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Research Article

Taste Masking by Spray-Drying Technique

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Abstract. The purpose of this research was to develop the taste-masked microspheres of intensely bitter drug ondansetron hydrochloride (OSH) by spray-drying technique. The bitter taste threshold value of OSH was determined. Three different polymers viz. Chitosan, Methocel E15 LV, and Eudragit E100 were used for microsphere formation, and the effect of different polymers and drug–polymer ratios on the taste masking and release properties of microspheres was investigated. The microspheres were characterized by Fourier transform infrared spectroscopy, scanning electron microscopy, Drug loading, *in vitro* bitter taste evaluation, and drug-release properties. The taste masking was absent in methocel microspheres at all the drug–polymer ratios. The Eudragit microspheres depicted taste masking at 1:2 drug–polymer ratio whereas with Chitosan microspheres the taste masking was achieved at 1:1 drug–polymer ratio. The drug release was about 96.85% for eudragit microspheres and 40.07% for Chitosan microspheres in 15 min.

KEY WORDS: microspheres; spray drying; taste masking.

INTRODUCTION

The biological definition of taste (Gustation) is a chemical reaction derived from sensory responses from the four main taste perceptions: salt, sour, bitter, and sweet. Taste sensation is the result of signal transduction from the receptor organs for taste, commonly known as taste buds. The taste buds contain very sensitive nerve endings which produce and transmit electrical impulses to the brain. The perception of taste only occurs when the substances are dissolved. The drug substance first gets solubilized in saliva, then they interact with taste buds and perception of taste occurs (1,2). Taking medicine orally is convenient and economical. It also requires cooperation from the patient. Unfortunately, many drugs have unpleasant taste primarily bitter. This has led to dilemma for modern pharmaceutical science as undesirable taste can hinder the acceptance and usefulness of many beneficial, safe, and efficacious drugs. Thus, elimination or reduction of bitterness is an important mainstay of product evaluation in oral pharmaceutical formulation.

Numerous approaches have been reported for masking the bitter taste of the drugs such as (1) use of flavors and sweeteners, (2) use of polymeric carriers, (3) drug resin complexes, (4) formation of inclusion complexes, etc. Taste masking by polymeric coating involves formation of a physical barrier between drug particle and the taste bud, thus, minimizing the interaction. Polymeric coating retards the release of the drug in oral cavity, thus, prevents the interaction of drug with taste buds. Various hydrophilic and hydrophobic polymers such as hydroxypropyl methyl cellulose, ethyl cellulose, polymethacrylates, microcrystalline cellulose, etc. are reported for taste masking. The methods used for taste masking with polymers includes wet granulation, fluidized bed coating, microencapsulation, etc. (3–11).

Ondansetron hydrochloride (OSH) is a 5-hydroxytryptamine subtype 3 ($5HT_3$) receptor antagonist used in management of nausea and vomiting (12). It is indicated for the treatment and prophylaxis of radiotherapy induced emesis and also used in early onset of alcoholism (13). OSH is used by oral and injectable administration. It is available as orodispersible tablets for rapid onset of action and ease of administration. The bitter taste of OSH may affect the palatability and acceptance by the patient.

The present investigation is aimed at use of polymers as a taste-masking agent. Eudragit E100, Chitosan and Methocel E15 LV are used to prepare microspheres. Eudragit E100 is a polymethacrylate with pH dependent solubility, specifically used for taste masking. It is insoluble at and above pH 5. Chitosan is a high molecular weight, polycationic polysaccharide derived from naturally occurring chitin by alkaline deacetylation and is insoluble above pH 6 (14). Methocel E15 LV is a cellulose hydroxypropyl methyl ether used as coating agent, film former and tablet binding agent. Spray drying was used for the preparation of the microspheres. Spray drying is widely used in pharmaceutical processing as it requires only a one-step process and can be easily controlled and scaled up.

