




Formulation and characterization of zaleplon buccal disks using grafted *Moringa oleifera* gum

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ABSTRACT

Natural modified gums act as drug release modifiers in novel drug delivery systems. These modified gums help to alter the physicochemical properties of the drugs. Zaleplon (ZLP) is a pyrazolopyrimidine that is used to treat insomnia. It has a significant problem from a pharmaceutical point of view that it undergoes extensive first-pass hepatic metabolism due to which it has a very short elimination half-life which leads to low bioavailability. The present investigation aimed to study the suitability of grafted *Moringa oleifera* gum as a mucoadhesive polymer in the formulation of ZLP buccal disks that would allow for pulsatile release via the buccal route, while avoiding extensive hepatic metabolism, increasing bioavailability, and avoiding early morning awakening. The modified *M. oleifera* gum was prepared using a microwave-assisted graft copolymerization reaction. The optimal calculated concentrations of *Moringa* gum, ceric ammonium nitrate, and acrylamide were found to be 1.0, 0.1, and 5.0 g, respectively, yielding a graft copolymer with a 65% grafting efficiency. The graft copolymer was further characterized using Fourier transform infrared spectroscopy, X-ray diffraction, differential scanning calorimetry, and scanning electron microscopy. The total ash content, bulk density, angle of repose, Carr's compressibility index, tapped density, and Hausner's ratio of naive *M. oleifera* gum and graft copolymer were determined. The ZLP buccal disks incorporated with gum and graft copolymer were prepared and evaluated for parameters like mucoadhesive strength, mucoadhesive time, and swelling index. The characterization results indicated that the modified *Moringa* gum exhibited decreased crystallinity and increased surface smoothness. A comparison of buccal disks made of graft copolymer and naive gum revealed that the graft copolymer had a longer *ex-vivo* mucoadhesion time and a more significant controlled release effect.

INTRODUCTION

Sleep, as well as food and shelter, is a significant necessity for all humans, and in a demanding environment, psychological stresses often contribute to bad sleep habits that abrupt their biological clock. Nearly 25% of the adults are affected by insomnia, although 10% are chronic (Levenson et al., 2015). Sleeplessness is categorized into four major types: irregular waking, early morning awakening, low sleep quality, and sleep

difficulties (Krystal et al., 2019). Recently, the buccal supply of medicines has become an efficient and secure substitute to other traditional medication paths. Administration into the buccal cavity easily releases the loaded drug used either for local or systemic effects. This route of administration is especially beneficial for pediatric and geriatric patients, as some individuals have difficulty swallowing conventional solid oral doses. Additionally, the buccal route is advantageous for those drugs that become unstable in the gastrointestinal tract and induce nausea and vomiting (Krystal et al., 2019). Several types of oral dosage, including tablets and mucoadhesive films, oral disintegrating tablets, hydrogels, and rapidly dissolving films, are now available commercially.

Zaleplon (ZLP) has a high affinity for the gamma-aminobutyric acid_A (GABA_A) receptor (subunit α 1) in the brain,

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stimulating GABA activity more selectively than benzodiazepines, which is a short-acting hypnotic used for sleep induction (Richter *et al.*, 2020). ZLP significantly reduces the time required to fall asleep by improving sleep latency and may therefore facilitate sleep induction rather than sleep maintenance. ZLP is affected primarily by extensive hepatic first-pass metabolism, which results in its low bioavailability (30%) and a short elimination half-life (1 hour) (Dudhipala and Janga, 2017). This issue can be avoided by incorporating ZLP into a mucoadhesive disk for buccal delivery. Therefore, buccal delivery has always been an attractive option because it bypasses the devastating metabolism associated with other conventional oral routes, resulting in increased bioavailability (Singh *et al.*, 2017). Extending the half-life of drugs with a short half-life reduces frequent dosing and, in this study, prevents early morning awakening without middle-of-the-night dosing. An increase in the dissolution rate of these drugs can also improve the oral bioavailability of these drugs, which improves both therapeutic effectiveness and patient compliance (Pagel *et al.*, 2018).

The interest in developing novel buccal drug delivery systems has risen significantly in recent years. Numerous studies demonstrate that novel buccal formulations containing lidocaine have gained popularity, including mucoadhesive films (Eleftheriadis *et al.*, 2020; Padula *et al.*, 2013), bilayered tablets (Kottke *et al.*, 2020), and several disks and patches (Abu-Huwajj *et al.*, 2007; Pather *et al.*, 2008; Yildir *et al.*, 2018).

Mucoadhesive polymers that adhere to the gastric mucin or buccal mucosa are advantageous for drug administration because they increase the contact time of the drug with the absorbing membrane. Due to the questionable biodegradability of synthetic polymers, natural gums have been extensively explored as pharmaceutical excipients mainly for achieving mucoadhesion properties. *Moringa* gum is a natural gum derived from the *Moringa oleifera* plant, belonging to the *Moringaceae* family. *Moringa oleifera* gum contains L-arabinose, D-galactose, D-glucuronic acid, L-rhamnose, D-mannose, and D-xylose in the mole ratio of 14.5 : 11.3 : 3 : 2 : 1 : 1, respectively. The generalized primary structure of *M. oleifera* gum is shown in Figure 1, in line with several studies (Badwaik *et al.*, 2020; Grewal *et al.*, 2019).

The gum has been studied for its potential use in pharmaceuticals as a binder, disintegrant, and release retardant (Panda, 2014). *Moringa* gum's side chains contain hydroxyl groups that interact with mucus, enhancing its mucoadhesive properties. *Moringa* gum has already been grafted with N-vinyl-2-pyrrolidone to improve its bioadhesion (Rimpy *et al.*, 2017). The current study is the first to report *Moringa* gum grafting to improve its mucoadhesive properties for buccal administration. The mucoadhesive property of the modified *Moringa* gum was compared to that of the unmodified *Moringa* gum using buccal disks containing ZLP as the test drug.

This study aims to formulate a ZLP mucoadhesive buccal disk that would allow for pulsatile release via the buccal route, while avoiding extensive hepatic metabolism, increasing bioavailability, and avoiding early morning awakening. A review of the literature reveals that no previous experiments involving the development of a ZLP mucoadhesive disk have been carried out (Di Benedetto *et al.*, 2020).

MATERIALS AND METHODS

Materials

ZLP was an *ex gratis* gift sample from Unichem Laboratories Ltd., Goa, India. *Moringa* gum was purchased from Yarrow Chem Products, Mumbai, India. Acrylamide and ceric ammonium nitrate (CAN) were purchased from VS Corporation, Chandigarh, India. Other ingredients, such as ethanol, di-calcium phosphate, PEG-4000, lactose, hydroxy propyl methyl cellulose (HPMC) K15, microcrystalline cellulose, magnesium stearate, acetone, as well as methanol, were purchased from Loba Chemie Pvt. Ltd., Mumbai, India.

Methodology

Characterization of ZLP

Drug identification by Fourier transformed infrared (FTIR)

The comparison between the obtained drug sample's FTIR spectrum with the standard FTIR spectrum of the pure drug and excipients used was performed. The ingredients were analyzed for the interactions and compared with the reported literature (Ahuja *et al.*, 2010).

Differential scanning calorimeter (DSC) study of the drug

The drug's thermograms were determined by using a DSC (Perkin Elmer). In a standard aluminum pan, a few mg of the finely powdered sample was sealed and heated at 10°C/minute between 40°C and 350°C. The experiment was carried out in a nitrogen environment, with a flow rate of 50 ml/minute (Ahuja *et al.*, 2010).

