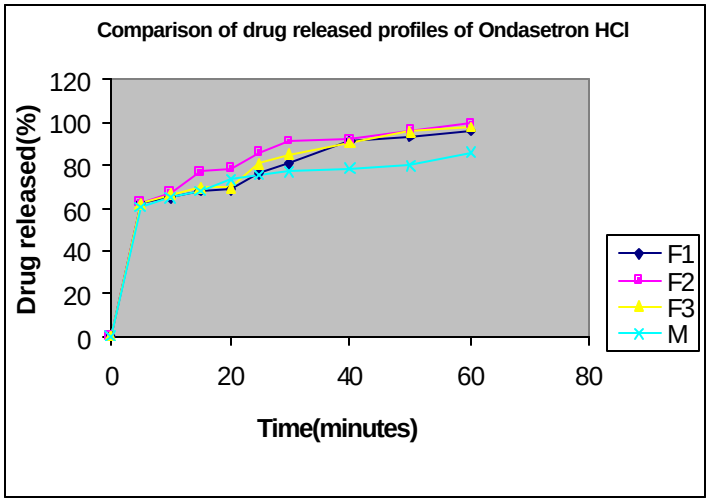

Fig 2: Comparison of drug released profiles from formulations, F_1, F_2, F_3 & Marketed Product

Table 3: Taste evaluaton of F_1, F_2 & F_3 formulations

Volunteers	Bitterness level after 10 sec			30 sec			1 min			2 min			Mouth feel		
	F_1	F_2	F_3	F_1	F_2	F_3	F_1	F_2	F_3	F_1	F_2	F_3	F_1	F_2	F_3
1	0	0	0	0	0	0	0	0	0	0*	0	×	+	+	+
2	0	0	0	0	0	0	0	0	0	0	×***	0	+	+	+
3	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+
4	0	0	0	0	0	0	0	0	0	0	×**	0	+	++	+
5	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+

* = No bitterness,+ = Gritty and pleasant feeling,** = Smooth and pleasant feeling, ++ = Gritty and unpleasant feeling,*** = Threshold bitterness

All formulations show smooth and pleasant mouth feeling, thus fulfill the requirements of oro-dispersible tablets. The complex was subjected to dissolution studies in 0.1N HCl using USP(XXIII) paddle apparatus at 100 rpm and 37°C temperature which shows that drug release was more than 90% within an hour. Stability study was conducted, there was no significant taste, colour and odour change at any temperature. There was no significant variation in the *in vitro* dispersion time, *in vivo* disintegration time, wetting time and *in vitro* dissolution profiles after three month of stability studies for all the formulations at different temperatures.

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