MATERIALS AND METHODS

Materials

Ondansetron Hydrochloride and Eudragit E100 were gifted by Gauri Fine Chemicals, Pune (India) and Degussa

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Table I. Formulation of Microspheres

Polymer	Drug–polymer ratio					
Eudragit E100	1:0.5	1:1	1:1.5	1:2	1:2.5	1:3
Methocel E15 LV	1:0.5	1:1	1:1.5	1:2	1:2.5	1:3
Chitosan	1:0.5	1:1	1:1.5	1:2	–	–

India Pvt. Ltd., Mumbai (India). Methocel E15 LV was provided by Colorcon Asia Ltd., Mumbai (India). Chitosan (86.60% degree of deacetylation) was purchased from Loba Chemie, Mumbai (India). The other chemicals and reagents used were of AR grade.

Preparation of Microspheres

The microspheres were prepared by spray-drying technique. The spray drying was performed by spray dryer Labultima (LU-222). The different drug–polymer ratios used for various microsphere formulations are described in Table I. The polymer solution was prepared by adding given quantity of polymer to the solvent. For Eudragit, dichloromethane was used as solvent whereas for Chitosan and Methocel 1% glacial acetic acid and water respectively were used as solvent (15). The given quantity of OSH was added to the polymer solution and the resulting mixture was spray-dried. The spray-drying parameters are described in Table II.

Taste Evaluation of Microspheres

1. Determination of bitter taste recognition threshold of ondansetron hydrochloride

The bitter taste threshold value of OSH was determined based on the bitter taste recognized by seven volunteers (three females and four males) in the age group of 21–28 years. Aqueous solutions of OSH with different concentrations (2, 4.5, 9.5, 14.5, and 19.5 μg/ml) were prepared. One milliliter of solution was placed on the center of the tongue of volunteer for 30 s. The solution was spat out after 30 s, and the mouth was thoroughly rinsed with distilled water. The same procedure was repeated for all solutions and volunteers. A gap of 30 min was maintained in between tasting two different solutions. The same procedure was repeated for OSH solutions with concentrations 5.5, 6.5, 7.5, and 8.5 μg/ml. The threshold value was selected on the basis of the lowest concentration that had a bitter taste (4,16,17).

2. *In vitro* evaluation of bitter taste of microspheres

Microspheres (equivalent to 8 mg of OSH) were placed in a volumetric flask with 25 ml of phosphate buffer pH 6.8 and stirred for 5 min. The mixture was filtered, and the filtrate was analyzed for OSH concentration at 310 nm by UV-Visible spectrophotometer (Jasco-V530, Tokyo, Japan) and that was compared with the threshold value.

Table III. Taste Recognition Threshold Determination

Concentration (μg/ml)	Volunteer						
	1	2	3	4	5	6	7
2	N	N	N	N	N	N	N
4.5	N	N	N	N	N	N	N
5.5	N	N	N	N	N	N	N
6.5	N	N	N	N	N	N	N
7.5	N	N	Y	Y	N	N	N
8.5	Y	N	Y	Y	Y	Y	Y
9.5	Y	N	Y	Y	Y	Y	Y
14.5	Y	Y	Y	Y	Y	Y	Y
19.5	Y	Y	Y	Y	Y	Y	Y

Y recognition of bitter taste, *N* no perception of bitter taste

Infrared Spectroscopy

Infrared (IR) spectroscopy was conducted using Fourier transform IR (FTIR) spectrophotometer (FT/IR-4100 Jasco Tokyo, Japan.) and the spectrum was recorded over the region 400–4,000 cm^{-1} for the OSH, polymers, drug and polymer physical mixtures and different batches of microspheres.

Drug Loading

The drug loading was determined by UV-Visible spectrophotometer. The microspheres were stirred with 100 ml 0.1 N HCl for 2 h. The drug concentration was determined at 310 nm after suitable dilution. The readings were taken in triplicate.

