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Isolation, Phytochemical Studies and Evaluation Of *Caesalpinia pulcherrima* Mucilage as a Potant Superdisintegrant

Mayuri Choundikar* Prmodkumar J Shirote

Department of Pharmaceutical Chemistry, Appasaheb Birnale College of Pharmacy, Sangli, Maharashtra, India

Research Article

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For Correspondence: Mayuri Choundikar , Department of Pharmaceutical Chemistry, Appasaheb Birnale College of Pharmacy, Sangli, Maharashtra, India
Email: PMayurichoundikar14@gmail.com
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ABSTRACT

The present work was carried out to study the phytochemical and physicochemical characteristics to explore the disintegration property of mucilage extracted from the seeds of *Caesalpinia pulcherrima* (family *caesalpinaceae*). Orally disintegrating tablet of Ondansetron hydrochloride dihydrate was formulated using different concentrations 2.5, 5, 7.5, 10, 12.5%w/w of isolated natural disintegrant. Ondansetron is a selective serotonin receptor antagonist used as an antiemetic in the treatment and or prophylaxis of post-operative or chemotherapy or radiotherapy induced emesis and also used in the early onset of alcoholism. The formulations were evaluated for precompression parameters such as bulk density, tapped density, compressibility index, hausner's ratio, angle of repose. Tablets were subjected to post compressional analysis such as weight variation, hardness, friability, drug content, disintegration time, dissolution studies and it was compared with marketed formulation ONDEM MD4. The formulation having disintegrant concentration 10% w/w gives shorter disintegration in 36 sec and showed 99.81% drug release within 3 minutes. Hence the present study revealed that this natural disintegrant showed better disintegrating property and act as a natural superdisintegrant.

INTRODUCTION

Plant derived substances have recently become of great interest owing to their versatile application. Mother nature has gifted India with great variety of flora and fauna. From the ancient time man has made effective use of material of natural origin in the medical and pharmaceutical field. Now- a- days the whole world is increasingly interested in natural drug and excipients. Plant products have more advantages over synthetic and semi-synthetic because they are non-toxic, cheap, bio-degradable, bio-compatible and freely available [1-4]. Many kinds of natural gums are used in the food industry and are regarded as safe for human consumption. In recent years plant derived polymers have evoked tremendous interest due to their versatile pharmaceutical application such as diluent, binder, disintegrant in tablet, thickeners in oral liquid, protective colloids in suspension, gelling agent in gels and bases in suppositories [5]. The term mucilage in plants is meant those substances which are soluble or at least swells in water and which upon addition of alcohol or acetone are precipitated in a more or less amorphous or granular form.

The oral route of administration is considered as the most widely accepted route because of its convenient for self-administration. Over a decade the demand for development of orally disintegrating tablets has enormously increased as it has significant impact on patent compliance. ODTs are very useful in populations particularly who have difficulty in swallowing in case of pediatric, geriatrics. ODT are also called as orodispersible tablet, quick disintegrating tablet, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapid melts. However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing. United States Food and Drug Administration (FDA) defined ODT as “A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue” The disintegration time for ODTs generally ranges from several seconds to about a minute [6-11]. Ondansetron HCl is a potent antiemetic drug indicated for the treatment and/or prophylaxis of post-operative or chemotherapy or radiotherapy induced emesis and also used in the early onset of alcoholism.

MATERIALS AND METHODOLOGY

Materials

Ondansetron hydrochloride dihydrate was procured as a gift sample from Agio pharmaceutical Ltd Pune, Maharashtra. Seeds of *Caesalpinia pulcherrima* were collected from the local area of Sangli, Maharashtra, and authenticated by Prof. Vadmare Botanist Department of Botany, Kasturbai Walchand College, Sangli, and all other chemicals of AR grade were obtained from Research lab fine Mumbai Maharashtra, India. The instrument used were Digital pH meter (Global DBH-500), JASCO-FTIR- 410 spectrophotometer, JASCO-V-550 ,UV/VIS double beam spectrophotometer, 10 station tablet punch machine (Fluid pack minipress model) Digital electronic balance (Shimadzu-Japan)

Methodology for extraction of mucilage

***Caesalpinia pulcherrima*:** Mucilage was isolated by soaking the seeds of *Caesalpinia pulcherrima* in distilled water for 24 hours, boiled for 1 hour and kept aside for 2 hours to release mucilage in to water. The material was squeezed in a muslin cloth to remove the marc from the filtrate. The mucilage collected and precipitated using alcohol in 1:1 proportions. The mucilage so obtained was then subjected to air drying for sufficient period of time and further dried in oven. Dried mucilage was scraped and powdered using pestle and mortar. Powder was sieved using mesh no 80.

