A novel oral medicated jelly for enhancement of etilefrine hydrochloride bioavailability: *In vitro* characterization and pharmacokinetic evaluation in healthy human volunteers

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**A B S T R A C T**

Etilefrine hydrochloride (ET) is a water-soluble drug that is used to treat hypotension, but it has a bitter taste and low bioavailability due to undergoing the first-pass effect. Thus, this study aimed to develop and evaluate oral medicated jelly (OMJ) containing ET that could offer an easily taken palatable dosage form with higher bioavailability. OMJ is a novel palatable drug delivery system that can easily be taken by pediatric and geriatric patients, as well as those with dysphagia. Moreover, OMJs offer rapid disintegration in saliva and rapid drug absorption through the buccal mucosa, avoiding the first-pass effect and increasing the drug bioavailability. Natural polymers such as pectin, guar gum, xanthan gum, tragacanth gum, and sodium alginate were used as jellifying agents, with the addition of calcium chloride as a crosslinking agent, to prepare OMJs using the heat and congealing method. The prepared OMJs were investigated by testing their viscosity, *in vitro* release, and texture analysis of firmness, consistency, stickiness, cohesiveness, springiness, gumminess, and chewiness using a texture analyzer. A full factorial design (2^1 × 5^1) was utilized to select the optimized OMJ. The optimized OMJ (J2), containing 4% pectin, had a 7563 ± 55 cps viscosity, 8.32 ± 0.21 N firmness, 5.72 ± 0.18 J consistency, 1.30 ± 0.04 mJ stickiness, and 96.02 ± 3.74% ET dissolved after 10 min. ET release was significantly increased (greater than 4-fold) from the optimized OMJ compared with the market tablet. Moreover, the obtained results clarified the stability and the acceptable palatability of the optimized OMJ. The clinical investigation on healthy human volunteers revealed that the optimized OMJ (J2) had significantly higher Cmax (1.7 folds) when compared with the market tablet with a relative bioavailability of 154.55%. Therefore, OMJs can be considered as promising, palatable, and easily swallowed dosage form that could enhance the bioavailability of drugs undergoing the first-pass effect.

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1. Introduction

Low blood pressure, or hypotension, is a disease that often leads to heart disease and vascular disorders in the brain. It is caused by genetic factors and/or conditions like cardiac ailments, anemia, and hormone or nerve disorders (Huang et al. 2017). Also, it is closely associated with physical condition and age (Rutan et al. 1992). Etillefrine hydrochloride (ET) is utilized in pharmacotherapy to treat hypotension. It is an α-β adrenergic receptor agonist that increases blood pressure (Bouaggad et al. 2000). Etillefrine is freely soluble in water (13.8 mg/ml), soluble in ethanol, and practically insoluble in methylene chloride (Sakata and Onishi 2020). Its molecular weight is 217.69 g/mol, and its pKa value was previously reported to be 8.9–9.0 (Onishi and Sakata 2018). ET is clinically available in a dosage form as parenteral injections and oral tablets. However, parenteral injection of ET is occasionally associated with irritation, pain, and necrosis around the injection site (Sakata and Onishi 2020). Moreover, it causes excessively high plasma levels, which lead to abnormal cardiovascular states, like lung edema, arrhythmia, cerebral hemorrhage, and cardiac palpitations (Karasawa et al. 1992). Oral ET tablets suffer from the first-pass effect, which reduces their bioavailability (50%) and decreases
their systemic drug concentration (Sakata and Onishi 2020). Hence, an alternative ET dosage form is needed to overcome the many disadvantages of conventional dosage forms. This encouraged different researchers to develop ET formulations to increase the drug bioavailability and reduce its oral and parenteral side effects. In 2018, Onishi and Sakata developed ET buccal aqueous droplet. They stated that ET buccal aqueous droplet showed a significantly higher bioavailability (2-fold) than the intragastric administration (Onishi and Sakata 2018). In 2020, the same authors developed ET buccal fast dissolving tablets that showed rapid disintegration and in vitro drug release (more than 50 % being released after 3 min). These tablets achieved similar plasma concentration–time curve to that of the previous aqueous droplets (Sakata and Onishi 2020). In 2021, the same authors developed ET buccal fast dissolving films that showed a rapid drug release (more than 70 % at 2 min) and achieved higher bioavailability than the intragastric administration (1.15-fold) but didn’t achieve higher bioavailability than the previous aqueous droplets nor the fast dissolving tablets (Onishi and Sakata 2021).

