Int. J. Pharm. Investigation, 2024; 14(2):462-471.
https://www.jpionline.org

Original Article

A Green Approach to Synthesize Ondansetron Oral Mucoadhesive Tablets by Using Natural Polymers and *in vitro* Characterization

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ABSTRACT

Background: Mucoadhesive buccal tablets are well established, widely used, and commonly accepted oral dosage forms that, by virtue of their adhesiveness, allow the drug to be released gradually over an extended period. Various parameters of the polymers being used in the formulation affect their adhesiveness. This includes the molecular weight, concentration, chain length, flexibility, hydration, and hydrogen bonding. **Materials and Methods:** Ondansetron, an antiemetic drug that is a selective 5-HT3 serotonin receptor antagonist, was formulated as a mucoadhesive buccal tablet consisting of guar gum, xanthan gum, Locust bean gum, microcrystalline cellulose, magnesium stearate, and silicon dioxide. The formulation consisted of nine batches with batch codes ranging from F1 to F9, which involved the use of various polymer combinations and concentrations to create a homogenous powder mixture. The tablets were formed in a single-punch tablet compression machine. **Results and Discussion:** The study analyzed the physicochemical characteristics of Ondansetron and its excipients, revealing a melting point of 232ºC and high solubility in various solvents. The formulation's pH was found to be within acceptable range for saliva, and the weight variation test showed average percentage variation within limits. The highest mucoadhesive strength was found in tablets with increased amounts of mucoadhesive polymers like guar gum, xanthan gum, and locust bean gum F7-F9. The release studies showed that F9 followed Fickian drug release transport, while F1 to F8 followed non-Fickian drug release transport, resulting in sustained or controlled release effects. **Conclusion:** The study uses sustained-release polymers like guar gum, xanthan gum, and locust bean gum to create mucoadhesive ondansetron tablets for treating emesis in chemotherapy. The transmucosal buccal route is optimal for oral administration, with formulations extending drug release for up to 24 hr without local irritant effects. The formulation is successfully synthesized, having optimal drug release to produce desired therapeutic outcomes.

Keywords: Natural polymers, Ondansetron HCl, Sustained Release, Chemotherapy, Mucoadhesion.

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Received: 12-11-2023;
Revised: 03-01-2024;
Accepted: 21-01-2024.

INTRODUCTION

Oral drug administration is preferred due to its non-invasive nature, ease of administration, and high patient compliance. Mucosal and transmucosal administration target specific areas of the mucosa.[1]

Sustained drug delivery systems provide optimal therapeutic outcomes by ensuring steady, homogeneous drug release over extended periods, offering better control of plasma drug levels, reduced dose frequency, and higher effectiveness.[2]

Approximately 60% of commercially available small-molecule drugs are taken orally.[3] The utilization of bioadhesive dosage forms for drug delivery through the buccal route presents a unique and innovative method of administering medications. Buccal delivery entails delivering the intended drug by applying it to the mucosal membrane lining of the oral cavity.[4]

Mucoadhesive drug delivery may be an effective solution for sustained drug release and maintaining the dosage form at the

DOI: 10.5530/ijpi.14.2.56

absorption site, overcoming drawbacks.[5] Mucoadhesive dosage forms are designed to adhere to mucosal surfaces, improving drug retention at the site and increasing its efficacy.[6] Recent developments in mucoadhesive delivery techniques for oral, buccal, nasal, rectal, and vaginal administration have produced systemic and local effects, with the mechanism of action occurring through contact and consolidation stages.[7]

Mucoadhesive polymers, categorized into hydrophilic and hydrogels, are ideal for their non-toxic, non-irritant properties, ease of drug incorporation, quick tissue adhesion, good shelf life, and affordability.[8] The development of innovative drug delivery routes aims to enhance the bioavailability of medications that are limited by the gastrointestinal tract's absorption window.[9] The buccal route of drug administration can prevent issues like high first-pass metabolism and drug degradation in the harsh gastrointestinal environment.[10] The establishment of a mucoadhesive bond among hydrophilic matrix formulations and the mucosal surface depends significantly on the swelling of polymers.[11] Natural gums and plant mucilage are highly valuable as pharmaceutical excipients, especially in the development of sustained-release drug formulations.[11] Locust bean gum, a neutral polysaccharide with a molecular weight of 310,000, is derived from the endosperm of Ceratonia siliqua Linne's seed.[12] Guar gum, a polysaccharide derived from Cyanopsis teragonolobus seeds, is not yet evaluated for its use in buccal formulations due to insufficient evidence.[13] Xanthan gum, produced by Xanthomonas campestris during biotechnological fermentation, has swelling capabilities, making it a mild adherence to biological membranes.[11]