Phytochemical screening of isolated mucilage : The phytochemical properties such as presence of carbohydrate were determined [12-15].

Physicochemical characterization of mucilage : The physicochemical properties such as solubility, Ph, and melting point of dried mucilage were determined at 250°C. The swelling index, moisture content, total ash content, acid insoluble ash, water soluble ash were determined according to Ayurvedic Pharmacopoeia of India. It was also subjected to thin layer chromatographic and spectral analysis.

Thin layer chromatography: 0.5 gm of mucilage was hydrolyzed with 50 ml of 0.1N sulphuric acid. The solution was neutralized using barium hydroxide and filtered. The filtrate was concentrated and subjected to thin layer chromatography on silica gel G plate. Mobile phases were used n- butanol: Toluene: pyridine: water 5: 1: 3: 3 and aniline phthalate as a spraying agent, n- butanol: Acetic acid: water 5: 3: 2 and p-anisidine as a spraying agent [15-16].

Spectral analysis

FTIR spectroscopy: The IR spectrum were recorded by using JASCO-FTIR- 410 spectrophotometer using potassium bromide pressed pellet technique.

HNMR Spectrum: The spectra were recorded using DMSO as a solvent.

Analysis of Ondansetron HCl, $2H_2O$

Construction of calibration curve of ondansetron HCl, $2H_2O$ in 0.1N HCl : Ondansetron HCl (10 mg) was dissolved in 0.1 N HCl (pH 1.2) and volume was made up to 100 ml in 100 ml volumetric flask. This solution (100 µg /ml) was further diluted with 0.1 N HCl to obtain solution of 5 to 25 µg/ml. Absorbance of each solution was measured at 310 nm using JASCO-V-550 ,UV/VIS double beam spectrophotometer and 0.1 N HCl as reference standard. The standard calibration curve was generated for the entire range from 0 to 25 µg/ml. A standard plot of absorbance vs concentration of drug was plotted.

Characterization of ondansetron HCl,$2H_2O$

Melting point determination: The melting point was determined by using Digital Melting Point Apparatus.

Estimation of wavelength (λmax) of ondansetron HCl, $2H_2O$: Accurately weighed quantity of λmax of Ondansetron HCl, $2H_2O$ (10mg) was dissolved in 100 ml 0.1N HCl and further diluted to suitable concentration and the resulting solution containing was scanned between 200 and 400 nm using 0.1 N HCl as blank and the max i.e. analytical wavelength was determined.

Fourier Transform Infra-red Spectroscopy (FTIR) : IR spectroscopy of Ondansetron HCl, $2H_2O$ drug was done by using FT-IR spectrophotometer (JASCO FTIR-410) by using potassium bromide pellet technique.

Compatibility study: The drug and the mucilage were equally distributed in glass ampoules. They were kept at 370°C. The samples were drawn after 1 month and analyzed for its physical appearance and drug stability by IR spectroscopy.

Formulation of orally disintegrating tablet of ondansetron HCl, $2H_2O$ using *Caesalpinia pulcherrima* mucilage as a superdisintegrant : The Orally Disintegrating Tablets were prepared by direct compression method using the mucilage of *Caesalpinia pulcherrima* at concentrations of 2.5% to 12.5%. All the powders were passed through 80 mesh sieve to

decrease the particle size. Required quantity of drug and excipients mixed thoroughly. The blend was compressed using 10 station tablet punch machine (Fluid pack minipress model) the composition of each formulation is given in Table1 [17-20]

Table 1. Formulation of orally disintegrating tablet of ondansetron HCl, $2H_2O$ chemicals.