Drug-Release Study

The drug release studies were performed by USP Type I dissolution test apparatus (TDT-082-Electrolab, Mumbai, India). Microspheres equivalent to 8 mg of OSH were filled in hard gelatin capsule shell size '0'. The 0.1 N HCl was used as dissolution medium. The temperature and speed of the apparatus were maintained at 37±0.5°C and 50 rpm, respectively. The samples were withdrawn at predetermined time (18) interval and analyzed for drug concentration at 310 nm by UV-Visible spectrophotometer after filtration. The readings were taken in triplicate.

Scanning Electron Microscopy

The photomicrograph of Eudragit and Chitosan microspheres were obtained by scanning electron microscopy

Table II. Spray-Drying Parameters

Polymer	Inlet temperature (°C)	Feed pump speed (ml/h)	Vacuum (mm Wc)	Aspirator level (kg/cm^2)
Eudragit E100	40	75	110	2.2
Chitosan	140	37	110	2.2
Methocel E15 LV	120	37	110	2.2

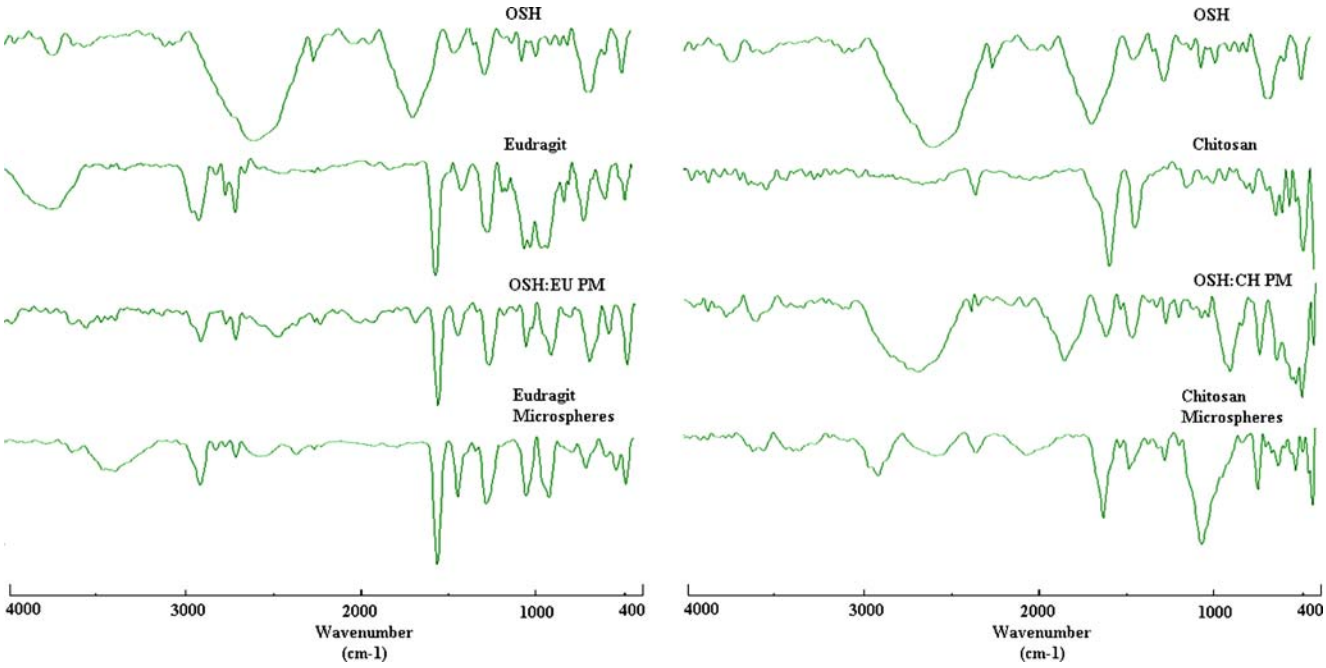

Fig. 1. FTIR spectra of drug, polymers, drug–polymer physical mixtures and microspheres

(JSM-35CF, Jeol, Japan). The microspheres were mounted on a double-faced adhesive tape and sputtered with platinum and the samples were scanned at 23 kV voltage. The micrographs were examined at a magnification ratio of ×2,000.

