

Taste masking of ondansetron hydrochloride by polymer carrier system and formulation of rapid-disintegrating films

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Abstract- The purpose of this research was to mask the intensely bitter taste of Ondansetron HCl and to formulate rapid disintegrating films (RDFs) of the taste-masked drug using methocel E15. Taste masking was done by complexing Ondansetron HCl with ion exchange resin (Polacriline Potassium) which also has disintegrating property, in different ratios and by using sucralose as sweetening agent in very low concentrations. Taste was further masked using vanilla flavor in combination with lychee and banana flavor. Drug-polymer complexes (DPCs) were tested for drug content, in vitro taste in simulated salivary fluid (SSF) of pH 6.2, and molecular property. Complex that did not release drug in SSF was considered taste-masked and selected for formulation RDFs. The complex with drug-polymer ratio of 2:1 did not show drug release in SSF; therefore, it was selected. The properties of films such as hydration study, folding endurance and in-vitro drug disintegration in the oral cavity were investigated. PEO N-10, 7% wt/wt gave the minimum disintegration time and elegance to the final product. Films of batch F4 containing mannitol and sorbital in the ratio 1:1 and 7% wt/wt PEO N-10 showed faster disintegration, within 12.5 seconds. Good correlation between in-vitro disintegration behavior and in the oral cavity was recognized. Taste evaluation of RDF in human volunteers revealed considerable taste masking with the degree of bitterness below threshold value (0.5) ultimately reaching to 0 within 15 minutes, whereas Ondansetron HCl was rated intensely bitter with a score of 3 for 10 minutes. Films of batch F4 also revealed rapid drug release (t_{90} , 60 seconds) in SGF. Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated films in the oral cavity.

Keywords: Ondansetron hydrochloride, Methocel E15, Polacriline Potassium, Poly ethylene oxide N-10, Rapid disintegrating films RDF, Simulated salivary fluid, Drug-polymer complexes, Hydration studies.

Introduction

Amongst the various routes of drug delivery, oral route is the most preferred by patients and clinicians. A renewed interest has been addressed to oral solid dosage forms designed for prompt availability of therapeutic dose. Mouth dissolve products (tablets and films) may show greater patient acceptability and convenience. They can be taken with ease at any time by the patient without water [1-2]. Oral film may be preferred over the mouth dissolve tablets in terms of flexibility and comfort [3]. In addition, they can also circumvent the sticky feeling in the oral cavity associated with oral gels. Moreover, the oral film is able to protect the wound surface, thus reduce pain and also could treat oral disease more effectively [4]. In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication [5-7]. Among the dosage forms developed to facilitate ease of medication, the rapid disintegrating films (RDF) is one of the most widely investigated and research product [8]. The RDF has remarkable disintegration properties; it can rapidly disintegrate without water in the mouth within a few seconds. When an RDF is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration [9]. RDFs are useful in patients, such as pediatric, geriatric, bedridden, or developmentally disabled, who may face difficulty in swallowing conventional tablets or capsules and liquid orals or syrup, leading to

ineffective therapy, with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life style [10-11]. RDFs are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething [12-14]. Ondansetron HCl is a potent antiemetic drug indicated for the treatment and/or prophylaxis of postoperative or chemotherapy- or radiotherapy-induced emesis and also used in the early onset of alcoholism [15]. In general, emesis is preceded with nausea and in such condition it is difficult to administer drug with a glass of water; hence it is beneficial to administer such drugs as RDFs. Ondansetron HCl is an intensely bitter drug [16]; hence, if it is incorporated directly into an RDF the main objective behind formulation of such a dosage form will definitely get futile. Thus in the present study an attempt has been made to mask the taste of Ondansetron HCl and to formulate RDFs with good mouth feel so as to prepare a "patient-friendly dosage form."