Ingredients (mg)	OD1	OD2	OD3	OD4	OD5
Ondansetron	4	4	4	4	4
Superdisintegrant (Mucilage)	2.50%	5%	7.50%	10%	12.50%
Mannitol	50	50	50	50	50
Microcrystalline Cellulose	88.25	84.5	80.75	77	73.25
Magnesium stearate	2	2	2	2	2
Talc	2	2	2	2	2
PTotal Weight (mg)	150	150	150	150	150

Pre-compression studies

The powdered blend was evaluated for flow properties such as bulk density, tapped density, compressibility index, hausner's ratio, angle of repose.

Evaluation of ODTs of Ondansetron HCl, $2H_2O$

The prepared tablets were evaluated for certain physical properties like thickness, uniformity of weight, hardness, friability disintegration time, drug content, dissolution studies and it was compared with marketed tablet ONDEM MD4.

Ten tablets were taken and their thickness was measured by using vernier calipers. In uniformity of weight, twenty tablets were selected randomly and average weight was calculated on Digital electronic balance (Shimadzu-Japan). Then individual tablets were weighed and the weight was compared with an average weight. Hardness of the tablet of each formulation was determined using Pfizer hardness tester. Roche friabilator was employed for finding the friability of the tablets; five tablets from each formulation were weighed and placed in Roche friabilator that rotated at 25 rpm for 4 minutes. The drug content was determined. For that five tablets were selected randomly and powdered. A quantity of this powder corresponding to 4 mg of Ondansetron HCl was dissolved in 100 ml of 0.1 N HCl, stirred and filtered. The drug content was measured by using Concentration of 5, 15, 20 µg/ml. Absorbance of this solution was measured at 310 nm using UV- Visible Double Beam Spectrophotometer. (Jasco-V-550) as a 0.1N HCl as blank and content of Ondansetron HCl was estimated. In disintegration time study disintegration of orally disintegrating tablets is achieved by saliva in the mouth, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate *in vivo* condition. The test was carried out on 6 tablets using the apparatus specified in I.P-1996 in distilled water and simulated salivary fluid and the composition is given in Table 2. The time in second taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

Table 2. Composition of simulated salivary fluid.

S. No.	Ingredients	Quantity (gm)
1	Disodium hydrogen phosphate	2.382
2	Potassium dihydrogen Phosphate	0.19
3	Sodium chloride	8
4	Distilled water	up to 1000 ml
5	Phosphoric acid	q .s. to pH 6.75

In vitro drug release studies, the Dissolution apparatus, USP 2 Paddle apparatus (Labindia instruments Pvt. Ltd. Mumbai) is used for this purpose which is the most suitable and common choice for orally-disintegrating tablets, with a paddle speed of 50 rpm commonly used. Typically the dissolution of ODT is very fast when using USP monograph conditions; hence slower paddle speeds may be utilized to obtain a profile. The USP 1 Basket apparatus may have certain applications but sometimes tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution.

In vitro drug release studies were carried out by using USP type 2 Paddle apparatus. The medium used was 500 ml 0.1N HCl having speed 50 RPM for 10 min and aliquots of 5 ml of dissolution medium were withdrawn at specific time interval and the volume replaced by fresh dissolution medium, pre warmed to 37 ± 0.50°C. The drug concentration was determined spectrophotometrically at 310 nm using UV- Visible.Double Beam Spectrophotometer. (Jasco-V-550) All the studies were performed in triplicate.

RESULTS AND DISCUSSION

The average yield of dried mucilage obtained from *Caesalpinia pulcherrima* was 12% w/w. The extracted mucilage was odorless and dark brown in color. The preliminary phytochemical screening of mucilage confirmed the presence of carbohydrate and mainly ketoses and ketohexoses and result of physicochemical characterization of mucilage are depicted in Table 3.

Thin layer chromatography

For detection of reducing sugars the TLC plate was sprayed with aniline phthalate and p-anisidine HCl as a spraying agent. The development of Pink and blue color spot with aniline phthalate confirmed the ketoses and hexoses respectively. The development of yellow color spot with p-anisidine HCl confirmed the Ketohexoses.

Table 3: Phytochemical and physicochemical characterization of mucilage.