Moisture Content

For Chitosan and Methocel microspheres, the moisture content was determined by Karl Fischer titrator (Matic D, Veego). Methanol was used as a solvent. Initially, moisture

Table IV. Evaluation of Microspheres

Microspheres	Drug–polymer ratio	% Yield	% Drug loading[a]	% Moisture content	% Drug release[a]
Eudragit microspheres	1:0.5	26.73	44.57±0.25	–	95.33±1.63 in 15 min.
	1:1	30.99	49.42±0.33	–	97.10±0.68 in 15 min.
	1:1.5	32.51	50.83±0.34	–	94.61±2.12 in 15 min.
	1:2	34.22	52.57±0.25	–	96.85±1.63 in 15 min.
	1:2.5	34.79	39.95±0.41	–	93.80±2.57 in 15 min.
	1:3	33.41	28.10±0. 57	–	96.39±0.96 in 15 min.
Chitosan microspheres	1:0.5	27.15	71.35±0.13	6.45	91.64±2.63 in 25 min.
	1:1	30.71	83.25±0.59	7.31	90.40±2.40 in 25 min.
	1:1.5	29.36	77.01±0.71	8.50	71.73±2.21 in 25 min.
	1:2	34.51	90.29±0.39	9.13	50.35±1.49 in 25 min.
Methocel microspheres	1:0.5	45.56	32.44±0.74	2.30	–
	1:1	46.71	33.12±0.86	3.10	–
	1:1.5	48.39	29.11±0.61	2.77	–
	1:2	51.12	27.68±0.57	3.20	–
	1:2.5	57.29	34.78±0.52	1.90	–
	1:3	61.73	41.17±0.48	2.43	–

[a] Data represent $n=3$, mean ± SD

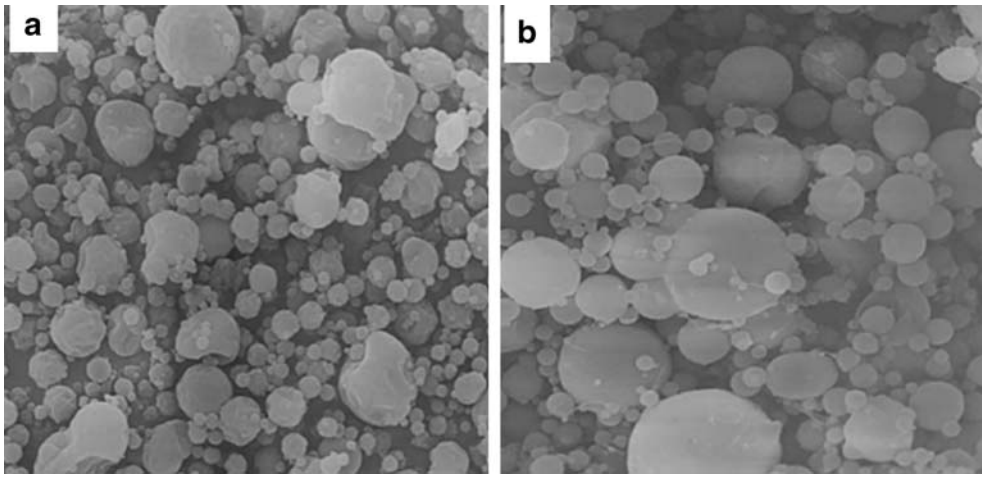

Fig. 2. SEM micrographs of Eudragit (**a**) and Chitosan (**b**) microspheres

present in methanol was neutralized by Karl Fischer reagent. The known quantity of water was added to the methanol, and the titer factor was determined. Hundred milligrams of spray-dried product was added to methanol, and the volume of Karl Fischer reagent required was determined. The moisture content of the sample was calculated by using following formula,

$$\% \text{ Moisture Content} = \frac{\text{Volume of KF reagent} \times \text{Factor}}{\text{Weight of Sample}} \times 100 \quad (1)$$

