FORMULATION AND EVALUATION OF TASTE MASKED ORO-DISPERSIBLE TABLET OF ONDASETRON HYDROCHLORIDE USING ION EXCHANGE RESIN

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Summary

Ondansetron Hydrochloride is a 5-HT_3 antagonist and anti-emetic agent. It blocks the depolarising action of 5-HT through 5-HT_3 receptors. The objective of the proposed research work was to develop an optimized formulation of oro-dispersible tablets of Ondansetron HCL by complexation using ion exchange resin to overcome the problem of swallowing and provide a quick onset of action of drug in pediatric and geriatric populations. Weak acidic cationic exchange resins like Kyron T-134 were utilized for the sorption of drug. Drug-resinates was prepared in drug to resin ratio of 1:3. The prepared tablets were evaluated for general appearance, hardness, taste evaluation, mouth feel, wetting time, *in vitro* disintegration time and *in vitro* dissolution studies. Tablets with both the resins have shown quick disintegrating features, i.e., within 20 second, which is very characteristic of oro-dispersible tablets. Also, the dispersion not showing any bitter taste, indicate the capability of ion exchange resins used. Almost more than 90 percent of drug was released from both the formulations within 1 h. Further formulations were subjected to stability testing for 3 months at temperatures 25±5ºC/60±5%RH and 40±5ºC/75±5%RH. There are no appreciable changes with respect to taste and dissolution profiles.

Keywords: Taste masking, Ondansetron hydrochloride, Kyron T-134, complexation, oro-dispersible tablet.

Introduction

The term ‘Orodispersible Tablet’ as appears in European Pharmacopoeia is defined as “uncovered tablet for buccal cavity, where it disperses before ingestion’’. They obviate the problem associated with conventional dosage forms, it has benefits like desired hardness, dosage uniformity, extremely easy administration and since no water is required for swallowing these tablets are suitable for geriatric, paediatric and travelling patients. These tablets display a fast and spontaneous de-aggregation in the mouth, soon after it comes in contact with saliva, dissolving the active ingredient and allowing absorption through all possible membrane it comes in contact during deglutition[1]. Most of pharmaceutical products are orally administered for several reasons and bitter taste is one of the important formulation problem encountered with such oral products[2]. Palatability is a special requirement for oral medication in children’s and old age

people. Thus, taste masking of oral pharmaceuticals has become an important tool to improve patient compliance and the quality of treatment especially in pediatrics and geriatrics[3,4].
Ondansetron HCl is a 5-HT_3 antagonist and anti-emetic agent. It blocks the depolarizing action of 5-HT through 5-HT_3 receptors. 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. It is a very bitter drug and slightly soluble in water[5]. The purpose of the present work was to formulate taste masked dispersible or oro-dispersible tablets of Ondansetron hydrochloride, and it increase the patient compliance as well as provide quicker onset of action.

Materials and Methods

Materials: Ondansetron hydrochloride, Kyron T-134, xanthan gum, HPMC K-4 and Sod. CMC were received as gift samples from Ranbaxy Laboratories, Gudgaon, India. Mannitol, aerosil and magnesium stearate, was of AR Grade.

Methods

Preparation of drug-resinate complex: Ion exchange resins like Kyron T 134 were used. Drug and resins were mixed in various ratios 1:1 to 1:3 on weight basis and stirred at magnetic stirrer for a period of 4 to 8 h using deionized water. The resinate obtained was separated by filtration and dried[6].

Effect of pH on drug loading: A series of solutions were prepared which contained fixed quantity of resin Kyron T 134 in deionized water and Ondansetron HCl. The pH of the solutions was maintained at 3, 4 and 7. The solution along with drug and resin was stirred at a magnetic stirrer for 4 hrs. The resinate was collected by filtration and washed with copious amount of deionized water to remove free and uncomplexed drug, followed by drying at 500C. Drug content was determined.

Characterization and evaluation of the tablet blend: Physical properties such as bulk density, tapped density, compressibility index, and the angle of repose of blend were determined.

Formulation of tablets: Granules of drug resinate earlier obtained were mixed with mannitol, microcrystalline cellulose, flavoring agents, sweetening agents, aerosil and magnesium sterate. Before compression, hardness was adjusted. Drug-resinates of Ondansetron HCl were compressed on single punch tablet press machine equipped with 10 mm flat faced beveled edge punches and same hardness was used for the required number of tablets.

Prepared tablets were evaluated for post compression parameters like thickness, hardness, weight variation, taste evaluation, wetting time, *in vivo* dispersion, *in vivo* disintegration time, and stability studies.

Hardness test: Hardness of the tablets was tested by using 'Monsanto' hardness tester[7].

Weight variation test and friability test: Weighed 20 tablets were selected randomly and the average weight was calculated. Then percentage deviation from the average was calculated and then friability of prepared tablets was determined using Roche friabilator.

Drug content uniformity: The tablets must complied with the test if not more than one of the individual values thus obtained is outside the limit 85 to 115% of the average value[8,9].

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

Wetting time: 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[10].