Parameters	Result
State	Granular powder
Odor	No characteristic odor
Taste	Tasteless
Color	Dark brown color
Identification	-
a. Mounted in Ruthenium red	Particles stained pink
b. Mounted in iodine solution	No color observed
Solubility	Forms viscous mass in water, Insoluble in ether, Chloroform, Methanol and Ethanol.
Test for carbohydrate	-
a. Molisch's test	Violet color ring observed at the junction of two layers, Carbohydrate present
b. Tollensphloroglucinol test for ketohexoses	Red color, Ketohexoses, Galactose present
pH	5.8
Moisture content (%)	12.66
Ash value (%)	2
Water soluble ash (%)	0.17
Acid insoluble ash (%)	Negligible
Swelling index (ml)	6.55
Melting point	Chars at 240°c

FTIR spectroscopy

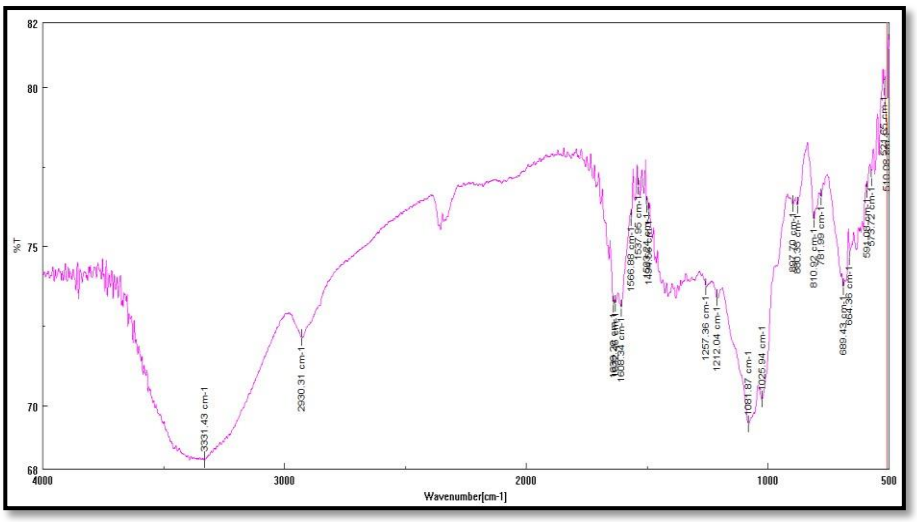
In comparison with the IR spectra of polysaccharides documented in literature, a characteristic absorption band appeared at 1639 cm^{-1} and was assigned to the stretching vibration of the carboxyl group while another absorption band at 2930 cm^{-1} was intensified and assigned to the stretching vibration of the methylene group (C–H). Furthermore, a continuous absorption beginning at approximately the region of 3331 cm^{-1} ischaracteristic of a carbohydrate ring. Characteristic absorption at 810 cm^{-1} suggesting the existence of mannose. The obvious absorption peaks at 910 and 880 cm^{-1} revealed the coexistence of α and β glycosidic bonds. IR spectrum is shown in Figure 1.

HNMR Spectrum: 2.975-4.016 (m, 13H, aliphatic proton), 4.022-5.213 (m, 4H, R-OH) The HNMR spectrum is shown in Figure 2.

Analysis of ondansetron HCl, $2H_2O$

Construction of calibration curve: The calibration curve was constructed in 0.1N HCl which is shown in Figure 3.

Figure 1. FTIR spectrum of *Caesalpinia pulcherrima* mucilage.