X-ray diffractometer (XRD) of the drug

Powder XRD studies were used to characterize the drug's solid state. The diffraction pattern was traced using an XRD (Xpert PRO) at room temperature from 0° to 80° (2 θ) diffraction angle with a scanning speed of 0.05 minutes⁻¹ (Ahuja *et al.*, 2010).

Scanning electron microscopy (SEM) of the drug

SEM (ZEISS, EVO 18, China) was used to examine the drug's surface morphology. The powdered sample, under a high vacuum, was mounted on double-sided adhesive carbon tape and sputter-coated with a thin film of gold. At various magnifications, the photomicrographs were taken with a 20 kV accelerating voltage (Ahuja *et al.*, 2010).

Modification of *Moringa* gum by the grafting technique

Microwave-assisted synthesis of polyacrylamide grafted *Moringa* gum using CAN as a free radical initiator

1 g of *Moringa* gum was dissolved in 40 ml distilled water. In 10 ml distilled water, an appropriate amount (5 ml) of acrylamide was dissolved and added to the above solution. They were thoroughly mixed before being transferred to the reaction vessel (250 ml beaker), where a catalytic amount of CAN (0.1 g w/w) was added. The reaction vessel was placed on the turntable of a domestic microwave oven (Samsung, MW71E, India), and

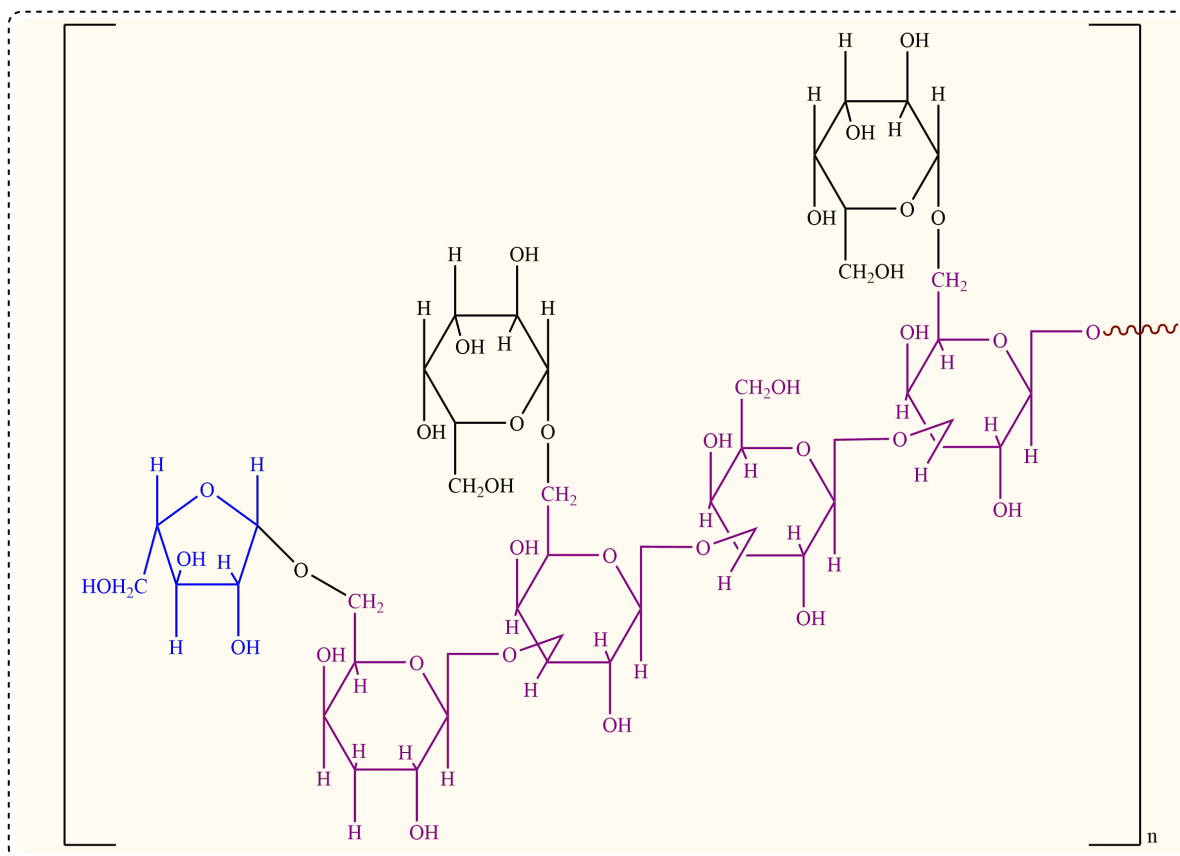


Figure 1. Chemical structure of *M. oleifera* gum.

microwave irradiation was performed at 800 W power. The microwave irradiation was stopped at one set of boiling (~65°C), and cooled by immersing the reaction vessel in cold water on a regular basis (Salaheldeen *et al.*, 2014).

The microwave irradiation cooling cycle was repeated until a gel-like mass was formed, or until a total of 3 minutes of irradiation time was used (in the absence of gelling). The reaction vessel and its contents were then cooled and left alone to allow the grafting reaction to complete. Later, an excess of acetone (30% v/v) was poured into the gel-like mass in the reaction vessel (Duan *et al.*, 2019). The graft copolymer precipitate was collected, dried at 40°C, pulverized, and sieved with a #100 sieve (Kokilambigai *et al.*, 2017; Shi *et al.*, 2019; Singh *et al.*, 2017). This was followed by purification (Panda, 2014).

The grafting efficiency (percentage GE) of this microwave-assisted synthesized grafted *Moringa* gum was determined as follows:

$$\% \text{ GE} = \frac{\text{Wt. of graft copolymer} - \text{Wt. of polysaccharide}}{\text{Wt. of monomer}} \times 100$$

Characterization of pure *Moringa* gum and modified *Moringa* gum

The swelling index (Grewal *et al.*, 2019), total ash, angle of repose (AR) (Elkhodairy *et al.*, 2014), bulk and tap densities, Hausner's ratio (HR) (Elkhodairy *et al.*, 2014), Carr's compressibility

index (Kumar and Rai, 2012), infrared spectral analysis (Singh and Kumar, 2018), DSC analysis (Rimpy *et al.*, 2017), XRD (Rimpy *et al.*, 2017), and SEM (Singh and Kumar, 2018) parameters of pure and modified *Moringa* gum were evaluated.

Swelling index

1 g of gum was blended with 96% ethanol (sufficient to damp the gum) and then 25 ml of purified water was added into a graduated cylindrical cylinder. The solution was shaken 1 hour per hand per 10 minutes and allowed to stand for 5 hours. The volume of the enlarged gum was then evaluated (Grewal *et al.*, 2019). The swelling index was represented as 1 g of the prescription after swelling, as volume in ml:

$$\frac{V_2 - V_1}{V_1} \times 100$$

where V_1 = the initial volume of material before hydration and V_2 = the final volume of hydrated material.

Total ash

The ash concentration was obtained after combustion in a furnace at 450°C to measure the remaining residue. The ash was boiled for 5 minutes using 25 ml 2M hydrochloric acid solution, and the insoluble material was filtered, cleaned, and ignited by hot water and the resulting weight was established. We then measured the proportion of insoluble acid ash (Elkhodairy *et al.*, 2014).

Angle of repose

The static rest angle “REAT” was calculated by a set funnel and standing cone system. A funnel was tightened on a flat plane with its tip 2 cm over a graphical paper. The powders were slowly pumped into the funnel before the cone apex reached the edge of the funnel (134) (Elkhodairy *et al.*, 2014). The median diameters of the base of the powder cones were determined and the tangent of the rest angle using the equation was measured as follows:

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

where θ = AR, h = height of granules, and r = radius of granules.