Materials

Ondansetron HCl (Batch No. CV 6783) was a gift from NU Therapeutics (Cherlapally, India). Polacriline potassium was a gift from Degussa India Private Ltd (Mumbai, India). The diluents used were sorbital (Ceolus KG 802, Asahi Kasei Chemicals Corporation, Tokyo, Japan), Mannitol (Parateck M 200, Merck, Darmstadt, Germany),

and lactose (Flowlac 100, Meggle, Wasseburg, Germany). The disintegrants were Poly ethylene oxide N-10, ISP Technologies, Inc, Calvert City, KY), Sucralose (Ac-Di-Sol, FMC Biopolymer, Wallingstown, Ireland) and glycerol (SD Fine Chemicals, Mumbai, India), maltodextrin (SD fine chemicals, mumbai). All other chemicals used in the study were of analytical grade.

Methodology:

Preparation of the RDFs

It involves preparation of two solutions

1. Base film solution
2. Drug solution

Base Film Solution

In this required quantity of Methocel E15 was dispersed in measured quantity of hot water followed by dissolving it by addition of remainder of cold water. Thus prepared solution was kept aside for few hours during which all the air bubbles surfaces which can be removed by addition of small drop of ethanol. If required color could be directly added to the base film solution or it can be added to the drug solution.

Drug Solution

It involves the addition of all the ingredients expect for base film. Initially the drug is wetted with small quantity of hot water until we get semi-solid consistency. To this, PK was added and stirred followed by addition of some more hot water. To the above drug solution Sucralose was added and stirred until it gets dissolved. This is followed by addition of PEO N10 and stirred until it dissolves. Duration of stirring is critical, longer the duration of stirring more uniform will be the preparation. This is followed by addition of Maltodextrin and Sorbital and stirred until homogenous dispersion is obtained. To the same 3 drops of concentrated solution of ponceau and 2 drops of Tartarazine color solutions were added and mixed well until color is uniformly distributed. Finally flavors were added and stirred until they get uniformly distributed. Now to the drug solution, base film solution was added slowly followed by addition of glycerin. This solution was carefully mixed to avoid bubble entrapment and kept aside for few minutes which help in removing any residual bubbles in the formulation. This final preparation was casted on a polyester film over glass plate using drawdown adjusted to required thickness and dried in hot air oven at 80°C until the film is completely dry, the films were then removed and cut as per the required sizes and stored. Different batches of formulations were prepared, the formulas of which are given in table I. of the different formulations the most optimized one was selected for further studies.

Mechanical properties of the RDFs

The RDFs were evaluated for mechanical properties using a universal testing machine (model LR 100 K Lloyd Instruments, Ametek, England) with load cell 100 N. RDFs of size 4 × 2.5 cm² and free of physical imperfections were held between two clamps held 2-cm apart. The 4 × 2.5 cm² dimension was selected because it is the minimum size required for sample testing on the machine. The RDFs were pulled by the clamp at a rate of 50 mm/min. Mechanical properties of the film were measured in triplicate for each batch. Tensile strength and elastic modulus were calculated for the RDFs as described below.

Tensile strength : It is the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied force at rupture as a mean of three measurements and the cross-sectional area of the fractured film as calculated using the equation:

$$\text{Tensile strength} = \text{Force break (N)} / \text{Initial cross sectional area of the film (mm}^2\text{)}$$

Elastic modulus: It is the ratio of applied stress and corresponding strain (force in N) in the region of approximately linear proportion of elastic deformation on the load displacement profile and calculated using the equation:

$$\text{Elastic modulus} = \frac{\text{Force at corresponding strain}}{\text{Cross-sectional area of the film}} \times 1 / \text{Corresponding strain}$$

In Vitro Disintegration Study

In vitro disintegration time for RDFs was determined using USP and modified disintegration apparatus with SSF (pH 6.2) as the disintegrating medium. Briefly, the apparatus consisted of a glass beaker of 1000-mL capacity with the wire basket positioned in the beaker with the help of a support in a way that when the beaker contained 900 mL of disintegrating medium, the basket had only 6 mL of it. A magnetic bead was placed at the bottom of the beaker maintained at 37 ± 2°C Fig. (1). Disintegration time was determined at 25 and 50 rpm and compared with results obtained from the USP disintegration test apparatus and the in vivo disintegration test.