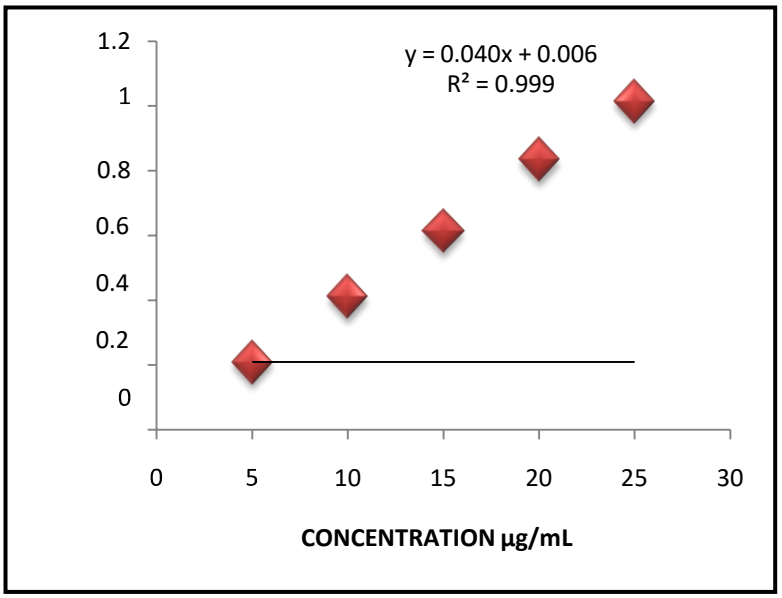


Characterization of ondansetron HCl, $2H_2O$

Melting point determination

The melting point of Ondansetron HCl, $2H_2O$ was found to be 177°C. The reported melting point ranges from 177-178°C, this confirms the purity of sample.

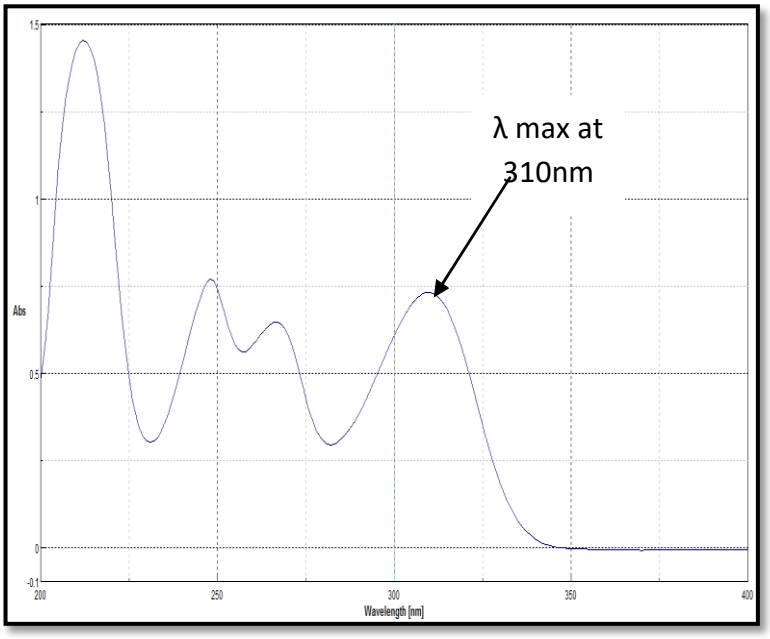
Figure 2. Calibration curve of Ondansetron HCl, $2H_2O$.



Estimation of wavelength (λ_{max}) of Ondansetron HCl, $2H_2O$

Maximum absorbance of Ondansetron HCl, $2H_2O$ was observed at 310 nm in 0.1 N HCl as asolvent. The UV spectrum is shown in Figure 3.

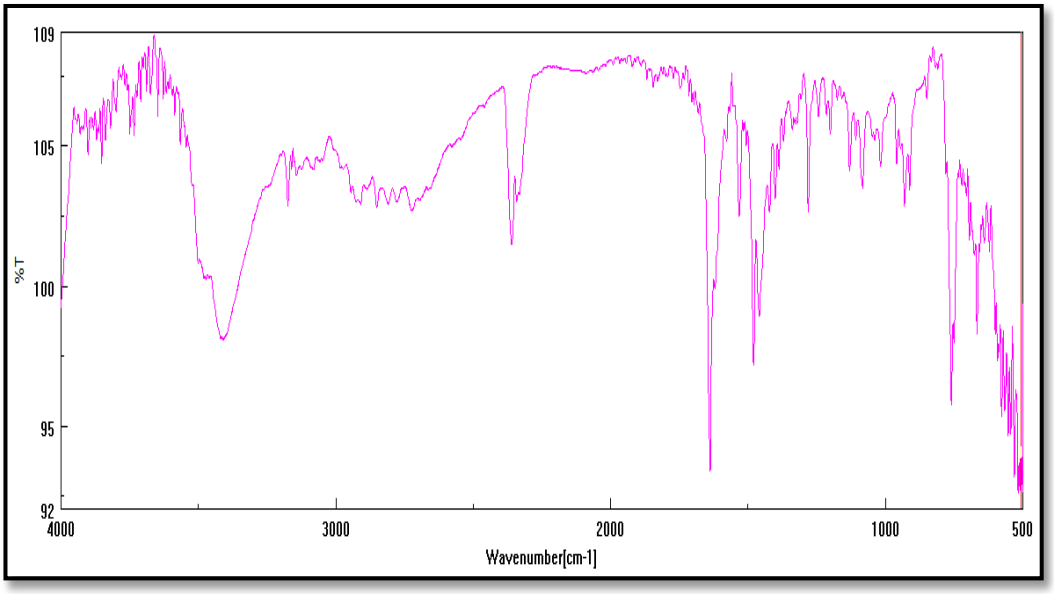
Figure 3. λ_{max} of Ondansetron HCl, $2H_2O$.