Oral medicated jelly (OMJ) is a novel oral mucosal drug delivery system. It offers many advantages over the abovementioned drug delivery systems. It is a palatable dosage form that has the advantages of both liquid and solid dosage forms. The proposed technique could be considered as one of the alternative techniques for modern drug formulations due to its ease of preparation and low-cost excipients (Karaiskou et al. 2020). The polymers used in OMJs preparation are safe, edible, biocompatible, biodegradable, locally available, tolerated well by patients, environmentally friendly, and low cost (Šešlija et al. 2018). Furthermore, OMJs are accepted by patients in the pediatric and geriatric population, as well as those with dysphagia (Gomaa and Ayoub 2021; Kim et al. 2020). Using OMJs is feasible in the local treatment of oral cavity diseases as well as the treatment of systemic conditions. They can overcome all the limitations of the available conventional dosage forms (Tsuij et al. 2006). OMJs offer rapid dissolution in saliva without the need for water, and rapid drug absorption through the buccal mucosa (pre-gastric absorption), bypassing the first-pass effect. Therefore, it significantly offers early onset of action and greater bioavailability of the drug than the available oral tablets (Gomaa and Ayoub 2021; Kim et al. 2020). Commercial oral medicated jelly products of metformin hydrochloride, tadalaflil, sildenafil, acyclovir, calcium gluconate, donepezil hydrochloride, amloidpine, and alendronate are available in some countries (Kim et al. 2020; Almurisi et al. 2020). In addition, several studies have also prepared medicated jellies, such as ondansetron hydrochloride jelly, vitamin C jelly, carbamazepine jelly, and salbutamol sulfate jelly (Almurisi et al. 2020). Natural polymers like pectin, guar gum, xanthan gum, and sodium alginate were used in this study as jellifying agents to achieve the desired stiffness for the prepared OMJs. Calcium chloride was added as a crosslinking agent. Pectin, similar to sodium alginate, forms strong gels via intramolecular crosslinking with divalent ions, such as calcium, due to the polyanionic nature of both components (Patel et al. 2020; Šešlija et al. 2018). Such cations can fix multiple binding sites to pectin or sodium alginate and form a three-dimensional network that provides swelling by holding large amounts of water molecules in the structure (Freitas et al. 2013; Junmahasathien et al. 2018). Moreover, gums obtained from natural sources also undergo crosslinking via Ca²⁺ cations. The crosslinked gums have improved viscosity and textural properties compared with the natural gums (Bakre and Akinsanya 2019). Calcium chloride was chosen because it is cheap, non-toxic, and environmentally friendly (Bakre and Akinsanya 2019). The Vascon® 5 mg market oral tablet, used as a reference in this study, causes side effects such as bradycardia, arrhythmias, and respiratory difficulty (Attia et al. 2016). The goal of this study was to develop and optimize ET OMJ using natural substances to avoid the many side effects of conventional ET dosage forms, increase patient compliance, better taste mask, and increase ET bioavailability by avoiding the first-pass effect.

2. Materials and method

2.1. Materials

Etilefrine hydrochloride (ET) was obtained from CID Co. (Cairo, Egypt) (E180201). Pectin was acquired from Oxford Lab Chem (Mumbai, India). Guar gum, xanthan gum, tragacanth gum and sodium alginate were provided by Alfa Aesar GmbH & Co. (Karl-sruhe, Germany). Sucrose, methylparaben, and propylparaben were provided by El- Gomhouria Chemical Co. (Cairo, Egypt). Calcium chloride (CaCl₂), potassium dihydrogen sulfate, and disodium hydrogen phosphate were provided by Merck (Damstadt, Germany). Citric acid was provided by Carl Roth GmbH & Co. KG (Karl-sruhe, Germany). Rosuvastatin, the internal standard, was obtained from Global Napi Co. (Cairo, Egypt) (patch number RV0140614). Vascon® 5 mg market oral tablets were provided by Hi Pharm, Egypt.

2.2. Compatibility of etilefrine with the used polymers

Differential scanning calorimetry and Fourier-transform Infrared spectroscopy were utilized to examine any possible interactions between ET and any of the utilized jellifying agents (pectin, guar gum, tragacanth gum, xanthan gum, and sodium alginate). The examined physical mixtures, composed of ET and each of the utilized jellifying agents, were in a ratio of 1:1 to maximize the likelihood of observing any interactions (Vueba et al. 2004).

2.2.1. Differential scanning calorimetry (DSC)

Thermal analysis of ET and the examined physical mixtures was carried out utilizing DSC (DSC-60, Shimadzu Corp., Kyoto, Japan) to assess the thermotrop properties and the possible incompatibilities between the drug and each of the used jellifying agents. Purified indium (99.9 %) was used in the reference pan. Each sample (3 mg) was placed in aluminum pans and heated to a temperature of 25–200 °C at a rate of 10 °C/min in an inert nitrogen flow (25 ml/min) (Hosseini et al., 2022; Alves et al. 2020).

2.2.2. Fourier-transform infrared spectroscopy (FTIR):

FTIR analysis of the samples was investigated to explore any possible chemical inter-molecular interactions between ET and each of the used jellifying agents utilizing Shimadzu, IRAffinity-1, Kyoto, Japan) (Hosseini et al., 2022). FTIR spectra of each sample were determined using the KBr disc technique with spectra between 4000 and 600 cm⁻¹. Smoothing of the spectra and the baseline correlation procedures were applied (Alves et al. 2020).