Bulk and tap densities

2 g was put in a 10 ml measuring cylinder for each of the powder samples and the volume, V_b , was observed without tapping each of the samples. The filled volume, V_t , was read after 100 taps on the table. The bulk and tap densities were determined by the following equations according to the ratio of weight and volume (V_b and V_t , respectively) (Elkhodairy *et al.*, 2014):

$$\text{Bulk density (BD)} = M/V_b$$

$$\text{Tapped density (TD)} = M/V_t$$

where M = weight of powder, V_b = volume occupied by powder without tapping, and V_t = volume occupied by powder after tapping.

Hausner's ratio

HR is an indirect powder flow facility table. The ratio of density to mass density was determined according to the following equation of the specimens (134–135) (Elkhodairy *et al.*, 2014):

$$\text{Hausner's ratio} = \text{TD} / \text{BD}$$

Carr's compressibility index

Carr's compressibility index specified the compression index of the powder blend. It is the straightforward measure for the measurement of the powder BD and TD and the rate it is packed (Kumar and Rai, 2012). The equation was determined as follows:

$$\text{Carr's index} = \text{TD} - \text{BD} / \text{TD} \times 100$$

Infrared spectral analysis of pure Moringa gum and modified Moringa gum

The *Moringa* gum and gum powder samples were triturated using potassium bromide agate and mortar with an IR (IR Hydraulic Press CAP-15T, PCI Analytics, Mumbai, India) pressing at an output of 75 kg/cm² per 30 seconds. At 75 kg/cm², the mixture was compressed into dishes. In FTIR (IR affinity I, Shimadzu) in the range of 4,000–400 cm⁻¹ was registered using the FTIR disk spectrum (Singh and Kumar, 2018).

DSC analysis of pure Moringa gum and modified Moringa gum

Moringa gum and grafted *Moringa* gum thermograms were obtained with a differential calorimeter scanning (Q10, TA systems, USA). A small amount (mg) of fine powder of the sample was sifted into a regular aluminum pan and heated at a rate of 40°C–350°C at 10°C/minute. The inert nitrogen atmosphere (50 ml/minute) analysis was carried out.

XRD of pure Moringa gum and modified Moringa gum

For the solid characterization of *Moringa* gum and grafted *Moringa* gum, powder XRD experiments were carried out. The diffractometer configuration was traced from 0°C to 80°C (2 pounds) with a 0.05 minutes to 1.1 scanning speed at room temperature by using XRDs (Miniflex II, Rigaku, Japan) (Rimpy *et al.*, 2017).

SEM of pure Moringa gum and modified Moringa gum

The *Moringa* gum and grafted *Moringa* gum surface morphologies were analyzed by SEM (ZEISS, EVO 18, China). The powdered sample was fixed on a double-sided adhesive carbon tape set on a holder and covered in a thin, high-vacuum gold film. At a various magnifications, the photomicrographs had a 20 kV acceleration voltage (Singh and Kumar, 2018).

Formulation of ZLP loaded-buccal disks of Moringa gum and grafted Moringa gum

Buccal disks were made in six batches, each with a different amount of gum or gum copolymer and lactose. To

Table 1. Composition of different batches of ZLP-loaded buccal disks.

Ingredients	MF1 (mg w/w)	MF2 (mg w/w)	MF3 (mg w/w)	MF4 (mg w/w)	MF5 (mg w/w)	MF6 (mg w/w)
ZLP	10	10	10	10	10	10
grafted <i>Moringa</i> gum	60	-	60	-	60	-
<i>Moringa</i> gum	-	60	-	60	-	60
Lactose	45	45	-	-	-	-
Dicalcium phosphate	-	-	45	45	-	-
MCC	-	-	-	-	45	45
HPMC	15	15	15	15	15	15
PEG-4000	25	25	25	25	25	25
Talc	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5
Total (mg)	160	160	160	160	160	160

summarize, *Moringa* gum or grafted *Moringa* gum (60 mg w/w), ZLP (10 mg w/w), PEG-4000 (25 mg w/w), lactose (45 mg w/w), dicalcium phosphate (45 mg w/w), HPMC K15M (15 mg w/w), microcrystalline cellulose (MCC) (45 mg w/w), talc (1.5 mg w/w), and magnesium stearate (3.5 mg w/w) were homogeneously mixed with the aid of a mortar and pestle, followed by compression in an IR hydraulic press (Hydraulic Press, CAP-15T) under a pressure of 50 kg/cm² for a dwelling time of 30 seconds (Table 1).

Evaluation of ZLP loaded-buccal disks

For evaluating ZLP loaded-buccal disks, several physical parameters include weight variation test for uniformity (Jangra *et al.*, 2013; Li and Castillo, 2020; Rani *et al.*, 2012), hardness test for crushing strength, friability test for durability, thickness test, and a percentage drug content for the tablet was performed.

Weight variation test

Ten disks were selected and weighed individually. Then the average weight and standard deviation (SD) was calculated. The test passes when not more than two disks deviate from average weight (Jangra *et al.*, 2013; Li and Castillo, 2020; Rani *et al.*, 2012).

Hardness

Hardness or crushing strength is the force required to break a disk in a diametric compression which was measured using Monsanto disks hardness tester. It is expressed in kg/cm² (Koirala *et al.*, 2021).

Disk friability

A preweighed sample (W_1) of 10 buccal disks was placed in the drum of a disk friability test apparatus (Remi Equipment's, Mumbai, India). The drum was rotated at 25 rpm for 4 minutes and the buccal disks were reweighed (W_2) (Koirala *et al.*, 2021). The (%) friability was calculated using the following equation:

$$(\%) = \left\{ W_1 - \frac{W_2}{W_1} \right\} \times 100$$

where

W_1 = Preweighed sample of buccal disks; and

W_2 = Reweighed sample of buccal disks.

Thickness

Ten randomly selected buccal disks were subjected to thickness testing by using the digital Vernier Caliper (YAMAYO digital caliper). Values are reported as mean \pm SD (Koirala *et al.*, 2021).

Percentage drug content

Drug content was determined by dissolving 1 disk (equivalent to 10 mg of drug) in methanol and kept in an

ultrasonicator for 20 minutes. The volume was adjusted to 100 ml with distilled water. The solution was filtered through Whatman filter paper no. 41, suitably diluted, and absorbance was measured at 254 nm using a UV spectrophotometer (Dhiman *et al.*, 2022).

Several additional parameters are discussed below

Mucoadhesive strength

The mucoadhesive strength of the formulated disks was determined with a texture analyzer by recording the force needed to separate the disks from freshly excised goat's gastric mucosal tissue (Rathee *et al.*, 2011). In a nutshell, gastric mucosal tissues from a goat were obtained from a local slaughterhouse and used right away. A cyanoacrylate adhesive tape fixed the test disks to the cylindrical probe (diameter 10 mm). The cylindrical probe (with attached tablet) was lowered down (speed maintained 0.5 mm/second) for making the contact of test disks and mucosal tissue. A force (1 N) was applied to the probe for a specified time (60 seconds). The probe was then moved upward (15 mm distance) with 0.5 mm/second speed. The mucoadhesive strength was obtained, i.e., the maximum force was required to separate the disks from the mucosal surface (Shaikh *et al.*, 2011).