Taste evaluation: Taste evaluation of Ondansetron HCl was carried out by 5 member's panel First pure drug 100 mg was given to the volunteers and taste was noted. After administration of water and after rinsing the mouth, the complex equivalent to 100 mg was given to the volunteer. The taste difference between pure drug and complex was noted and compared.

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

***In vitro* dissolution studies:** The dissolution rate of Ondansetron hydrochloride from the tablets was studied D.M. water using USP paddle Type 2 dissolution test apparatus and assayed spectrophotometrically at 310 nm.

Stability studies: Stability studies were carried out at 25±5˚C/60±5%RH and 40±5˚C/75±5%RH for a period of 3 months for optimized formulations as per ICH guidelines[11].

Results

Preparation of resinate: The resinate was prepared by batch process, the weighed amount of resin was stirred for 4 hr for swelling of resin then drug was added to it.

Selection of Drug Resin ratio: For the selection of the proper drug resin ratio, the ratio of the drug resin was varied, keeping concentration of drug constant. The pH of the solution was maintained at 4. The result shows that drug resin in the ratio of 1:3 has better drug loading as compared to the other. The results were shown in table 1.

Table 1 Effect of drug-resin ratio

Batch	Drug:Resin ratio	Taste	%Drug Loading
F1	1:1	Very Bitter	43.65

F2	1:2	Bitter	67.54
F3	1:3	Palatable	99.08

Effect of pH on drug loading: The presence of drug was influenced by pH of the solution, which therefore exerts an influence on loading efficiency. This behavior was investigated by varying the pH of the drug resin solution, keeping the drug resin ratio 1:3 as constant. The result showed that at pH 4 maximum loading of the drug on the resin occurs (Table 2).

Table 2 Effect of pH on drug loading

Batch	pH of reaction medium	%Drug loading
F3.1	3.0	81.09
F3.2	4.0	87.86
F3.3	7.0	66.76

Evaluation of Taste of Resinate: Taste evaluation of DRC was performed by volunteers in the age group of 18 to 22 years. Resinate of ondansetron hydrochloride (1:3) was held in the mouth for 5 seconds by each volunteer. Bitterness levels were recorded instantly and then after 30 to 150 sec. The bitterness level was recorded against pure drug using a numerical scale (3 – strong bitter, 2 – moderate bitter, 1 – slight bitter, X – threshold bitter, 0 – no bitter). The results are revealed in table 3.

Table 3 Evaluation of taste of resinate

Volunteer	Bitterness level after					
	10 sec	30 sec	60 sec	90 sec	120 sec	150 sec
1	0	0	0	0	0	0
2	X	X	0	0	0	0
3	0	0	0	0	0	0
4	X	0	0	0	0	0
5	0	0	0	0	0	0

X – threshold bitter, 0 – no bitter

Evaluation of tablet blend: The tablet blends were evaluated for the bulk density, shape and angle of repose. The results of tablet blends are shown in table 4.

Table 4 Physical characteristics of tablet blends

Parameter	Optimized Batch
Bulk density	26.54^0
Shape	Iregular
Angle of repose	0.78 gm/cm3

Evaluation of optimized batch: The formulations were prepared by direct compression technique. The formulation was characterized for various parameters such as hardness, friability test, drug content uniformity; taste evaluation, wetting time, and *in vivo* disintegration time are shown in the table 5.

Table 5 Evaluation of prepared tablets

Parameter	Optimized Batch
Taste	Sweet
Mouth feel	Good
In vitro disintegration time (sec)	11 sec
Content uniformity	99.08 %
Hardness (kg/cm2)	3.2
Friability	0.683
Wetting time	19.33

***In Vitro* Dissolution Study:** The tablet was subjected to dissolution studies in D.M. water using USP Type 2 paddle apparatus at 50 rpm and 37°C temperature which shows that drug release was more than 90% within an hour (Table 6).

Table 6 *In vitro* drug release data

Time (min)	%drug release
5	80.27
15	85.73
25	90.08
35	95.16
45	99.09

Stability Study: Stability study was conducted. There was no significant taste, color, and odor change at any temperature. There was no significant variation in the *in vitro* dissolution profiles after three months of stability studies at different temperatures.

Discussions

Non bitter complex was yielded at 1:3drug to resin ratio using deionized water of pH 4 and also maximum percentage drug loading (99.08 percent) was determined at the same ratio. The formulations show smooth and pleasant mouth feeling, thus fulfill the requirements of oro-dispersible tablets. The complex was subjected to dissolution studies which show that drug

release was more than 90% within an hour. There was no significant change in taste, color, and odor and *in vitro* dissolution profiles after three months of stability studies for both the formulations at different temperatures.

Conclusion

In the present study, an attempt was made to mask bitter taste of ondansetron HCl by Kyron T-134 (cation exchange resin). Various parameters affecting taste masking like drug-resin ratio, pH was optimised. It is concluded that by adopting a systemic approach an optimum point can be reached in the shortest time with minimum efforts. The volunteers rated the optimised complexes as tasteless and palatable. This leads to improved patient compliance. Taste masking of tablets help in administration of ondansetron HCl in a more palatable form without water during emesis.

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