Fourier Transform Infra-red Spectroscopy (FTIR):

IR spectroscopy of Ondansetron HCl, $2H_2O$ drug was done by using FT-IR spectrophotometer (JASCO FTIR-410) by using potassium bromide pressed pellet technique is shown in Figure 4.

Figure 4. FTIR spectrum of ondansetron HCl, $2H_2O$.

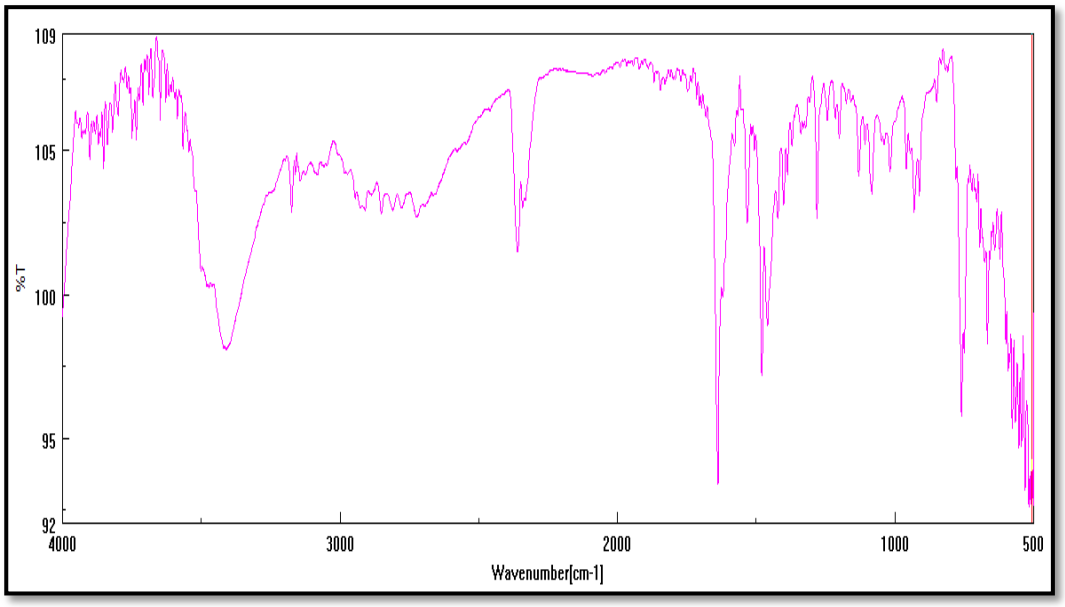


IR spectra of Ondansetron HCl, $2H_2O$ showed characteristic absorption bands at 3412 (O-H Stretch), 1091 (C-N stretch), 1637 (C-O stretch), 3174 (C-C stretch), 1637(C=N stretch), 1458 (C=C stretch), 1280 (C-N Vibration).

Compatibility Study

There is no any change in principal peak of Ondansetron HCl, $2H_2O$. Hence it iscompatible with mucilage and shown in Figure 5.

Figure 5. FTIR spectrum of drug and mucilage.



Pre-compression studies

Since, the flow properties of the powder mixture are important for the uniformity of mass of the tablets, the flow of the powder mixture was analyzed before compression to tablets. Low Hausner ratio, compressibility index and angle of repose values indicated a fairly good flowability of powder mixture. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property which is shown in Table 4.

Table 4. Pre-comprssional parameters of all formulations.