Bioadhesive polymers not only promote adhesion but also have the ability to regulate the rate at which drugs are released.[14] Ondansetron is the main active ingredient in this formulation, which is a selective antagonist of 5-HT3 receptors, which are responsible for inducing nausea and vomiting. It is used for the treatment of nausea in patients undergoing cancer treatment and anesthesia.[15] It consists of an elimination half-life of 3 to 4 hr. The study focuses on utilizing locust bean gum and guar gum, which are cost-effective and easily accessible, as mucoadhesive components in buccal tablets. The objective is to investigate the effectiveness of these natural biocompatible substances in promoting adhesion and the sustained release of ondansetron hydrochloride from buccal mucoadhesive tablets. Additionally, the study evaluates their potential for improving the bioavailability of drugs that have limited absorption due to the narrow absorption window in the gastrointestinal tract.[16]

MATERIALS AND METHODS

Pre-formulation studies

The formulation's components were subjected to pre-formulation testing using the methodologies listed below to examine their physicochemical characteristics.[17]

Organoleptic properties

The sample of Ondansetron HCl was studied for organoleptic properties such as color, odor, and appearance by visual inspection.

Melting Point Determination

A digital melting point instrument was used to heat a small amount of a drug in a capillary tube, which was then placed in an MP apparatus and the temperature at which the drug began to melt was recorded.[18]

Bulk Density (Apparent)

Powder is measured in a calibrated cylinder, and 100g of sample is poured into the cylinder, granule mass is calculated, volume is read, and apparent density is determined.[19]

$$Apparent\ density = \frac{Mass\ of\ grains}{Volume\ of\ the\ grains\ in\ bulk}(without\ tapping)$$

Tap Density

Tapped density of materials was estimated by comparing granule mass and read volume after agitation, ensuring no additional variations in volume were detected.[20]

$$Tap\ density = \frac{Mass\ of\ the\ grains}{Volume\ of\ grains\ after\ tapping}(\text{With tapping})$$

Hausner's Ratio

Using tap density and bulk density, Hausner's ratio is used to assess the flow properties of granular powder. This ratio can be applied to provide an index of the flow characteristics of granules. The Hausner ratio is an indicator of the flowability of bulk solids.[21]

$$Hausner's\ ratio = \frac{Tap\ Density}{Bulk\ Density}$$

Carr's Index

Carr's ratio, based on the assumption that compressibility is related to flowability, can be calculated using tap density and bulk density using a formula.[21]

$$Carr's\ Index\ = \frac{Tap\ density\ -\ bulk\ density}{\text{Tap density}} \times 100$$

Angle of Repose

The rectifying technique is used to compute the angle of repose.[22] A funnel was used to pour powder, determining mean diameters, tangent of angle of repose, height, and radius of granules, and determining the angle of repose.[18]

$$\theta\ = \tan^{-1}\frac{h}{r}$$

pH Determination

For the pH determination, digital pH meter was used.[18]

Determination of Drug Solubility

A drug was dissolved in distilled water and various solvents to determine its solubility through qualitative analysis, using HCl 0.1 N, saline phosphate buffer pH 7.4, phosphate buffer pH 6.8, ethanol, acetone, and chloroform.[18]

Drug stability studies

The study involved weighing 250 mg of drug and excipient samples and exposing them to various temperature and humidity settings in a stability chamber for up to 12 weeks. The samples were then withdrawn at 1, 2, and 3-month intervals and analysed for interaction among themselves.[18,23]

Preparation of Calibration Curve

Ondansetron HCl (25 mg) was accurately weighed and then transferred to a volumetric flask (25 mL). Dissolve it with a small amount of pH 6.8 phosphate buffer solution to increase the volume. The dilutions were studied using a UV-spectrophotometer with a maximum wavelength range of 310 nm. The calibration curve was plotted by taking the concentration (micrograms/mL) of the drug on the x-axis and absorbance on the y-axis as shown in Figure 1.[19]

Materials

The active ingredient ondansetron was purchased from Sigma Aldrich. High viscosity polymers Guar gum, Xanthan gum, Locust bean gums were purchased from Sigma. Magnesium stearate, silicon dioxide was purchased from Sigma. Microcrystalline Cellulose (50 µm) was purchased from Dea Jung. All materials were of laboratory reagent grade and used as received. Guar gum, Xanthan gum, Locust bean gums were used as mucoadhesive polymers. Microcrystalline Cellulose (MCC) was used as a diluent, silicon dioxide was used as moisture absorbing and Magnesium Stearate (Mg-St) was used as a lubricant.