Mucoadhesion time

The adhesion of the formulated disks was carried out by determining the mucoadhesion time to the goat's gastric mucosa (Reddy *et al.*, 2011). The gastric mucosal tissue was first pasted using cyanoacrylate tape onto a slide (glass). On the surface of the test disks, a drop (pH 6.8) was poured, making the disks wet so that they could adhere to the mucosal tissue. A beaker buffer medium of pH 6.8 (200 ml) was filled, and the temperature was maintained to 37°C \pm 0.5°C. The slide with the pasted disks on mucosal tissue was kept inside the beaker. The stirrer was allowed to rotate at 50 rpm and the time required for the disks to detach from the goat's gastric mucosal tissue was recorded as mucoadhesion time (Shaikh *et al.*, 2011).

In-vitro swelling percentage (SP) of tablet formulation in (pH 6.8)

In a petri dish, individual disks were soaked in buffer solutions (pH 6.8) after weighing. After the specified time (2, 4, 6, 8, 12, and 24 hours), the disks (swollen) were removed and dried superficially using blotting paper. The weight of the swollen tablet was then noted, and the SP calculation was done using the following formula:

$$SP = \frac{w_f - w_i}{w_i} \times 100$$

where w_f is the final weight of the sample after swelling and w_i is the initial weight of the sample.

Also, the physical observation of the disk's swelling was recorded by measuring the diameter of the disks using graph paper stuck to the base of a petri dish (Grewal *et al.*, 2019).

In-vitro drug dissolution studies

Dissolution studies of various mixtures and marketed formulations (control) were carried out in 900 ml of phosphate buffer (pH 6.8) at $37^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and a stirrer rotation speed of 50 rpm using a United States Pharmacopoeia dissolution apparatus equipped with a paddle stirrer (Type II). At 1, 2, 4, 6, 8, 10, and 12 hours, a 5ml aliquot of dissolution medium was removed and replaced with the same amount of buffer using a pipette. The samples were appropriately prepared and analyzed spectrophotometrically at a wavelength of 254 nm (Jangra *et al.*, 2013; Rani *et al.*, 2012).

Mathematical models for drug release

The cumulative amount of ZLP released from formulated disks at various time intervals was fitted to zero-order kinetics, first-order kinetics, the Higuchi model, the Hixon–Crowel model, and the Korsmeyer–Peppas model to characterize the mechanism of drug release.

Data analysis

The results of the one-way analysis of variance (ANOVA) (Sigma Stat 3.5 software) were analyzed using the student's *t*-test. The difference was considered statistically significant if it was less than the probability level of 0.05.

Stability studies for the optimized batch

For the determination of the effect of temperature, humidity, moisture, and light on the drug's quality, stability studies were carried out. These findings are used to determine the storage conditions, the test period, and shelf life (Li and Castillo, 2020). The optimized formulation (F3) was stored in a stability chamber at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity for a period of 1 month. The samples were analyzed for various parameters after 1 month by spectrophotometer at 254 nm.

RESULTS AND DISCUSSION

Characterization of the drug

Drug identification by FTIR

The IR spectrum of the drug clearly shows the peaks of the various functional groups present (Ahuja *et al.*, 2010). The IR spectrum exhibits characteristic bands of the stretching vibration of C-H stretch vibrations at $3,087.7\text{ cm}^{-1}$ and $2,933.7\text{ cm}^{-1}$. It also exhibits characteristic bands of stretch vibrations of $-\text{C}=\text{N}$ (alcohol) at $1,614.4\text{ cm}^{-1}$ and $1,223.5\text{ cm}^{-1}$ for C-N. It shows stretch bands of $-\text{C}=\text{C}-$ (aromatic) at $1,576.3\text{ cm}^{-1}$. ZLP exhibits strong absorption peaks at $2,232.7\text{ cm}^{-1}$ and $1,651\text{ cm}^{-1}$ suggesting the existence of cyanide and amide carbonyl groups, respectively. The IR spectrum of a pure drug (ZLP) obtained is shown in Figure 2 (Singh and Kumar, 2018).

Differential scanning calorimeter

In the case of pure drug, a sharp endotherm was observed at 184.94°C (Fig. 3) (Rimpy *et al.*, 2017). The observed peak was

compared to the drug's standard peak, which indicates the purity of the drug.

SEM studies of the pure drug (ZLP)

The drug particles show a spherical shape, smooth surface, and crystalline geometry as observed both at 2,000 and $8,000\times$ (Fig. 4) (Rimpy *et al.*, 2017).

XRD of the drug

From the diffractogram of the drug, sharp peaks can be observed at $2\theta = 10, 14, 16, 18, 21, 22, 25, 26,$ and 29 , which show its crystalline nature in the pure form shown in (Fig. 5) (Ahuja *et al.*, 2010). This shows that the drug, which was in crystalline form, has reduced to an amorphous form.

Modification of Moringa gum by grafting technique: synthesis of grafted Moringa gum

The properties of *Moringa* gum were modified via microwave-assisted graft copolymerization of acrylamide onto *Moringa* gum (Elkhodairy *et al.*, 2014). *Moringa* gum is composed of galactose (25.9%), rhamnose (5.6%), and traces of uronic acid with pendent hydroxyl groups. When polysaccharides are microwave irradiated, the pendant hydroxyl groups exhibit localized rotation, resulting in dielectric heating and increasing the reaction rates at these groups (Elkhodairy *et al.*, 2014). Additionally, microwave irradiation decreases the activation Gibbs energy of the reactions, resulting in faster reaction rates. Additionally, CAN, which was used as a free radical initiator in the reaction, generates free radicals that abstract hydrogen atoms from polysaccharides molecules and generate macro radicals (Elkhodairy *et al.*, 2014). These free radicals then reacted with the acrylamide monomer to form acrylamide free radicals, initiating a chain reaction that results in the formation of *Moringa* gum-g-poly (acrylamide) and poly(acrylamide) homopolymers.

Graft copolymer synthesis is a combination of microwave-assisted and conventional methods, in that it is based on a free radical mechanism that uses microwave radiation in conjunction with a chemical-free radical initiator (CAN) to create extra radical sites on the *Moringa* gum backbone. By varying the concentrations of CAN and acrylamide (monomer), different grades of the graft copolymer were formed. In each case, the reaction mixture was microwave irradiated until it solidified into a viscous gel-like mass. The optimized grade was determined by its higher grafting percentage. When the microwave power is kept at 800 W, the grafting is optimized with a 5 g acrylamide and a 0.1 g CAN in the reaction mixture (~50 ml). The optimal batch with a concentration of CAN is an electron-deficient molecule. As a result, it borrows electrons from *Moringa* gum's alcoholic oxygen to form a new bond. The optimal calculated parameters were 1.0 g *Moringa* gum, 0.1 g CAN, and 5.0 g acrylamide, which resulted in a graft copolymer with a GE of 65%. This bond is more polar (than the OH bond), and it breaks easily in the presence of microwave irradiation, forming a free radical site on the backbone of *Moringa* gum.