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Compressiblity index (%)	Hausner's ratio	Angle of repose (θ)
OD1	0.23 ± 0.004	0.22 ± 0.002	15.36 ± 0.41	1.18 ± 0.01	29.99 ± 0.12
OD2	0.19 ± 0.006	0.23 ± 0.004	16.51 ± 0.62	1.19 ± 0.05	29.43 ± 0.83
OD3	0.21 ± 0.002	0.22 ± 0.009	14.74 ± 0.82	1.17 ± 0.02	29.81 ± 0.89
OD4	0.20 ± 0.02	0.22 ± 0.003	15.88 ± 0.64	1.18 ± 0.06	29.62 ± 0.67
OD5	0.19 ± 0.007	0.21 ± 0.006	13.72 ± 0.69	1.13 ± 0.03	29.97 ± 0.08

Post compression parameters of ondansetron HCl, $2H_2O$ ODT

The data obtained for post compression parameters such as, weight variation, thickness, hardness, friability, drug content, disintegration time, dissolution are depicted in Table 5 and 6.

Table 5. Post-compressional parameters of all formulations.

Formulation	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)
OD1	3.19 ± 0.06	4.03 ± 0.15	0.59 ± 0.07	147.7	98.23 ± 0.86
OD2	3.20 ± 0.05	4.23 ± 0.15	0.54 ± 0.03	149.9	98.97 ± 0.98
OD3	3.19 ± 0.05	4.10 ± 0.26	0.62 ± 0.02	150.6	99.02 ± 0.33
OD4	3.19 ± 0.01	3.9 ± 0.15	0.77 ± 0.17	147.8	99.13 ± 0.83
OD5	3.19 ± 0.05	4.06 ± 0.15	0.82 ± 0.06	150.75	99.29 ± 0.60
ONDEM MD 4	2.28 ± 0.04	4.02 ± 0.15	0.75 ± 0.06	100.56	100 ± 0.32

Table 6. Compressional parameters of all formulations.

Formulation	Disintegration time (sec) in water	Disintegration time (sec) in simulated salivary fluid
OD1	109.6 ± 1.52	1.20 ± 1.20
OD2	86 ± 1.00	115 ± 1.15
OD3	55.6 ± 1.15	60.06 ± 1.25
OD4	36.6 ± 1.5	45 ± 1.25
OD5	29.3 ± 1.52	140 ± 125
ONDEM MD4	10 ± 1.02	12 ± 1.00

Formulations OD1 to OD5 showed the thickness in the range of 3.19 ± 0.06 to 3.20 ± 0.05 mm. The hardness was found to be in the range of 3.9 ± 0.15 to 4.23 ± 0.15 kg/cm2 in all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations the friability value is less than 1% and meets the IP (Indian Pharmacopoeia) limits. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The percentage drug content of all the tablets was found to be between 98.23 ± 0.86% and 99.29 ± 0.60 % of Ondansetron HCl, 2H20. The disintegration time was increases with increases in concentration of disintegrant. The rapid disintegration was seen in formulation OD5 29 sec but it is having concentration of mucilage which is act as disintegrant at a concentration 12.5%w/w which is beyond the limit.

This is due to the rapid uptake of water from the medium, swelling and burst effect. The disintegration time was also determined in simulated salivary fluid and the formulation OD4 shown the disintegration time of 45 sec. Dissolution profiles of the formulations are depicted in. The dissolution profile of optimized formulation (OD4) was compared with marketed formulation of Ondansetron HCl, $2H_2O$ (ONDEM MD 4). Marketed formulation of Ondansetron HCl, $2H_2O$ released 100% drug in 1 minute. Whereas optimized formulation OD4 released 99.81% drug in 3 minutes.

CONCLUSION

In the present study the superdisintegrant property of *Caesalpinia pulcherrima* has been explored. Extensive swelling, porosity, wicking action of the natural substance in the ODT were found to be act as a superdisintegrant. This study has demonstrated the potential of *Caesalpinia pulcherrima* seed mucilage to act as a disintegrant in ODT formulation as it shows better disintegrating property (10% w/w). This superdisintegrant is cheap, biocompatible, biodegradable, easy to manufacture hence can be used as a superdisintegrant in place of currently marketed synthetic superdisintegrant. Direct compression method (by the addition of superdisintegrants) was found to be the best approach in the formulation of orally disintegrating tablet. The prepared tablet also gives benefit in terms of patient compliance, rapid onset of action, increased bio-availability, low side effect and good stability which make these tablets popular as a dosage form for the treatment of cancer chemotherapy.

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