Method of Preparation

The tablets were prepared by the direct compression method using different combinations of polymers. All the powders were weighed precisely. With the aid of a pestle and mortar, the ingredients were geometrically mixed to create a homogenous powder mixture. The particle size distribution was remarkably similar. Magnesium stearate was added to the powder mixture by geometric mixing for a further 1 min. The powder blend was then put into a mould for tableting in a tablet compression machine (single punch). Nine formulations were prepared and coded from F1 to F9 by varying the different concentrations of polymers as shown in Table 1.[24]

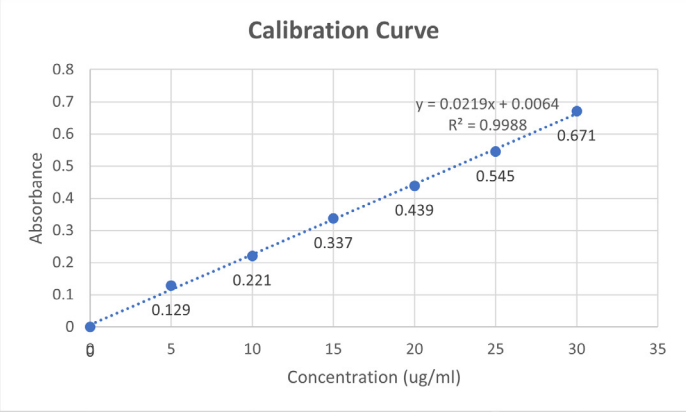

Figure 1: Calibration curve of ondansetron.

Post Formulation Studies

Weight Variation

Weight variation is crucial for determining drug content in tablets. 20 ondansetron tablets were accurately weighed, and the average weight was calculated. The USP standard acceptable weight variation ranges from 130 mg to 324 mg, and if two tablets are outside this limit, they meet the test.[24]

Hardness Test

The sustained release tablet hardness test was conducted to maintain physical strength and desired release. A barrel with compressible springs was used, and nine tablets were weighed and placed in contact with the lower plunger. The upper plunger was forced until the tablet fractured, and the crushing strength was recorded in kg/cm^2.[19]

Friability Test

Friability testing for Roche tablets involves a maximum weight loss of 1%, with smashed or broken tablets not acceptable. Nine tablets from each batch were tested, falling from a height of 6 inches in each turn. After 4 min or 100 revolutions, the tablets were recovered, weighed, and compared to their initial weight. The formula for friability is:[24]

$$\%\,\text{Friability} = (Wi - Wf)/Wi \times 100$$

Whereas, Wi = initial weight and wf = final weight

Thickness Test

Tablet thickness is crucial for reproducing identical appearance. Ten tablets from each formulation were randomly selected and measured using digital Vernier calipers, with results presented as mean values.[20]

Content Uniformity

In a glass pestle and mortar, ten tablets were precisely weighed and crushed. The assay was done spectrophotometrically at 310 nm using an accurately weighed quantity corresponding to 5 mg of pure drugs.[25] The formula content uniformity was calculated,

$$\text{Content uniformity} = (\text{Absorbance of sample/absorbance of standard}) \times 100$$

Surface pH

Ondansetron mucoadhesive tablets were swelled in distilled water for 2 hr, and the pH was measured using a pH metre electrode, with the mean of three values recorded.[26]

Swelling Studies

The swelling study used 1% agar gel plates and Petri dishes to hold four tablets. The tablets were removed at specific intervals, 1, 2, 4, and 6 hr.[27]

The formula for calculating the swelling index is:

Swelling index = (wet weight - dry weight)/wet weight x 100

Determination of Mucoadhesive Strength

The mucoadhesive strength of tablets was measured using a texture analyzer, using fresh buccal mucosa from sheep from a local slaughterhouse as a model membrane. The samples were cut into 22 cm slices and adhered to the top probe of the device. The mucosa was partially immersed in a PBS (pH 6.8) liquid at 37°C, and the probe was lowered at 0.5 mm/s until tablet contact was achieved. The peak Detachment Force (DF) was measured, and the test was repeated three times for each formulation.[28] The mucoadhesive force was calculated by following equation,

Force of adhesion(N)=Bioadhesive strength (g)/1000 × 9.81

Fourier Transform Infrared Spectroscopy (FTIR)

The mucoadhesive tablets were analyzed using Infrared Spectrometry (FTIR), which uses Michaelson's interferometer and Fourier transform to analyze data. Each material had a unique spectrum of bands, representing vibrations of a specific functional group region or bond in the chemical and fingerprint regions. The FTIR analysis resulted in an inferogram, a plot between wavenumber and light transmission. The scanning range was 400 to 4000 cm^{1}, with 1400 to 600 for the functional group region and 4000 to 1400 for the fingerprint region. The samples were evaluated for characteristic and identifiable peaks.[18]

Thermogravimetric Analysis (TGA)

The TGA requires a precision balance and a furnace programmed to show a linear temperature increase over time. It provides information on all physical phenomena except crystalline transitions and fusions. A 5 mg sample was weighed and placed