Taste evaluation: Taste acceptability was measured by a taste panel with 10 mg drug and subsequently 10-mg film sample held in the mouth for 5–10 s, then spat out, and the bitterness level was recorded (6, 14). Volunteers were asked to gargle with distilled water between the drug and sample administration. The following scale was used:

- + = very bitter
- ++ = moderate to bitter
- +++ = slightly bitter
- ++++ = tasteless or taste-masked.

Results and discussion

Study of mechanical properties

A suitable RDF requires moderate tensile strength, good percentage elongation, and low elastic modulus. RDFs containing 2% and 4% Methocel E-15 without drug (i.e., blank films) showed extremely high tensile strength, poor percent elongation, and very high elastic modulus. The same formulation in the presence of drug and plasticizer demonstrated lower tensile strength with percent elongation values increased and elastic modulus values decreased. The taste-masked batches had acceptable mechanical properties. The tensile strength was in a moderate range (4–9 N/m²). The percent elongation and elastic modulus were also satisfactory. These changes in the mechanical properties can be attributed to the presence of plasticizer. Final formulation showed the most acceptable mechanical properties along with complete taste masking, which might be attributed to the presence of suitable plasticizers and flavors. Some of the mechanical properties in brief of the final formulation are

Drawdown thickness	: 0.3mm
Drying time	: 10 min
Drying temp	: 80oC
Strength	: excellent
Pealability	: excellent
180O bending	: good
Dissolution time	: within 10 secs
Texture	: good
Bitterness	: 95% masked

In-vitro disintegration studies

Disintegration studies were carried out in 500 mL SGF without enzymes using USP type II (paddle) apparatus at 50 rpm and 37 ± 0.5°C. From fig. (2), nearly 78% drug release in 2 min in simulated saliva. The dissolution process might have involved both ion exchange and solubilization of Methocel E15. The viscosity grades of Methocel E 15 affected the mechanical properties, disintegration, and dissolution characteristics of the RDFs. By increasing the concentration of Methocel E15, the formulations exhibited increased in vitro disintegration and dissolution times. Although batches containing 1g Methocel E 15 and 500 mg Methocel E15 in presence of drug had an in vitro disintegration time of 45 s, the in vitro dissolution time was 30 min and 45 min in distilled water, respectively. RDFs containing ONDCT prepared with Methocel E 15 possessed satisfactory mechanical properties, in vitro disintegration, and in vitro dissolution time and with complete taste mask of the drug. Therefore, further trials are required to be carried out using Methocel E 15 as the polymer for RDF formulation development.

Conclusion

RDFs containing taste-masked ONDCT showed acceptable properties such as tensile strength, elasticity, percentage elongation and in vitro dissolution characteristics. The RDFs were transparent, without any air entrapment. The drug-release profiles indicated that it could be used for the oral delivery of ONDCT in chronic and acute postoperative or chemotherapy- or radiotherapy-induced emesis. Taste masking could be achieved using suitable ion exchange resins, sweeteners and flavors. Good correlation between in-vitro disintegration behavior and in the oral cavity was recognized. Thus in the present study, the main objective to mask the taste of Ondansetron HCl and to formulate RDFs with good mouth feel so as to prepare a “patient-friendly dosage form” has been accomplished.