2.3. ET oral medicated jelly preparation

OMJs loaded with ET were prepared using the heat and congealing method (Gomaa and Ayoub 2021). All the utilized ingredients were weighed accurately. In one beaker, a precise amount of the natural jellifying agents (pectin, guar gum, tragacanth gum, xanthan gum, and sodium alginate) were gradually added to boiled distilled water (10 ml) with uniform and continuous stirring utilizing a magnetic stirrer (Wheaton, Rc-2, Japan). This dispersion was stirred for 25 min to aid in the hydration of the jellifying agents (Karaiskou et al. 2020). After completely dissolving the jellifying agent, calcium chloride (0.5 % w/v), utilized as the crosslinking agent, was added to that beaker (Patel et al. 2020; Bakre and...
Akinsanyam 2019). In another beaker, sugar syrup was prepared by dissolving 67.7 gm of sucrose in distilled water (100 ml) (Katman et al. 2014). Next, 60 ml of the prepared syrup was added to the first beaker. Subsequently, citric acid (1 % w/v) and propylene glycol (3 % w/v) were added to the above mixture with continuous stirring. Propylparaben (0.02 % w/v) and methylparaben (0.18 % w/v) were added to that solution with continuous and uniform mixing. Thereafter, the accurately weighed amount of ET was dissolved in a small amount of hot water and added before the jelly was allowed to set and mixed well to ensure the uniform distribution of the drug. Strawberry flavoring agent (0.1 % w/v) and amaranth coloring agent (0.1 % w/v) were added (Kim et al. 2020). Next, the final volume of the mixed solution was increased to 100 ml using purified hot water with continuous stirring. All these steps were carried out at 90 °C using a hot plate magnetic stirrer at 1500 rpm. Subsequently, the whole prepared solution was poured into suitable molds and allowed to cool in order to form a jelly-like texture. Finally, the prepared jellies, each contained 5 mg ET, were properly wrapped with butter paper and stored in a dry place (Gomaa and Ayoub 2021).

2.4. Study statistical design

Full factorial design (2^1 × 5^1) was studied to apply the effect of the different variables on the characteristics of ET OMJ by using design expert software (Stat-Ease Inc., Minneapolis, MN, USA). This design included two independent variables: the jellifying agent type (X1) and the jellifying agent percentage (%w/v) (X2). The inspected responses were viscosity (Y1), firmness (Y2), consistency (Y3), stickiness (Y4), and percentage of ET dissolved after 10 min (%ET dissolved after 10 min) (Y5). This design required the performance of ten runs; each run was triplicated to detect the results repeatability (Araujo et al. 2010; Khuri and Mukhopadhyay 2010). Table 1 displays the composition of the formed OMJs. The optimum OMJ was chosen after the calculation of desirability.

2.5. Characterization of the prepared ET OMJs

2.5.1. Weight variation and content uniformity

The prepared OMJs were weighed separately utilizing an electrical balance (Sartorius C224, Goettingen, Germany), then the mean weight was estimated. The individual weight of each OMJ was compared with the mean weight to determine the weight variation degree (British Pharmacopoeia Commission 2008).

Content uniformity = \( \frac{\text{Actual ET amount in OMJs}}{\text{Theoretical ET amount in OMJs}} \times 100 \)  \( \text{(1)} \)

Each test was repeated three times.

2.5.2. pH determination

The pH of the prepared OMJs was assessed at room temperature using a digital pH meter (Hanna-213, Lisbon, Portugal). 0.5 g of each prepared OMJ was dissolven in distilled water (50 ml) to prepare a 1 % solution. Then the pH was determined by dipping the pH meter’s electrode in the resulting solution and allowing it to equi-
librate for one minute (Pandey et al. 2010). This test was carried out in triplicate.

2.5.3. Syneresis

Syneresis means the jelly contraction during storage where water separates from the jelly, resulting in a reduction in the quality of the product (Silva et al. 2019). The prepared OMJs were tested for any signs of syneresis at (8 °C ± 1 °C) and at room temperature (25 °C ± 5 °C) for 24 h (Almurisi et al. 2020).

2.5.4. Viscosity

Viscosity is a vital parameter for evaluation in oral mucosa formulations. The viscosity of the prepared OMJs can affect their mechanical characteristics and the release of the drug. The viscosity of each ET OMJ was determined utilizing a Brookfield cone and plate rheometer (CPE-40 spindle, DV3T, MA, USA) (Tomczykowa et al. 2018). This test was repeated in triplicate, and the mean viscosity ± SD was recorded.

2.5.5. Texture analysis

Texture profile analysis (TPA), often called the “two-bite test,” is employed to imitate the mouth’s biting action (Xu et al. 2020). Recently, it has become a valuable technique in the pharmacy field to characterize semisolid dosage forms (Jones et al. 1996). This is in accordance with Coviiolo et al., who confirmed the potentiality of the TPA in the pharmacy field (Coviiolo et al. 2003). TPA is useful for predicting sample behavior under physiological conditions upon its administration in the oral mucosa (Wróblewska et al. 2020).

TPA was carried out utilizing a CT3 Texture Analyzer (Brookfield Laboratorizes, Middleboro, USA) to study the mechanical properties of ET OMJs (Sampath Kumar et al. 2021; Kim et al. 2020). TPA is a penetration/withdrawal experiment where a solid probe penetrates twice to a certain depth within the sample, and then it returns back to the sample surface. Consequently, different texture parameters are calculated (Almurisi et al. 2020). The texture analysis probe type was TA-AACC, which is a cylindrical probe with a 21 mm diameter. TPA was set with a trigger of 7 g. 50 ml of each prepared OMJ was placed in a calibrated beaker (100 ml) that was then placed directly below the probe (Hurler et al. 2012). The first compression was started by lowering the cylindrical probe with a constant speed of 2 mm/s until it reached the sample surface. Next, the probe continued down into the sample at a depth of 5 mm. Subsequently, the probe was returned back to the sample surface with the same speed (2 mm/s), and then the second compression was started (Carvalho et al. 2013). The mechanical properties of firmness, consistency, stickiness, cohesiveness, springiness, gumminess, and chewiness were determined from the obtained force–time plots (Tomczykowa et al. 2018; Hurler et al. 2012; Carvalho et al. 2013). Texture ProCT Software 1.5 (Brookfield Engineering Laboratories) was utilized to record the obtained results. TPA was carried out in triplicate for each sample (Almurisi et al. 2020; da Silva et al., 2019).