Table 1: Different formulations of mucoadhesive tablets are made by using different polymeric concentrations.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)
Ondansetron HCl	16	16	16	16	16	16	16	16	16
Guar gum	100	150	100	150	_	_	75	100	125
Xanthan gum	50	60	_	_	50	100	50	40	30
Locust bean gum	_	_	50	60	50	100	50	40	30
Microcrystalline cellulose	69	9	69	9	119	19	44	39	34
Silicon Dioxide	10	10	10	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total	250	250	250	250	250	250	250	250	250

Table 2: Precompression parameters of dry powder blends of ondansetron mucoadhesive tablet formulation F1-F9

Batch Code	Bulk density g/cm^3	Tapped density g/cm^3	Angle of repose	Carr's Index	Hausner ratio
F1	0.25	1.26	29.08	11.96	1.11
F2	0.23	1.52	27.57	13.53	1.18
F3	1.21	2.98	27.69	14.42	1.00
F4	1.85	2.98	32.43	13.25	1.14
F5	1.04	1.98	28.01	11.95	1.15
F6	0.83	1.97	31.46	12.69	1.17
F7	0.44	1.86	36.28	12.36	1.13
F8	1.84	2.86	33.28	13.64	1.12
F9	1.84	2.87	35.46	14.81	1.16

in metal containers, conducted in a nitrogen atmosphere and heated at 10°C/min between 25 and 300°C.[29]

X-ray Diffraction (XRD) Analysis

The rotating anode X-ray diffractometer (Smart Lab 9kW) was set to 45 mV of voltage and 20 A of current, and the diffraction patterns were expressed in units of 2.1 throughout a temperature range of 5 to 10°C/min.[29]

Differential Scanning Calorimetry (DSC)

The PerkinElmer Diamond differential scanning calorimeter was calibrated using indium with a purity of 99.98%, a melting point of 156.61°C, and a fusion enthalpy of 28.71 J/g. Samples were accurately weighed and placed in 50-L aluminium pans. The tests were conducted in a pure nitrogen atmosphere with a flow rate of 25 mL/min and heating rate of 10°C/min, with each sample measured in triplicate.[29,30]

In vitro Drug Release

The *in vitro* release of a dosage form was tested using a standard BP or USP dissolution apparatus, which consisted of a cylindrical vessel with simulated gastric or intestinal fluid. The fluids were maintained at 37°C and rotated at 1.2 rpm. The dissolution of the dosage form was controlled by the media's properties, with stirring speed set at 50 to 100 rpm for apparatus I and II. Disintegration tests were also conducted using a Standard Pharmacopoeia (USP) apparatus, consisting of six basket apparatus tubes against a 10-mesh screen. Tablets were placed 2.5 cm below the fluid surface in upward motion, and an acidic solution with a pH of 1.2 and a phosphate buffer of pH 7.4 was used as a dipping intermediate. The disintegration process was conducted at a constant 37°C.[31-33]

Drug release kinetics

The release kinetics of formulations were determined using various statistical models, including the zero-order model, Higuchi model, Hixon Crowell model, first-order model, and Korsmeyer peppas model.[34]

RESULTS

Preformulation

The study evaluated the organoleptic properties of ondansetron mucoadhesive tablets, finding no color, appearance, or texture differences after four weeks. The melting point of the ondansetron was found to be nearly 232°C, within the specified range for ondansetron, indicating its purity. The drug is highly soluble in water, DMSO, methanol, and ethanol at concentrations of 50 mM, 100 mM, methanol, and 10 mg/mL at 25°C.

The study evaluated precompression parameters to ensure the flow properties of granules and dry powders during tablet punching. Formulations F1 to F9 showed different bulk densities, with F1, F2, F6, and F7 having bulk densities between 0.23 to 0.83 g/cm^3. Formulations F3, F4, F5, F8, and F9 had densities between 1.04 to 1.84 g/cm^3, and tapped densities between 1.26 and 2.98 g/cm^3. Formulations with increased bulk density had decreased particle size distribution and ratio of void space to particles. Tap density increased compared to bulk density, resulting in decreased sample volume after tapping. Carr's index values below 10 indicated excellent flow characteristics, while Hausner's ratios between 1.15 and 1.18 indicated excellent to good flow characteristics as shown in Table 2. The angle of repose values for all nine formulations were between 27.69 and 36.28°, indicating good flow characteristics. The active pharmaceutical ingredient showed compatibility with all excipients after a month of treatment at 40°C and 75% relative humidity, indicating no interaction between drugs, polymers, and other excipients.[26]

Table 3: Evaluation of post compression parameters of ondansetron mucoadhesive tablets formulation F1-F9.