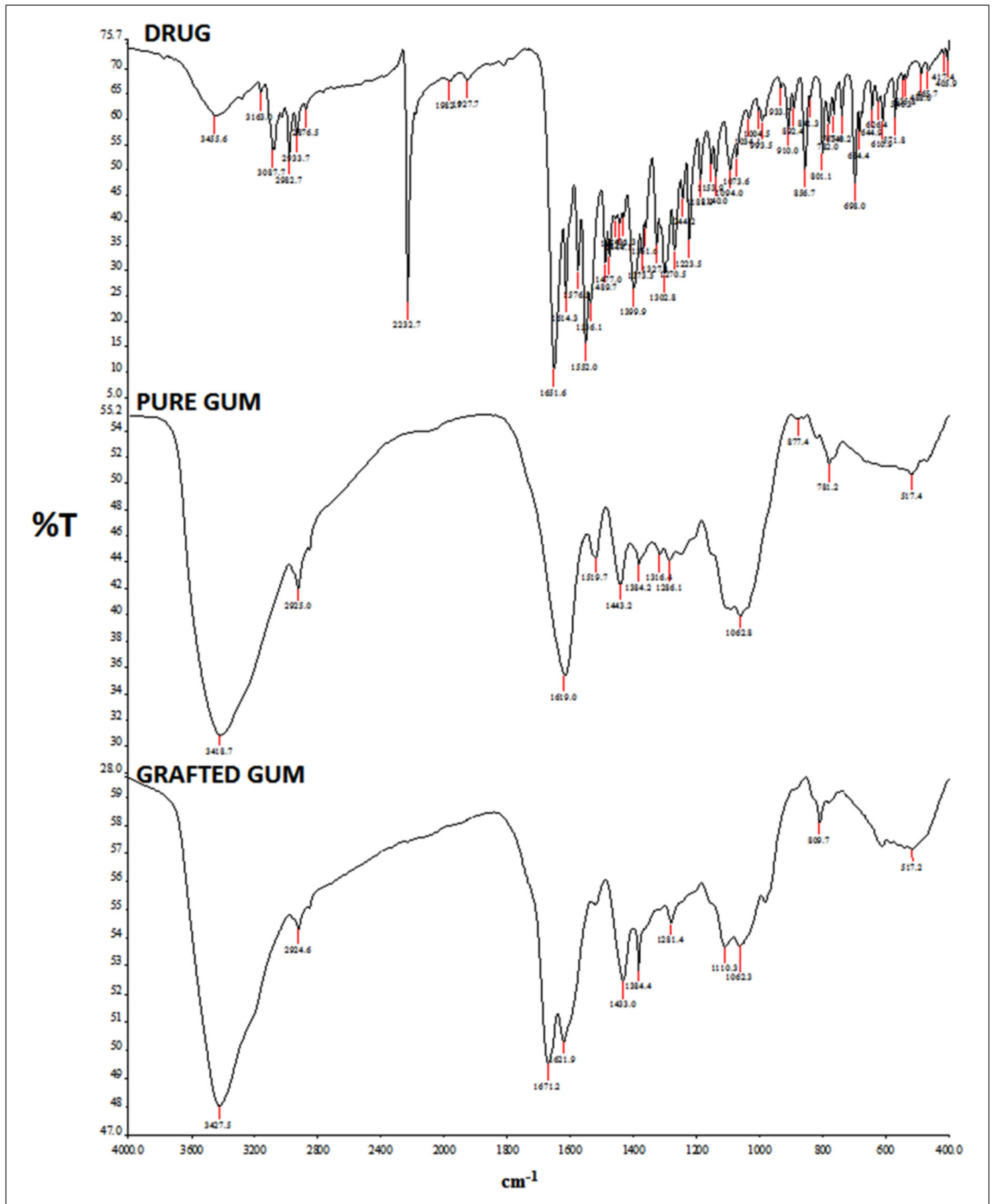


Figure 2. FTIR spectrum of the drug (ZLP), pure gum, and grafted gum.

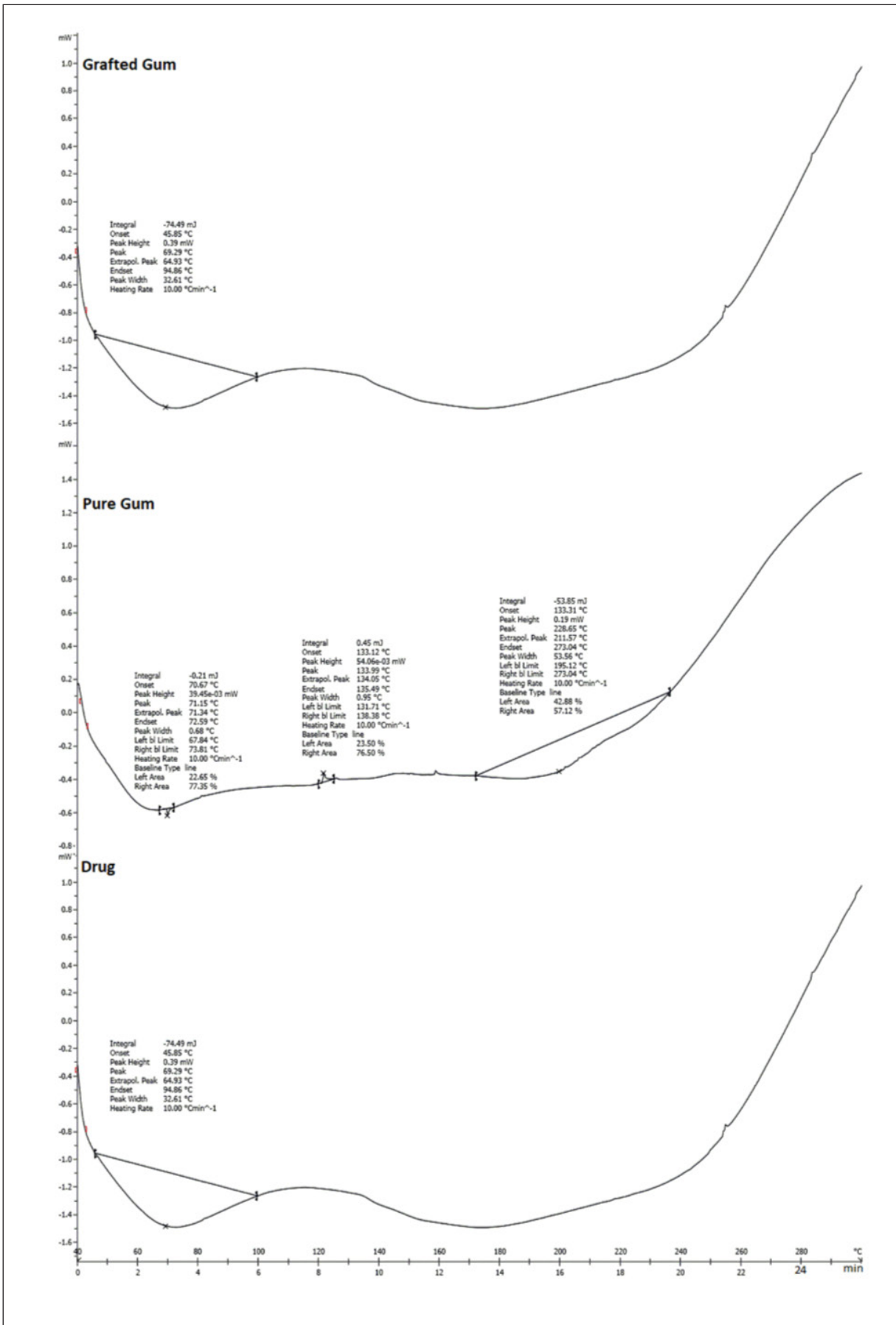


Figure 3. DSC showing of drug (ZLP), pure gum, and grafted gum.