2.5.6. In vitro dissolution study

ET in vitro release was implemented with USP dissolution apparatus II (Pharm Test, Hainburg, Germany) using 250 ml of Soren-sen's phosphate buffer (pH 6.8) (Nair et al. 2013). During the test, the speed of the shaft rotation was 50 rpm, with maintaining the temperature at 37 ± 0.5 °C. Each prepared ET OMJ was placed at the bottom of the dissolution apparatus vessel (Sakata and Onish 2020). Thereafter, 3 ml samples were withdrawn at intervals of 2, 4, 6, 8, 10, 15, 30, 45, and 60 min, followed by adding the same volume of the phosphate buffer to maintain the medium at a constant volume (Elsayed et al. 2020; El-Dahmy et al. 2014). ET concentra-

tion was then determined spectrophotometrically in each sample at λ_max 272 nm.

2.6. Characterization of the optimized ET OMJ

2.6.1. Comparative dissolution study of optimized ET OMJ and the market tablet

A comparative dissolution study between the optimized OMJ (J2) and the market tablet was carried out to study the success of the optimized OMJ in boosting ET dissolution rate. Both the optimized ET OMJ and the market tablet were put at the bottom of the dissolution apparatus vessels. This study was executed utilizing the same conditions mentioned earlier in the in vitro dissolution study. The similarity factor ($f_2$) and the dissolution T50% were calculated for comparing ET release profiles from the optimized ET OMJ (J2) and the market tablet (Costa and Lobo 2001).

2.6.2. Stability studies

The optimized ET OMJ was stored in a desiccator containing a magnesium nitrate saturated solution to maintain a 60 % relative humidity (RH) at 25 °C, and retained for 6 months (Kulkarni and Londhe, 2021; Karaiskou et al. 2020). Stability was estimated by comparing the first results with post-storage results (Zeb et al. 2016). After 3 and 6 months, the optimized jelly was analyzed for any changes in drug content, viscosity, firmness, consistency, stickiness, and percentage of ET dissolved after 10 min ($\%Q_{10}$). The obtained results were statistically analyzed by Student’s t-test using SPSS 17.0 software (SPSS Inc., Chicago, USA). The results were considered significantly different if $P \leq 0.05$.

2.7. Clinical studies

2.7.1. In vivo palatability and disintegration time studies

Masking the bitter taste of drugs presents a major challenge for formulators during the OMJs preparation, as most active ingredients have a bitter taste that may affect patient acceptance (Kulkarni and Londhe, 2021; Allam and Fetih 2016). The study was implemented in compliance with the revised Declaration of Helsinki for biomedical research involving human subjects and the Good Clinical Practice (GCP) standards (World Medical Association Declaration of Helsinki 2013). This study protocol was reviewed and approved by the institutional review board of the Genuine Research Center (Cairo, Egypt). A double-blind cross-over study was implemented on eight healthy human volunteers to estimate gustatory responses (Anand et al. 2007). Before starting the study, all the volunteers were informed of the study’s purpose, nature, risks, and duration. Afterward, written informed consents were signed and obtained from all volunteers who participated in the study. Volunteers were asked to maintain their normal physical activity and standard dietary conditions for four days before dosage form intake (Auda et al. 2014). The volunteers administered the optimized ET OMJ (J2) by placing and keeping it in their mouths until it was completely disintegrated. They were then requested to evaluate the texture, palatability (masking of the bitter taste), aftertaste, and disintegration time of the optimized OMJ. The intensity of the bitter taste had a numerical five-level scale: 1 means very bitter, 2 means bitter, 3 means acceptable, 4 means pleasant, and 5 means very pleasant (Khan et al. 2007). ET pure powder was used as a control for the bitter taste and aftertaste tests. Both ET pure powder and the optimized OMJ contained 5 mg ET.

2.7.2. In vivo pharmacokinetic study in healthy human volunteers

2.7.2.1. Study design and subject population. A single-dose, two-period, randomized crossover design was adopted to evaluate and compare the pharmacokinetic parameters of both the opti-
mized ET OMJ (J2) and the conventional market tablet (Vascon® 5 mg). Six healthy male adult volunteers were enrolled in the study. Their mean age was 40.7 ± 5.0 years, and their mean body weight was 72.5 ± 6.7 kg. Written informed consent forms were signed and obtained from all the enrolled volunteers after explaining all the aims and risks of the study. All volunteers were instructed not to take any medication for two weeks before starting the study till its ending. The study was implemented in compliance with the revised Helsinki Declaration for biomedical research involving human subjects and the standards of Good Clinical Practice (GCP) (World Medical Association Declaration of Helsinki 2013). The approval number (RC/1/21/R5) was obtained after reviewing and accepting the study protocol by the institutional review board of the Genuine Research Center (Cairo, Egypt). All volunteers were observed by a specialized physician.