Batch Code	Thickness (*mm*)	Average Weight variation (*mg*)	Hardness (*kg/cm*^{2})	Friability %	Content Uniformity	Mucoadhesion Strength	Surface PH	Swelling Index	Mucoadhesion Time (hr)
F1	1.34±0.04	251±2.43	7.00±0.15	0.12	99.15	12.4+0.32	6.39±0.03	44.98	12
F2	1.29±0.01	252±2.29	7.00±0.16	0.20	98.12	14.8±0.44	6.68±0.05	49.22	12
F3	1.30±0.02	253±2.28	7.50±0.18	0.19	98.43	18.12±0.57	6.70±0.04	50.87	12
F4	1.48±0.02	254±2.43	7.25±0.30	0.25	97.92	20.20±1.24	6.75±0.09	55.04	12
F5	1.53±0.03	251±2.54	7.30±0.25	0.29	98.45	25.34±1.39	6.76±0.06	69.09	12
F6	1.68±0.18	252±2.51	7.00±0.20	0.31	99.36	27.45±1.43	6.79±0.08	72.06	12
F7	1.67±0.12	250±2.52	7.40±0.24	0.29	99.58	28.64±1.52	6.80±0.03	89.23	12
F8	1.68±0.34	251±2.59	7.15±0.19	0.22	98.67	27.70±1.32	6.80±0.02	87.12	12
F9	1.65±0.01	250±2.60	7.25±0.23	0.34	99.15	26.85±1.44	6.81±0.01	89.19	12

Post Compression Studies

Weight variation test

Weight variation for tablets of different formulations was found to be 250±2.52 to 253±2.43. The average percentage variation of all tablet formulations was found to be within the limit as describe in Table 3, and hence all formulations passed the official weight uniformity test.[18]

Hardness test

The study found that all ondansetron mucoadhesive tablet formulations had a hardness below the specified 10-20 kg/cm^3, indicating that they were not too hard, as they were found to be in the range of 7.0±0.15 to 7.50±0.18 kg/cm^3.[18]

Friability test

The percentage friability of all formulations F1 to F9 ranged from 0.12% to 0.35% as describe in Table 3. It was observed that all nine formulations complied with the official limits, and it was concluded that all the tablets of each formulation showed the ability to withstand use.[18]

Thickness test

The average thickness of the tablets ranged from 1.34±0.04 to 1.68±0.34 mm, and all formulations were within permissible limits. The results showed in Table 3, a small value of difference, which indicated that the thickness was uniform and consistent throughout all the batches of tablets.[18]

Table 4: Data for cumulative *in vitro* drug release for all formulations.

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	5.11	3.4	6.0	7.9	18.8	10.0	2.0	4.3	19.9
1	13.1	5.9	13.0	15.8	26.3	21.1	6.9	10.7	30.3
2	24.5	10.4	23.2	25.3	38.7	33.9	10.1	21.4	43.6
3	37.9	17.1	35.7	38.0	48.9	43.3	16.5	35.7	53.9
4	52.1	26.7	50.6	55.7	56.9	52.6	24.4	48.1	61.1
5	60.5	40.9	60.0	70.5	74.6	63.6	34.1	59.3	69.6
6	68.3	60.5	70.7	80.1	84.9	71.8	46.4	67.5	77.8
8	75.7	75.8	78.1	86.0	90.6	79.2	59.9	75.5	82.3
10	81.2	85.1	82.8	90.9	94.8	87.5	67.4	81.1	83.2
12	84.9	90.5	85.3	93.0	95.3	94.3	74.9	85.0	85.1
14	87.4	94.9	89.8	96.2	97.1	95.0	79.9	88.4	88.9
16	90.8	95.2	92.8	96.2			82.0	90.2	90.1
18	94.9	95.2	93.4				86.4	92.8	91.9
20	94.9		94.7				90.3	93.7	92.6
22			96.0				94.6	93.9	
24							97.9	94.3	

Table 5: Release kinetic data of different mucoadhesive formulations.

Formulation	Zero order		First order		Higuchi		Korsemeyer
	K0	R sq	k1	R sq	kH	R sq	kKP
F1	6.233	0.5584	0.17	0.9917	0.9349	24.144	0.489
F2	6.69	0.8702	0.138	0.9238	0.8557	13.058	0.739
F3	5.828	0.4966	0.172	0.9897	0.9178	25.102	0.468
F4	8.034	0.608	0.213	0.9746	0.9111	25.386	0.525
F5	9.316	0.4212	0.26	0.9768	0.9372	31.629	0.462
F6	8.657	0.6816	0.203	0.9959	0.9724	24.72	0.54
F7	4.895	0.875	0.104	0.9745	0.9197	12.355	0.675
F8	5.33	0.4691	0.161	0.9887	0.9083	24.803	0.457
F9	6.3810	-0.4144	0.237	0.9258	0.7818	37.490	0.327

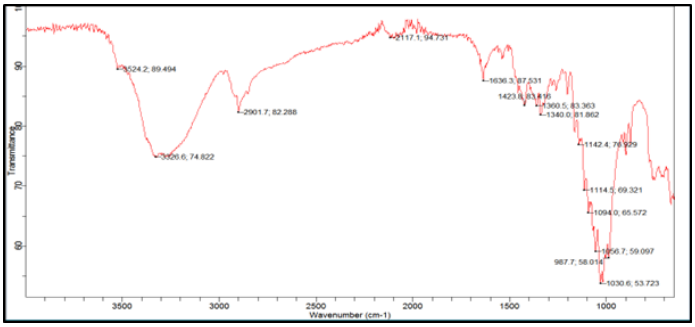

Figure 2: FTIR analysis of mucoadhesive tablet of ondansetron.