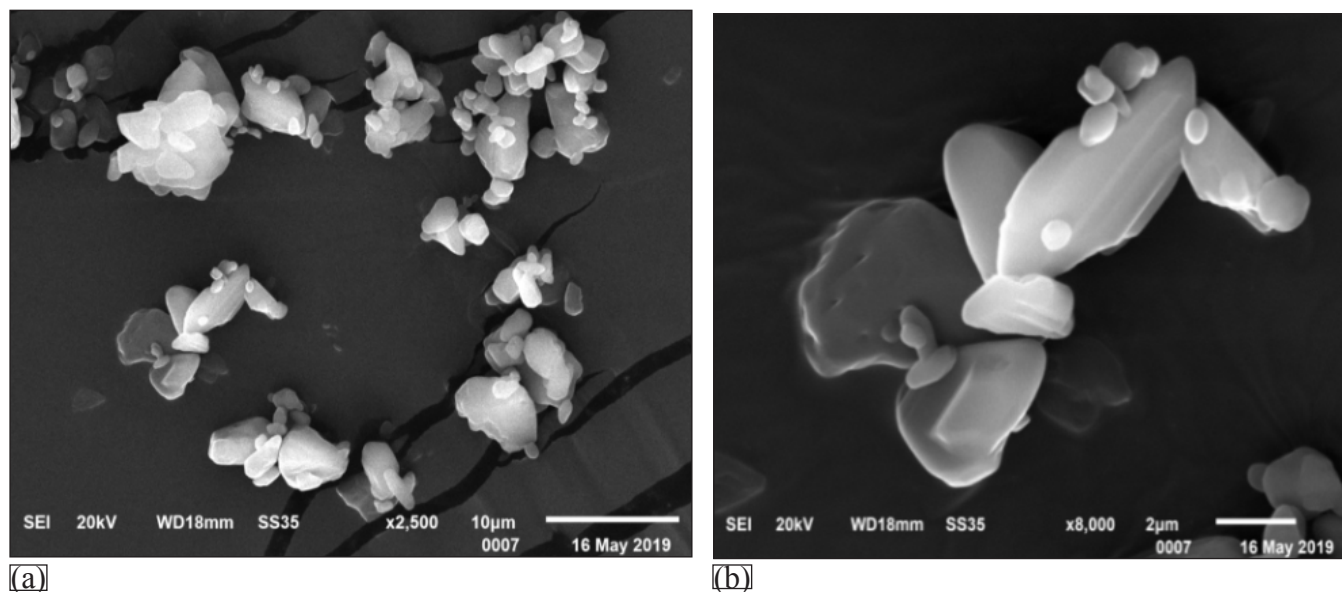


Figure 4. SEM images of pure drug showing shape and surface topology. (a) 2,000 \times and (b) 8,000 \times .

Physicochemical characterization of pure gum and modified *Moringa* gum

Swelling index

An optimized method was used to calculate the swelling index (Koirala *et al.*, 2021). The grafted gum shows a marginally higher SP in phosphate buffer (pH 6.8) compared with pure *Moringa* gum (Kumar and Rai, 2012; Singh *et al.*, 2017).

Powder flow properties

The BD, TD, AR, HR, and Carr's index of pure gum as well as modified *Moringa* gum are shown in Table 2. Dried gum powder shows excellent flow properties and compressibility, making them suitable for direct compression tableting (Singh *et al.*, 2017).

Ash content

The total ash content of pure *Moringa* gum and modified *Moringa* gum is presented in tabular form (Table 2).

PRECOMPRESSION PARAMETERS

HR was <1.13 , indicating that all powder blends, i.e., MF1–MF6 have good flow properties. The compressibility index of powder blend MF1–MF6 was between 6% and 12%, indicating good flow properties. The various formulations showed an AR between 25°C and 30°C, which indicates that all formulation blends have good flow properties (Fig. 6).

Postcompression parameters

The weight variation, tablet thickness, hardness, friability, and drug content have all been evaluated and illustrated as postcompression parameters (Fig. 7). The mucoadhesion time and mucoadhesion strength are shown in Figure 8.

In line with a previous study (Grewal *et al.*, 2019), the introduction of a new functional group by grafting resulted in enhanced charge density (anionic charge) on modified *Moringa* gum, making it susceptible to bind to the opposite charge present on the mucin layer, thus increasing the mucoadhesion strength and mucoadhesive time. Compared to the formulation (MF2, MF4, and MF6) (6 hours), the

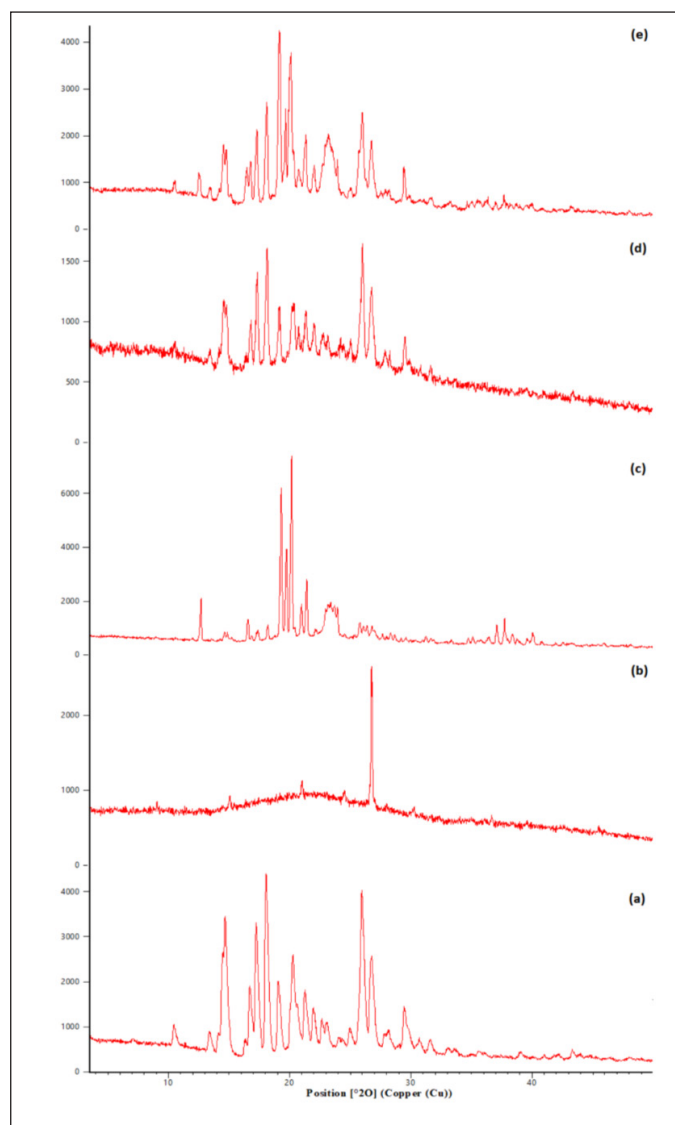


Figure 5. XRD diffractogram showing (a) drug, (b) pure gum, (c) modified gum, (d) drug and pure gum physical mixture, and (e) drug and modified gum.

Table 2. Physicochemical characterization of pure gum and modified *Moringa* gum.

S. No.	Parameters	<i>Moringa</i> gum	Modified <i>Moringa</i> gum
1.	AR (°)	37.20 ± 2.22	29.60 ± 2.15
2.	Bulk densities (g/ml)	0.42 ± 0.01	0.45 ± 0.01
3.	Tapped densities (g/ml)	0.51 ± 0.02	0.53 ± 0.02
4.	HR	1.21 ± 0.14	1.17 ± 0.11
5.	Compressibility index (%)	17.64 ± 0.35	15.09 ± 0.27
6.	Swelling index	78.43	94.57
7.	Total ash content (% w/w)	1.10 ± 0.12	0.96 ± 0.05

mean ± SD, *n* = 3.