2.7.2.2. Drug administration and sample collection. All the enrolled volunteers were randomly divided into 2 groups; each consisted of three volunteers. Group I administered the optimized ET OMJ (J2), while group II administered the market tablet. Both the treatments contained 5 mg of etilefrine hydrochloride. The study was repeated after a wash-out period of 7 days to implement the cross-over study design. All volunteers fasted overnight (10 h) prior to the study day. In group I, the participants placed the optimized ET OMJ (J2) in their buccal cavity, and after its complete disintegration and disappearance, they drank 200 ml water. In group II, the participants swallowed the market tablet with 200 ml water. Volunteers were permitted to drink water 2 h post-dosing, then they were allowed to have food and drinks 4 h post-dosing. Thereafter, standard meals of breakfast, lunch, and dinner were provided to all volunteers in accordance with a predetermined schedule. All the enrolled volunteers were under continuous medical supervision throughout the study.

For ET analysis, 4 ml of blood samples were collected into stoppered heparinized tubes at time intervals of 0.0, 0.166, 0.33, 0.5, 1, 2, 4, 6, 8, and 12 h after dosing. Plasma was obtained by centrifuging (Remi Laboratory Centrifuge R32 A, Bombay, India) all the gathered blood samples at 4 °C for 10 min at 5000 rpm. Thereafter, the collected plasma was stored at −20 °C (Ultra-Low Freezer, Environmental Equipment, Albany, NY, USA) till the drug analysis.

2.7.2.3. Sample preparation. After thawing all frozen human plasma samples, 0.5 ml from each plasma sample was added to 50 μl of 100 ng/ml rosvastatin (the internal standard) (IS). Next, those mixtures underwent vortexing first for 1 min (Paramix II, Julabo Laboratechnik GmbH, Seelbach, Germany), then for 2 min after adding four ml of methyl-ter-butyl-ether (MTBE). After that, the obtained samples were subjected to centrifugation for 10 min at 37 °C at 4000 rpm. The resultant clear supernatant was transferred into clean vials and evaporated till dryness utilizing a centrifugal vacuum concentrator (Vacufuge® 5301, Schönwalde-Glien, Germany) at 40 °C. Thereafter, the obtained dry residues were reconstituted utilizing 200 μl of the mobile phase, then 20 μl of the obtained solution was injected for analysis via the LC-MS/MS method utilizing the autosampler (Elshafeey et al. 2010).

2.7.2.4. Chromatographic conditions. ET human plasma samples were analyzed using the LC-MS/MS method. This method is a sensitive, accurate, and selective method developed and validated in accordance with international guidelines (Shah et al. 1991). The internal standard stock solution’s final working concentration (50 mg/ml) was prepared by dissolving the IS (10 mg) in methanol followed by serial dilution with the mobile phase. A Shimadzu Prominence (Shimadzu, Tokyo, Japan) series LC system provided with an autosampler (SIL-20 AC), degasser (DGU-20A3), and solvent delivery unit (LC-20AB) was utilized for the injection of 20 μl of the processed samples. All the analyses were implemented at room temperature. The utilized mobile phase was a mixture of 0.1 % formic acid solution in deionized water and acetonitrile (20:80 v/v), which was delivered by employing a Luna C18 column (Phenomenex, Torrance, CA, USA) (5 μm, 4.6 × 50 mm) with 1 ml/min flow rate into the electrospray ionization chamber of the mass spectrometer (Kong et al. 2014).

The analysis was carried out by API 3200 mass spectrometer in a positive ion mode for both etilefrine and rosvastatin. The ion spray voltage was adjusted at 5500 V and 600 °C. Zero grade air was used as the nebulizer gas, whereas nitrogen gas was the auxiliary gas. The ion source parameters of declustering potential, collision energy, collision exit potential, and entrance potential were 41, 17, 4, and 5.5, respectively, for etilefrine, and 96, 23, 6, and 8 for rosvastatin. Detection of the ions was performed in the multiple reactions monitoring (MRM) mode investigating the transition of m/z 182.09 precursor ion to m/z 164.10 for etilefrine and m/z 481.74 precursor ion to m/z 366.89 for rosvastatin. Analyst® software (version 1.6.3) was used to process analytical data.

2.7.2.5. Statistical analysis of pharmacokinetic Data. Etilefrine pharmacokinetic analysis was carried out by the non-compartmental approach, employing Kinetica® 5.1 SP1 software (Thermo Fischer Scientific Inc., MA, USA). ET maximum concentration (Cmax, ng/ml) and the time of reaching Cmax (Tmax, h) were obtained from the plasma concentration–time curves. The area under the curves from zero to the last analyzed time and to infinity (AUC0–12, AUC0–∞, ng.h/ml) were calculated according to the linear trapezoidal rule. t1/2 (h) equaled 0.693/K, Cmax, AUC0–12, AUC0–∞, and t1/2 of both the treatments were compared using the ANOVA test. The % relative bioavailability (%RB) of ET was calculated utilizing the following equation (Sharma et al. 2019):

\[
\% \text{ Relative bioavailability} = \frac{AUC_{0–\infty} \text{ of ET optimized OMJ}}{AUC_{0–\infty} \text{ of ET market tablet}} \times 100
\]

(2)

The results of the two related parameters were considered significantly different when P ≤ 0.05.