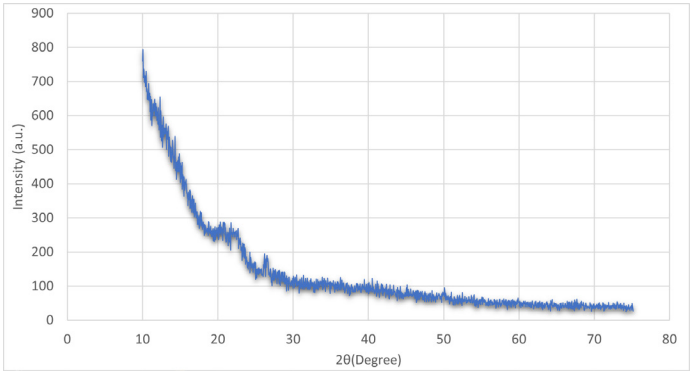

Figure 3: XRD analysis of mucoadhesive tablet of ondansetron

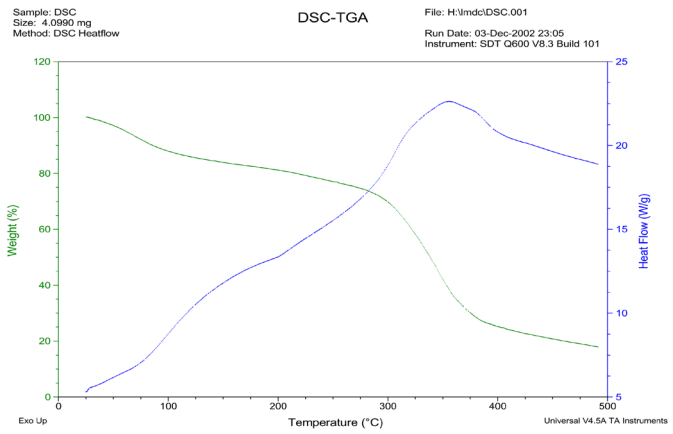

Figure 4: DSC/TGA analysis of mucoadhesive tablet of ondansetron.

Content uniformity

The mucoadhesive buccal tablet formulation's percent uniformity ranged from 97.92 to 99.58, indicating that the individual content of all nine formulations was within acceptable limits and showed a degree of uniformity in the amount of drug substance.[27]

Surface pH

The study evaluated the surface pH of all formulations, revealing that they ranged from 6.39±0.03 to 6.81±0.01, which is within the acceptable salivary pH range of 5.5-7.0. The ondansetron mucoadhesive tablets did not cause local irritation to the mucosal surface. The pH of different formulations were describe in Table 3.[27]

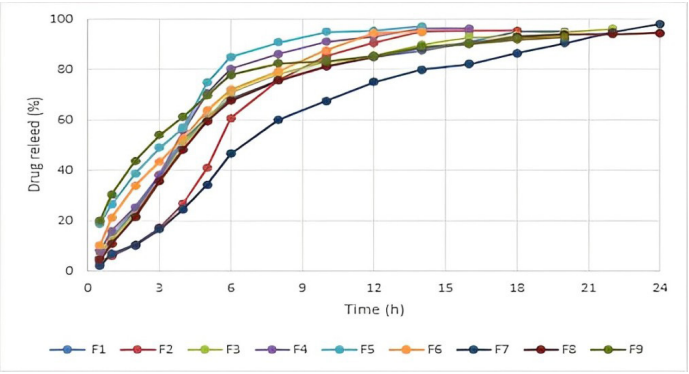

Figure 5: Comparative *in vitro* drug release profiles of ondansetron from various mucoadhesive tablets.