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Table 1- Composition for Rapid Disintegrating films (RDFs)

S.No	Composition	Batch I(Qty in gms)	Batch II(Qty in gms)	Batch III(Qty in gms)
1	Methocel E-15	0.5gm	1gm	1gm
2	Drug	0.75gm	0.75gm	0.75gm
3	Polacriline potassium	0.2gm	0.3gm	0.35gm
4	Sucralose	0.25gm	0.8gm	0.5gm
5	PEO N-10	0.5gm	0.25gm	0.2gm
6	Malto-dextrin	0.6gm	0.5gm	0.35gm
7	Sorbital	0.25gm	0.4gm	0.5gm
8	Banana flavor	0.3ml	0.1ml	0.2ml
9	Vanilla flavor	0.2ml	0.05ml	0.1ml
10	Lychee flavor	0.3ml	0.2ml	0.2ml
11	Glycerin	0.5ml	0.6ml	0.7ml
12	Color	P+T	P+T	P+T
13	Water	10ml	12ml	13.5ml

Among the three batches Batch III was found to be most satisfactory with 97% taste mask of the drug and all the film properties were found to be satisfactory

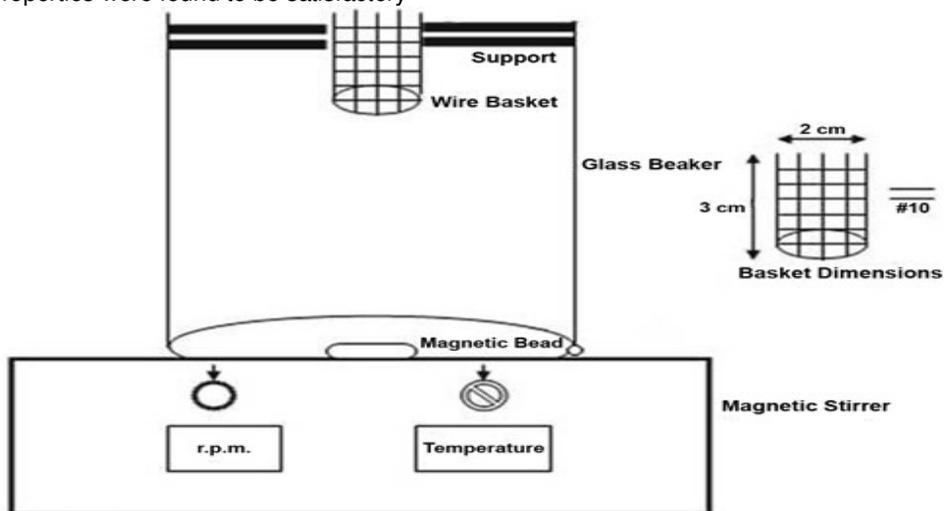


Fig. 1- Schematic representation of the disintegration test apparatus

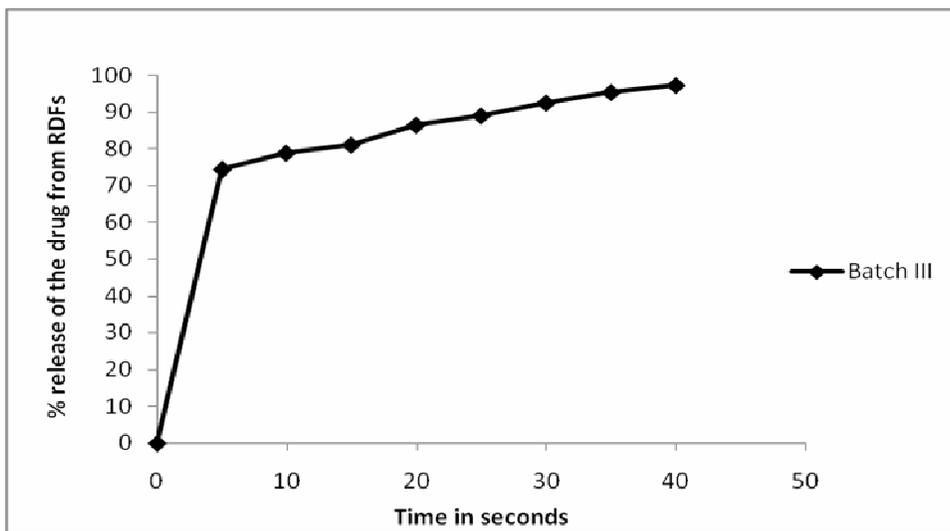


Fig. 2- Disintegration profile of Optimized Rapid Disintegrating film (Batch III)