3. Results and discussion

3.1. Compatibility of ET with the used polymers

3.1.1. Differential Scanning Calorimetry (DSC)

ET compatibility with the utilized jellifying agents, pectin, guar gum, tragacanth gum, xanthan gum, and sodium alginate, was examined with DSC. Fig. 1 illustrates the thermograms of ET and the physical mixtures of ET with each polymer. The DSC scan of pure ET showed a broad endothermic peak at 122 °C. It is notable that the ET peak didn’t shift in the DSC scan of all the physical mixtures, indicating physical and chemical compatibility. A slight reduction in peak intensity was noticed in some thermograms, and this could be attributed to the drug dilution by the added polymers, which led to a reduction in the purity of each component (Botha and Lötter, 1990).

3.1.2. Fourier-transform infrared spectroscopy (FTIR):

It is clear from Fig. 2 that ET had three peaks, including two peaks of (–OH) group that appeared at 3556 and 3322 cm⁻¹, -CH aliphatic peak at 2998 cm⁻¹ (Reddy et al. 2018). Such results indicate that there is a conforming spectra for the tested powder and the reference (Attia et al. 2017). All polymers used had several aliphatic (–CH) groups which masked those of the drug. So, the two peaks corresponding to the (–OH) in ET were considered the characteristic peaks for the drug. Fig. 2 shows the FTIR spectroscopy of
each physical mixture of drug-polymers with ratio (1:1) w/w. There was no change in the characteristic peaks of all physical mixtures, as they appeared at the same area just as the pure ET FTIR spectroscopy. This denoted the absence of any chemical interactions between ET and the utilized excipients. The slight decrease in the characteristic peaks strength could be due to the drug dilution by the added polymers.

### 3.2. Preparation of ET oral medicated jellies (OMJs)

A heat and congealing method was successfully utilized to prepare ten ET OMJs, as shown in Supplementary Fig. S1. The different natural polymers used as jellifying agents, such as pectin, guar gum, tragacanth gum, xanthan gum, and sodium alginate, achieved different degrees of stiffness for the prepared OMJs. The higher the concentration of the jellifying agent, the firmer the prepared OMJs, and vice versa. The addition of calcium chloride as a crosslinking agent succeeded in boosting the consistency, viscosity, and texture properties of the prepared OMJs compared with those prepared in the premilitary trials before the addition of calcium chloride. Sucrose syrup was used as a bulking agent providing a body to the prepared OMJs (Karaiskou et al. 2020). Furthermore, sucrose improved the taste of the formulations, and it can act as a preservative (Mennella et al. 2015). Propylene glycol was added to
enhance the softness and slipperiness of the prepared OMJs. Citric acid was used to stimulate the secretion of the saliva in the buccal cavity, boosting the disintegration of the prepared OMJs (Irfan et al., 2015). Methylparaben and propylparaben were used as preservatives as OMJ is susceptible to microbial contamination as a result of its hydrophilic nature, so for this reason, a preservative was an essential component to retain the required shelf-life of the prepared OMJs. An amaranth coloring agent and a strawberry flavoring agent were added to increase the jelly’s aesthetic value and mask the unpalatable bitter taste of ET, respectively. Each OMJ weighed 3 g approximately and contained 5 mg of ET.

3.3. Statistical analysis of factorial design

In this study, the chosen factors and their levels were based on preliminary experimental trials (data not shown) to determine the expected ranges of the independent variables. A full factorial (2^3 x 3^3) design was applied using ANOVA to investigate the impact of each factor, with its different levels, on the studied responses. The model chosen was the sum of squares (Type II model). As shown in Table 2, adequate precision ratio was above four in all responses, which is desirable, assuring that the utilized model can be applied to navigate the design space (Alexander et al., 2015). Additionally, the values of both predicted and adjusted R^2 were in good harmony, confirming the absence of any problems with the model or the data (Annadurai et al., 2008). The P-values of all dependent variables were considered significant (<0.05). Table 2 shows all the studied factors and the estimated responses of the experimental design. The influence of each factor on the responses and the graphical response surface plots were determined using Design expert® 7 software (Stat-Ease Inc., Minneapolis, MN, USA).

3.4. Characterization of the prepared ET OMJs

3.4.1. Variation and drug content

As presented in Table 1, the weight of the prepared ET OMJs ranged from 2.85 ± 0.15 g to 3.12 ± 0.23 g. These findings indicate the absence of any significant weight variation, which confirms the efficiency of the employed method to achieve uniform drug distribution. As shown in Table 1, ET content in all the prepared OMJs ranged from 95.08 ± 3.04 to 99.14 ± 0.88, which complies with the pharmacopeial limit (British Pharmacopoeia Commission, 2008). These results ensure drug uniformity in each OMJ.

3.4.2. Determination of pH

The pH of all the prepared OMJs needed to be similar to the neutral pH of the oral cavity. Table 1 displays that the pH values of all ET prepared OMJs varied from 6.47 to 7.12, ensuring their safety and avoiding any irritation to the oral cavity mucosal lining (El-Feky et al., 2020).