Swelling studies

Swelling studies on ondansetron mucoadhesive tablets showed that higher polymer concentrations increased the swelling index. Formulations F7-F9 showed the greatest swelling, while other formulations had lesser swelling indexes. Therefore, formulations F7-F9 had a higher swelling index due to the mucoadhesive polymer content, suggesting that higher polymer concentrations were effective as shown in Table 3.[23]

Determination of mucoadhesive strength

The mucoadhesive force determination is crucial for mucoadhesive formulation, determining its adherence to the mucosa membrane. The maximum mucoadhesive strength was found in tablets with increased amounts of mucoadhesive polymers like gum, xanthan gum, and locust bean gum (F7-F9), indicating that the mucoadhesive strength increases with polymer concentration as shown in Table 3.[23]

Fourier Transform Infrared Spectroscopy (FTIR)

During preformulation studies, FTIR studies were conducted to identify drugs in a drug polymer combination. The analysis revealed peaks in the FTIR analysis of sustained-release mucoadhesive ondansetron HCl tablets, possibly due to OH hydrogen bonding. The presence of all drug peaks in the FTIR spectrum indicated no drug-carrier interaction, with peak 2983.77 containing 1754.78 attributed to carbonyl group vibrations. Ring stretching was also detected in 1556.22, 1508.11, and 1507.27.[35]

The purity of ondansetron hydrochloride was demonstrated through the comparison of pure bands with normal IR spectra, revealing all typical peaks in pure form in both formulations. The FT-IR spectra of xanthan gum showed absorption peaks at 3277 cm^{1} due to O-H axial deformation, as well as symmetric and asymmetric stretching vibrations of the C-H group in methyl and methylene groups, with 1710 cm^{1} bands attributed to C=O stretching vibrations.[36] The hydroxyl group in locust bean gum,

found at 3300 cm^{1}, exhibits a significant OH stretching peak due to hydrogen bonding between the gum molecules.[37] The FTIR analysis of guar gum revealed a stretching CH_2 group peak at 2912 cm^{1}, followed by a stretching ring peak at 1636 cm^{1}, deformation of the CH_2 group at 1375 cm^{1}, OH group-induced peak at 1146 cm^{1}, and C-OH peak at 1146 cm^{1}. The highest peak (1023 cm^{1}) was generated by twisting the CH_2 group, and linkage was confirmed by a peak at 659.7 cm^{1}. Galactose and mannose are related sugars, all peaks were shown in Figure 2.[19]

X-ray Diffraction (XRD) Analysis

X-ray diffraction (XRD) analysis on the ondansetron mucoadhesive tablet revealed no significant diffraction peaks as shown in Figure 3, indicating that the active ingredient, ondansetron, has mixed well with the other excipients and is incorporated into the tablet, proving its stability.[29]

Thermal Gravimetric Analysis (TGA)

Thermal Gravimetric Analysis (TGA) studies were conducted on ondansetron mucoadhesive tablets at temperatures ranging from 25 to 300°C as shown in Figure 4. The results showed that from 0°C to 40°C, the initial weight of the tablet remained stable. As the temperature rose above 305°C, a sharp deflection peak was observed, indicating the degradation of the sample. The weight decreased by 80% during the phase transition from 300 to 375°C. In conclusion, the sample remained stable until it reached 305°C. The study also revealed that the initial weight of the tablet remained relatively stable from 0°C to 40°C.[29]

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies were used to identify drugs. A peak was observed at 375°C, indicating that the crushed powder began melting and converting into a liquid, confirming the exothermic process by releasing energy into the environment. The sample's DSC thermogram showed an exothermic peak at 375°C as in Figure 4, indicating the crushed powder melting and converting into a liquid by releasing energy into the environment, confirming the exothermic process.[29]

In vitro analysis

Disintegration testing

In vitro disintegration studies were also performed on mucoadhesive tablets of ondansetron. The sustained-release mucoadhesive tablets were placed in the disintegration apparatus under the proper medium, but no disintegration of the mucoadhesive tablets was observed.[26]

Dissolution testing

The drug release properties of ondansetron were investigated.[34] *In vitro* dissolution studies on ondansetron's mucoadhesive tablet showed continuous increase in drug dissolution rate for up to 24 hr in formulations F1 to F9, comparing drug release rate.[38] The drug release was observed for 24 hr, with most formulations showing 80% release after 12 hr, except F7, and the initial period was relatively slow, with most formulations showing a similar release.[31] F1, F3, F4, F5, F6, and F9 showed more than 50% drug release within 4 hr; however, F2, F7, and F8 showed more than 50% drug release within 6 hr,8 hr and 5 hr, respectively as describe in Table 4.[38]

The study found that formulations F5 and F6 showed drug release within 14 hr with a 97.1% or 95.0% rate, while F7 and F8 showed prolonged drug release for up to 24 hr. The reason for this was the addition of polymers like guar gum, xanthan gum, or locust bean gum, which exhibit mucoadhesive properties and control drug release. Excessive polymer concentrations in F7 and F8 retarded drug release, resulting in no drug release from tablets. F5 and F6 formulations had optimal amounts of polymers with mucoadhesive behavior and maximum drug release. Increased polymer concentrations resulted in retarded drug release. Microcrystalline cellulose, a hydrophilic polymer with disintegrant properties, increased water penetration into tablets, causing drug release within 14 hr in F5 and F6 formulations. The comparative *in vitro* drug release profiles of ondansetron from various mucoadhesive tablets are shown in Figure 5.[39]