Percentage Yield

The yield of microspheres was determined by the formula,

$$\% \text{ Yield} = \frac{\text{Total Weight of Microspheres}}{\text{Total Weight of Raw Material}} \times 100 \quad (2)$$

RESULTS AND DISCUSSION

The glass transition temperature (T_g) is the second-order phase change temperature at which a solid glass is transformed to a liquid-like rubber. As the temperature increases above, T_g various changes, such as increase of free volume, decrease of viscosity, increase of specific heat, and increase of thermal expansion, are noticed. During spray drying, if the drying temperature exceeds the T_g of the polymer, the powder becomes soft or sticky while still warm. This causes sticking of the powder to the side walls of drying chamber. The T_g of Eudragit E100 as provided by the manufacturer is 48°C, whereas T_g of Methocel E15 LV and Chitosan are 170–180°C and 203°C, respectively (14). Therefore, dichloromethane was selected as solvent with boiling point 36°C, i.e., lower than the T_g of Eudragit E100 and for Methocel and Chitosan microspheres water and 1% glacial acetic acid were used as solvent.

Determination of Bitter Taste Recognition Threshold of OSH

All the seven volunteers could not recognize the bitter taste of OSH at 4.5 μg/ml. Five out of seven volunteers can percept the bitter taste at 9.5 μg/ml, whereas all the seven

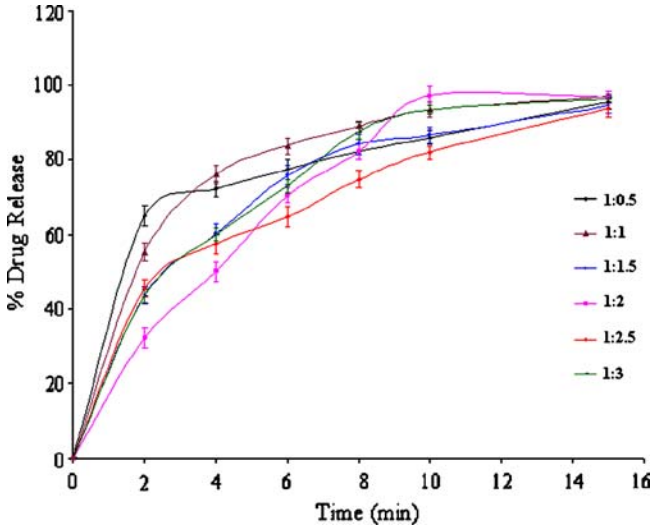

Fig. 3. *In vitro* drug release from Eudragit microspheres

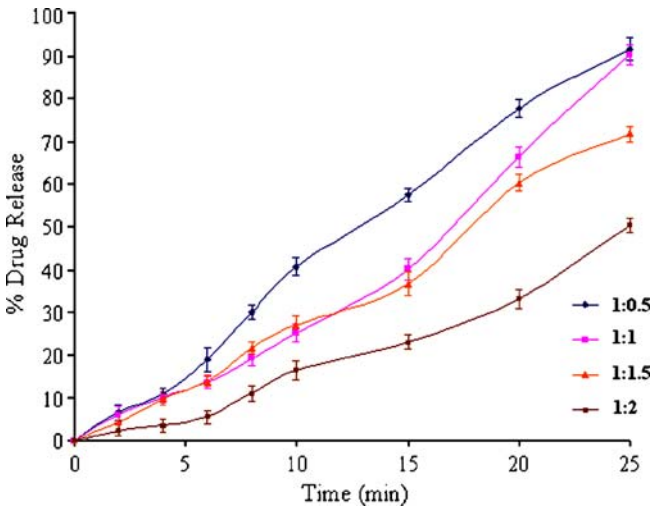

Fig. 4. *In vitro* drug release from Chitosan microspheres

volunteers reported that the solutions of 14.5 and 19.5 μg/ml were bitter. Thus, the threshold bitterness value lies in between 4.5 and 9.5 μg/ml. Therefore, the OSH solutions of 5.5, 6.5, 7.5, and 8.5 μg/ml concentrations were prepared, and the same procedure was repeated. From Table III, the bitter taste threshold value of OSH is 7.5 μg/ml.