3.4.3. Syneresis

Jelly undergoes syneresis as a result of releasing liquid leading to shrinkage of the jelly and a reduction in quality (Akesowan, 2012). Formulae J1, J2, J4, J6, J8, and J10 showed no signs of syneresis. Formulae J5 and J9 showed syneresis at room temperature while formulae J3 and J7 showed syneresis at 8 °C ± 1 °C. These findings show that syneresis was more noticeable when a lower concentration of jellifying agents was used (2 % w/v of jellifying agents).

3.4.4. Viscosity

An ideal OMJ should have sufficiently high viscosity to provide adequate consistency to withstand the normal handling and provide a sufficient long contact time on the oral mucosa (Wróblewska et al., 2020). The viscosities of ET OMJs were found to be between 1618 ± 28 and 7563 ± 55 cps, as displayed in Table 1.

It can be seen from Table 1 and Fig. 3A that both the investigated factors, jellifying agent type (X1) and jellifying agent percentage (X2), had a significant impact on viscosity. It is clear that the viscosity significantly changed according to the type of nature of the utilized polymers (jellifying agents). The OMJs prepared with pectin showed the maximum viscosity, followed by guar gum > sodium alginate > tragacanth gum > xanthan gum. These findings are supported by Newman et al. and Leonard et al., who reported that utilizing different types of jellifying agents significantly affected the measured viscosity (Newman et al., 2016; Leonard et al., 2014). Moreover, it is notable that the viscosity of the prepared OMJs was significantly increased with increasing the jellifying agent concentration. Polymers with a 4 % concentration showed a more significant increase in viscosity than those with a 2 % concentration. These findings are in harmony with that presented by Elsayed et al. and Cabana et al., who stated that increasing the utilized polymer concentration led to an increase in the viscosity of the semisolid preparations (Elsayed et al., 2020; Cabana et al., 1997).

3.4.5. Texture analysis

3.4.5.1. Firmness. Firmness, or hardness, is the maximal force recorded during the probe penetration (Xu et al., 2020). High values of firmness provide the adequate strength and structure tightness needed to remove the prepared formulations from the container easily and to be able to handle and administer them at the application site (Matulyte et al., 2021). Table 1 presents the firmness values of all formulæ ranging from 1.04 ± 0.06 to 8.32 ± 0.21 N.

It can be seen from Table 1 and Fig. 3B that both the investigated factors, jellifying agent type (X1) and jellifying agent percentage (X2), had a significant impact on the firmness values. It was

| Responses | Viscosity (cps) | Firmness (N) | Consistency (µl) | Stickiness (mJ) | % ET dissolved after 10 min |
|-----------|----------------|--------------|-----------------|----------------|-----------------------------|
| Minimum   | 1618 ± 28      | 1.04 ± 0.06  | 0.66 ± 0.03     | 1.30 ± 0.04     | 34.38 ± 1.74               |
| Maximum   | 7563 ± 55      | 8.32 ± 0.21  | 5.72 ± 0.18     | 8.94 ± 0.36     | 99.78 ± 2.52               |
| F-value   | 283.41         | 91.14        | 44.71           | 27.20           | 110.3                      |
| P-value   | <0.0001        | 0.0003       | 0.0014          | 0.0003          | 0.0002                     |
| Adequate precision | 46.81 | 24.99 | 18.01 | 12.43 | 30.35 |
| Adjusted R^2 | 0.924 | 0.981 | 0.960 | 0.936 | 0.983 |
| Predicted R^2 | 0.982 | 0.945 | 0.888 | 0.841 | 0.955 |
| R^2       | 0.997          | 0.991        | 0.982           | 0.989           | 0.993                       |
| Significant factors | X1 and X2, X1 and X2, X1 and X2, X1 and X2, X1 and X2 |
| Observed values of optimized OMJ (J2) | 7563 ± 55 | 8.32 ± 0.21 | 5.72 ± 0.18 | 8.94 ± 0.36 | 99.78 ± 2.52 |
| Predicted values of optimized OMJ (J2) | 7458.2 | 7.88 | 5.92 | 1.22 | 95.43 |

Data represented as mean ± SD (n = 3).
clear that the firmness significantly changed according to the type or nature of the utilized polymers (jellifying agents). ET OMJs prepared with pectin showed the highest firmness. This could be attributed to the higher gel formation ability of pectin when compared with other gums. These findings are supported by Slavutsky and Bertuzzi (Slavutsky and Bertuzzi 2019).

In addition, it is notable that there is a positive relationship between the type of polymer, i.e., viscosity, and the final gel firmness. The highest values of firmness were recorded in the OMJs that had the highest viscosity (pectin-based OMJs). These findings are supported by Ashkar et al. and Gravelle et al., who reported that the firmness results of the semisolid preparations were parallel to their viscosity (Ashkar et al. 2019; Gravelle et al. 2014). These findings are also in harmony with that stated by Tomczykowa et al., who found that the firmness of semisolid preparations increased as their viscosity increased (Tomczykowa et al. 2018).