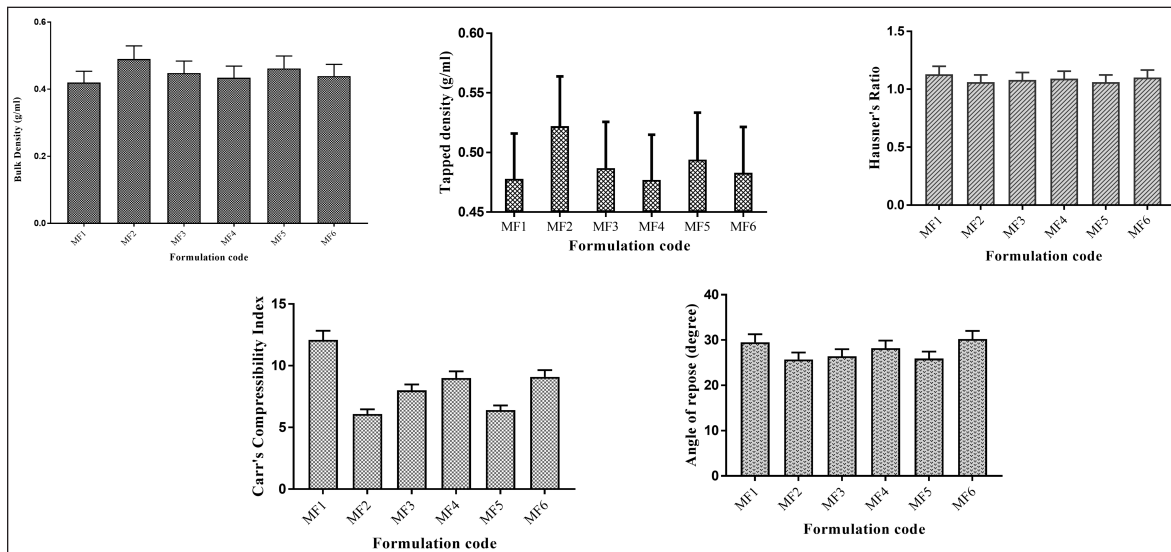


Figure 6. Precompression parameters of ZLP buccal disks using *Moringa* gum and grafted *Moringa* gum. *(mean ± SD; *n* = 3).

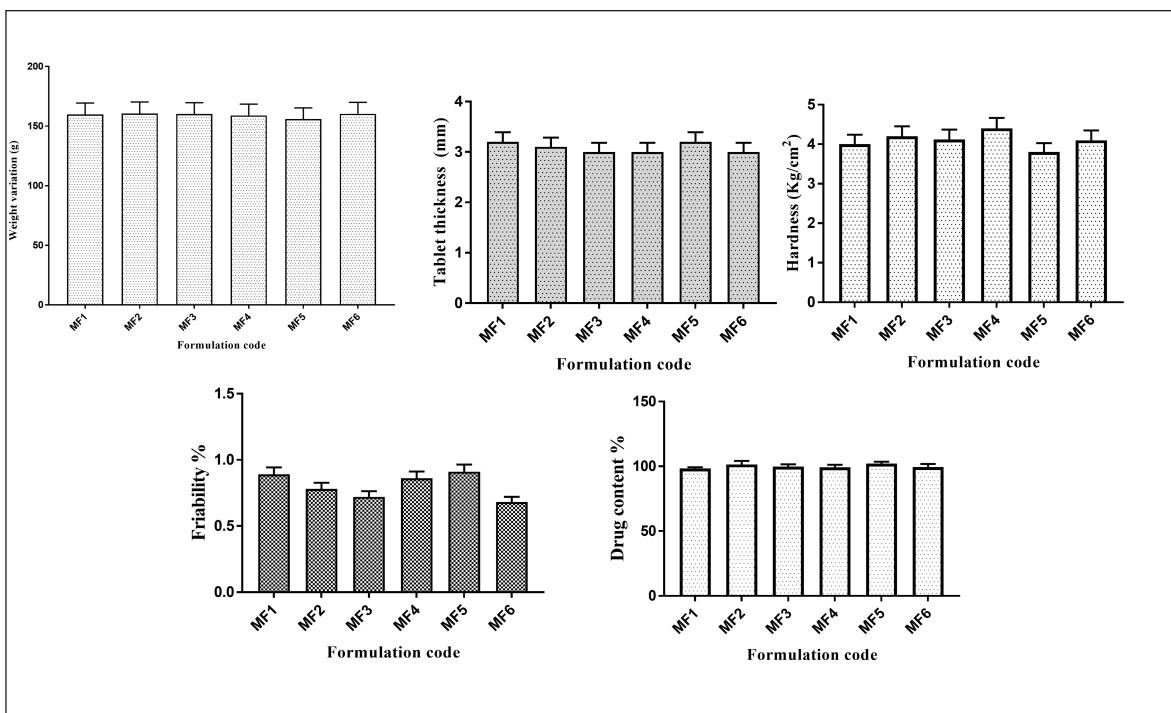


Figure 7. Postcompression parameters of ZLP buccal disks using grafted *Moringa* gum. (mean ± SD; *n* = 3).

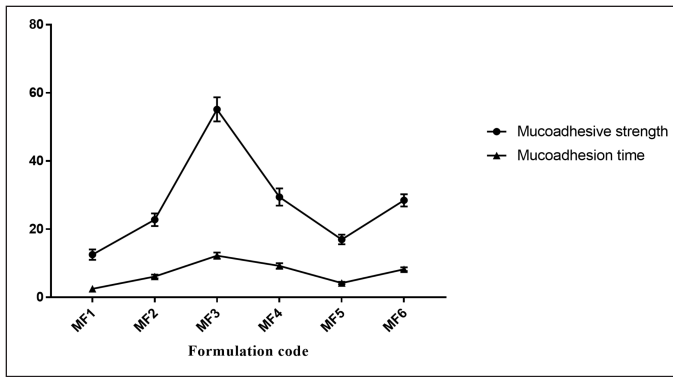


Figure 8. Mucoadhesive strength and mucoadhesive time of ZLP buccal disks using grafted *Moringa* gum. ^a(mean ± SD; n = 3).

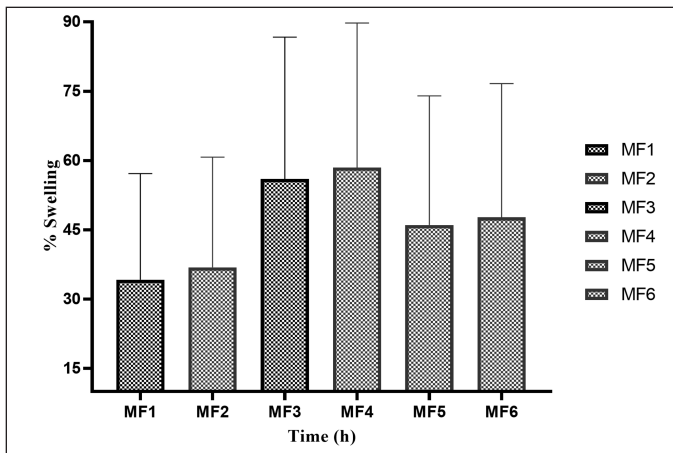


Figure 9. SPs of ZLP buccal disk in pH 6.8 ^a(mean ± SD; n = 3).

formulations containing modified *Moringa* gum (MF1, MF3, and MF5) required a longer time (12 hours) for complete detachment. The possible reason might be that the modified *Moringa* gum has uronic acid molecules containing $-COO^-$ groups, while the mucosal mucin protein surface has $-NH_3^+$ groups, both carrying opposite charges.

In-vitro SP of buccal disks in (pH 6.8)

The weight gain and swelling were proportional. The SPs of ZLP buccal disks (pH 6.8) are shown in Figure 9.