In Vitro Evaluation of Bitter Taste of Microspheres

The drug release in pH 6.8 phosphate buffer was studied to evaluate taste masking. The drug release from eudragit microspheres (drug–polymer ratio 1:2) and Chitosan microspheres (drug–polymer ratio 1:1) was less than the threshold bitterness value, i.e., 7.5 μg/ml. The drug release for Methocel microspheres was above the threshold value for all the drug–polymer ratios studied. The microspheres were prepared with different drug to polymer ratios. The Eudragit exhibited excellent taste masking at drug–polymer ratio 1:2. This is because of the property of Eudragit, i.e., the polymer is insoluble at and above pH 5. Taste masking was also achieved at drug–polymer ratio 1:2.5 and 1:3. All the other ratios studied did not show taste masking as the drug release at pH 6.8 phosphate buffer was above the threshold bitterness value. This may be because of incomplete film formation by the Eudragit which fails to control the release of OSH at salivary pH. Chitosan is insoluble in alkali solutions at pH above 6. Chitosan exhibited taste masking at drug–polymer ratio 1:1.

Infrared Spectroscopy

The FTIR spectrum of drug, polymer, drug and polymer physical mixtures (OSH:EU PM, OSH:CH Pm), and microspheres are depicted in Fig. 1. The OSH exhibited characteristic peaks at 3,544 and 1,623 cm^{-1}, attributed to O–H stretching and C=O stretching vibrations. The physical spectrum showed no significant shift in peaks of OSH, only slight change in intensity of peaks was observed. The spectrum of Eudragit depicts characteristic peaks of C=O stretching at 1,731 cm^{-1}. The Eudragit microspheres exhibited both the characteristic peaks of OSH at 3,544 and 1,623 cm^{-1} and 1,731 cm^{-1} corresponding to C=O of Eudragit whereas Chitosan microspheres depicted no shift in both the characteristic peaks of OSH. The band at 3,544 cm^{-1} for O–H stretching and 1,623 cm^{-1} for C=O stretching were observed. The results of IR spectroscopy reveal that there was no chemical interaction between drug and the polymer.

Drug Loading, Production Yield, and Moisture Content

Table IV summarizes the results of drug loading, production yield and moisture content.

Drug Release

The drug release results are depicted in Table IV. The Eudragit and Chitosan microspheres passed the bitterness evaluation test; therefore, they were selected for drug-release study (Fig. 2). The Eudragit microspheres (1:2 drug–polymer ratio) showed 96.85% release in 15 min, whereas Chitosan microspheres (1:1 drug–polymer ratio) depicted 90.40% release in 25 min. The drug release from all the batches of Eudragit microspheres in 0.1 N HCl was above 90% in 15 min (Fig. 3). The effect may be attributed to the solubility of the polymer. Chitosan microspheres exhibited drug release of about 90.40% in 25 min (Fig. 4). The slight delay in drug release form Chitosan microspheres as compared to Eudragit microspheres may be because of solubility of Chitosan, i.e., Chitosan does not dissolve as rapidly as eudragit in 0.1 N HCl.

Scanning Electron Microscopy

The SEM micrographs of Eudragit (a) and Chitosan (b) microspheres are depicted in Fig. 2. The microspheres prepared by spray drying were spherical in shape with small diameter in the range 1–10 μm. The SEM images confirmed the uniformity and fine nature of the microspheres which contributed for rapid drug release from the microspheres. Thus, the objective of masking the bitter taste of OSH was successfully achieved without affecting the release kinetics.

CONCLUSION

Spray-dried microspheres of Eudragit and Chitosan depicted excellent taste-masking ability. Eudragit E100 did not affect the drug release whereas Chitosan exhibited slight delay in drug release as compared to Eudragit, but the slight delay can be outweighed by the virtue benefit achieved of taste masking and better acceptance by the patient.

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