Drug release kinetics

In vitro dissolution studies were analyzed using various release kinetic models, including zero-order, first-order, Higuchi, and Korsemeyer Peppas. The Korsemeyer Peppas model was analyzed using the n value, which represents the release exponent and Fickian or non-Fickian release of the drug. The range was observed to evaluate the drug's release.[23]

The release studies of ondansetron mucoadhesive tablets as describe in Table 5 showed that formulations F1 to F8 had n values between 0.45 and 0.89, except for F9. F9, with a less than 0.45 n value, followed Fickian drug release transport, resulting in a sustained release effect. F1 to F8 showed non-Fickian drug release transport, leading to a controlled release effect.

The analysis of regression square values in kinetic models revealed that the best formulation for ondansterone follows first-order release kinetics, with F1 to F7 following this model. F6 showed the highest regression square value, 0.9959, indicating a sustained drug release mechanism. The release of the drug is dependent on the drug's concentration, indicating a sustained mechanism. F7 and Higuchi models also showed maximum values closer to 1, 0.875 and 0.9724, respectively, with less deviation from the expected values. The study concluded that the drug release is dependent on the drug's concentration and a sustained mechanism.[40]

DISCUSSION

The formulation of ondansetron tablets underwent pre-formulation testing to examine their physicochemical characteristics. The tablets were prepared by wet granulation using different polymer combinations and weighed precisely. Nine formulations were prepared and coded from F1 to F9, with varying concentrations of polymers. Post-formulation characterizations revealed that the ondansetron had a melting point of nearly 232°C, indicating its purity. The active pharmaceutical ingredient showed compatibility with all excipients after a month of treatment at 40°C and 75% relative humidity. The average percentage variation of all tablet formulations was within the limit, and the ondansetron mucoadhesive tablet formulations had a hardness below the specified limit. The percentage friability ranged from 0.12% to 0.35%, and all nine formulations complied with official limits. The average thickness of all formulations was within permissible limits, and the mucoadhesive buccal tablet formulation's percent uniformity ranged from 97.92 to 99.58. After examination through the pH meter, the surface pH of all formulations was within the acceptable salivary pH range of 5.5-7.0. The study reveals that the mucoadhesive strength of tablets increases with the concentration of mucoadhesive polymers like gum, xanthan gum, and locust bean gum. FTIR analysis revealed that the peaks are due to the specific functional groups present in the ondansetron HCl and other excipients, which will confirm the presence of ingredients without any interaction. X-ray Diffraction (XRD) analysis on the tablet showed no significant diffraction peaks, indicating that the active ingredient, ondansetron, has mixed well with other excipients, proving its stability.

During the TGA analysis, a sharp deflection peak was observed as the temperature rose above 305°C, indicating the degradation of the sample. The weight decreased by 80% during the phase transition from 300 to 375°C, but the sample remained stable until it reached 305°C. The initial weight of the tablet remained relatively stable from 0°C to 40°C. The sustained-release mucoadhesive tablets were placed in a disintegration apparatus under the proper medium, but no disintegration was observed. The drug release was observed for 24 hr, with most formulations showing 80% release after 12 hr. The initial period was relatively slow, with most formulations showing a similar release. The study concluded that drug release is dependent on the drug's concentration and a sustained mechanism.

CONCLUSION

The study uses sustained-release polymers like guar gum, xanthan gum, and locust bean gum to create mucoadhesive ondansetron tablets for treating emesis in chemotherapy. The transmucosal buccal route is the best option for oral administration, allowing for lower dosages. The study found that increasing the polymer concentration decreases the release rate. Formulations F7 and F8, made from these polymers, extended drug release for up to 24 hr without local irritant effects and had excellent surface pH and physical characteristics.

ACKNOWLEDGEMENT

We would like to extend our sincere gratitude to the Deanship of the Faculty of Pharmaceutical Sciences at Lahore University of Biological and Applied Sciences (UBAS) for providing the necessary resources and support that made this research possible. Their commitment to fostering academic excellence has been invaluable.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

ABBREVIATIONS

HCl: Hydrochloric acid; **M.P:** Melting Point; **UV:** Ultraviolet-Visible; **Wi:** Initial Weight; **Wf:** Final Weight; **PBS:** Phosphate Buffer Solution; **DMSO:** Dimethlysulfoxide.

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Cite this article: Mustafa MA, Khan AM, Arif M, Khan N, Rasheed N, Ghaffari MA, *et al*. A Green Approach to Synthesize Ondansetron Oral Mucoadhesive Tablets by Using Natural Polymers and *in vitro* Characterization. Int. J. Pharm. Investigation. 2024;14(2):462-71.