In-vitro dissolution study

The *in-vitro* dissolution study of ZLP mucoadhesive buccal disk (MF1–MF6) with control (marketed formulation) is shown in Figure 10. The optimized batch (MF3) showed a drug release of 95.22% in 12 hours.

Drug release kinetics and mechanism

Data from ZLP buccal disks drug release kinetics fitted to zero order, first order, Korsmeyer–Peppas, Higuchi, and Hixon–Crowel release models are shown (Fig. 11). The “n” values obtained ranged from 0.54 to 0.80. The best-fitted model, as depicted in, was found to be the Korsmeyers–Peppas model. The mechanism involved in the Korsmeyers–Peppas model was found to be a combination of diffusion and erosion-based drug release.

ANOVA- analysis of variance

The analysis of variance indicated that swelling behavior, mucoadhesion strength, mucoadhesion time, and %CDR (12 hours) of ZLP-loaded buccal disks were found to be significant ($p < 0.05$) and adequate, without a significant lack of fit.

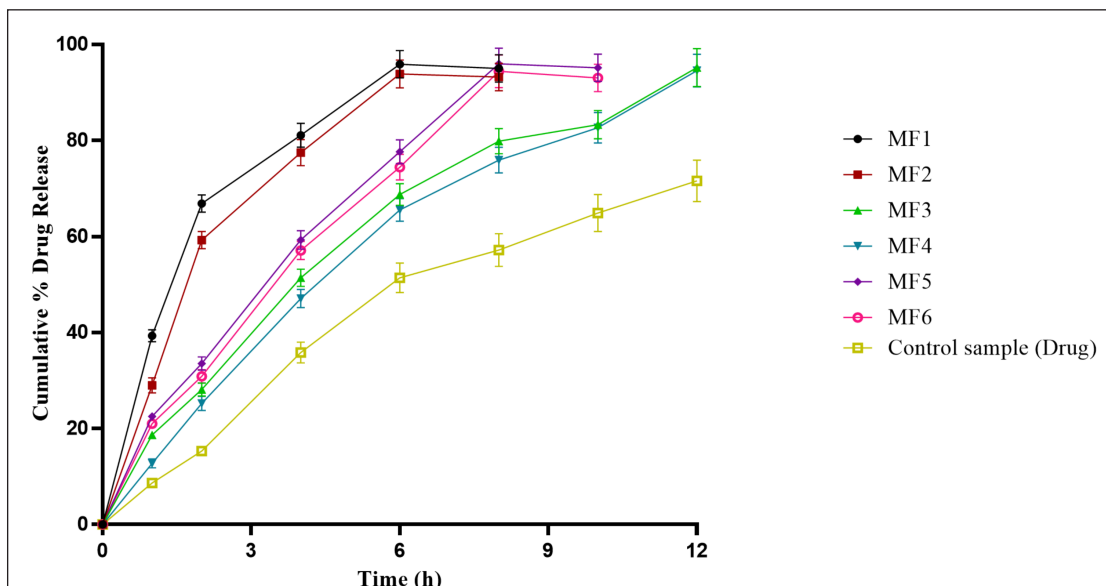


Figure 10. *In-vitro* drug release data of drug-loaded formulation (MF1–MF6) ^a(mean ± SD; n = 3).

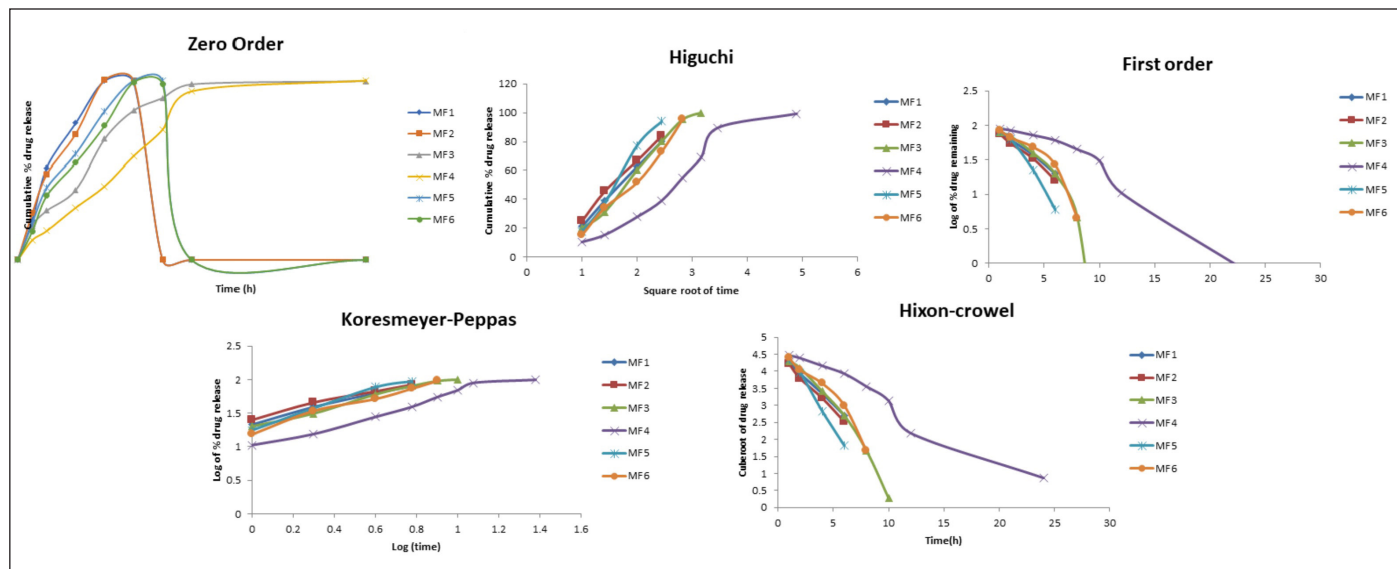


Figure 11. Drug release model of ZLP buccal disks.

Table 3. Stability data of the optimized batch of ZLP buccal disks.

Evaluation parameters for MF3	Initial	1 month
Hardness (kg/cm ²)	4.12	4.02
Drug content (%)	99.81 ± 1.81	98.10 ± 0.13
Cumulative % drug release	95.22 ± 3.95	94.67 ± 0.36

Stability study for optimized batch (MF3)

The accelerated stability studies' results showed no appreciable modification observed in hardness, drug content, and cumulative percentage drug release in the stored tablets under specified conditions (Table 3) (Li and Castillo, 2020).

CONCLUSION

This study aimed to develop and evaluate ZLP buccal disks made of grafted *Moringa* gum polymer. Additionally, a modified polymer was used to enable controlled release of ZLP via the buccal route, avoiding extensive hepatic metabolism, increasing bioavailability, and avoiding early morning awakening without the use of a middle-of-the-night dose. *Moringa* gum was modified using graft copolymer synthesis. This method combines microwave and traditional methods of synthesis. It is based on the free radical mechanism. It utilizes microwave radiation with a radical initiator (CAN) to make free radical sites on the backbone of *Moringa* gum. ZLP buccal disks were developed to investigate the grafted *Moringa* gum further. The disks containing grafted *Moringa* gum demonstrated a longer mucoadhesion time when compared to unmodified *Moringa* gum. Based on the findings of this study, modified *Moringa* gum (optimum batch MF3) proved to have excellent potential as a mucoadhesive polymer that can be effectively used to formulate modified ZLP buccal drug delivery systems able to extend the release of the drug, thereby avoiding

early hours awakening, improving sleep quality, and enhancing its bioavailability.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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