On the other hand, the firmness of the prepared OMJs gradually increased as the concentration of the utilized polymers increased. These results confirmed the findings of Ashkar et al., who stated that such behavior is expected because increasing the polymer concentration means increasing the number of molecules available for the formation of a network, thus resulting in a stronger matrix (Ashkar et al. 2019).

3.4.5.2. Consistency. Consistency represents the work required to overcome the sample’s internal bonds and deform it during the probe compression. High values of consistency provide adequately consistent jelly that can be easily removed from the container and can be handled and administered at the application site.

Table 1 shows that the consistency values of all OMJs ranged from 0.66 ± 0.03 to 5.72 ± 0.18 (mJ). It can be seen from Table 1 and Fig. 3D that both the investigated factors, jellifying agent type (X₁) and jellifying agent percentage (X₂), had a significant impact on the consistency of the prepared OMJs. It is clear that the consistency values significantly changed with the type of jellifying agent used. ET OMJs prepared with pectin showed the highest consistency. These findings are in harmony with the results of Barrangou et al., who declared that using different types of gelling agents with different viscosities, leads to a change in the consistency and other mechanical parameters of the prepared gels (Barrangoum et al. 2006).

Moreover, the consistency of the prepared OMJs significantly increased with increasing the concentration of the utilized jellifying agents. This is comparable to that stated by Coviello et al. and Tan et al., who studied the impact of increasing polymer concentration on product consistency in several studies (Coviello et al. 2003; Tan et al. 2000).

3.4.5.3. Stickiness. Stickiness (adhesiveness) is the maximum force produced on probe withdrawal. It symbolizes the work required to remove the probe from the sample or overcome the adhesive force between the probe and the sample. Lower stickiness values are desirable in the case of OMJs intended for use on the buccal mucosa in order to avoid the sticky texture of the prepared formula and ensure easy handling during administration. Moreover, the lowest adhesion is desirable as increased adhesiveness during mastication causes slower chewing frequencies (Wróblewska et al. 2020).

Table 1 shows that the stickiness values of all OMJs ranged from 1.30 ± 0.04 to 9.46 ± 0.36 (mJ). It can be seen from Table 1 and Fig. 3D that the jellifying agent type (X₁) was the only factor that significantly impacted the stickiness properties of the prepared OMJs. It was clear that the stickiness of the prepared OMJs significantly varied with the different types of utilized jellifying agents. OMJs prepared with pectin had the least stickiness, and OMJs prepared with xanthan gum showed the highest stickiness. This could be due to the nature of the different polymers types.
3.4.5.4. Cohesiveness, Gumminess, Springiness, and chewiness. Cohesiveness indicates the sample’s ability to withstand sequential deformations, like those occurring during mastication (Ashkar et al. 2019). It is related to the strength of the internal bonds in the examined samples (Xu et al. 2020). Gumminess, which equals (firmness × cohesiveness), indicates the energy required to disintegrate the semisolid sample in the oral mucosa (da Silva et al., 2019). Springiness corresponds to the samples' ability to recover their original form after removing the deforming force and indicates the sample's elasticity (da Silva et al., 2019; Matulyte et al. 2021). Chewiness corresponds to the work needed to masticate the sample in the oral mucosa and equals (firmness × cohesiveness × springiness) or (gumminess × springiness) (Xu et al. 2020).

Cohesiveness, gumminess, springiness, and chewiness play a vital role in mastication physiology, where high values of these aforementioned parameters cause an increase in jaw movement, muscle activity, and chewing time (Foster et al. 2006). Moreover, high values of these parameters are usually associated with a high risk of aspiration and poor acceptability by pediatric and geriatric patients (Momosaki et al. 2013). Therefore, lower values of cohesiveness, gumminess, springiness, and chewiness are required in the case of oral mucosa preparations. The lower the values of the aforementioned parameters, the less the amount of mastication needed to deform the oral mucosa preparation, and hence the faster the release of the drug from it, enabling rapid absorption and fast therapeutic effect (Almurisi et al. 2020; da Silva et al., 2019).

Results of cohesiveness, springiness, gumminess, and chewiness parameters are presented in Table 1. In all the prepared OMJs, the cohesiveness, gumminess, springiness and chewiness values ranged from 0.50 ± 0.03 to 0.72 ± 0.02, 0.58 ± 0.01 to 4.51 ± 0.35 N, 0.31 ± 0.02 to 0.61 ± 0.03 and 0.31 ± 0.01 to 2.02 ± 0.02 N, respectively. Collectively, ET OMJs prepared with pectin were considered the most suitable OMJs as they showed the least cohesiveness and springiness values and acceptable values of gumminess and chewiness.

The values obtained from the texture profile analyses showed good repeatability; hence TPA could be considered a good indicator of the properties of semisolids.

3.4.6. In vitro dissolution testing

Time can be considered a fundamental factor in the case of OMJs, as the loaded drug should be dissolved within minutes. ET dissolution from OMJs involves water diffusion, polymer chains relaxation, swelling, and erosion of the jelly (Kraisit et al. 2018). Fig. 4 displays the dissolution profiles of all the prepared OMJs.

The percentage of ET dissolved after 10 min (%Q10min) from all the prepared OMJs ranged from 34.38 % to 99.78 %, as demonstrated in Table 1.

It is clear that both the independent variables, jellifying agent type (X1) and jellifying agent percentage (X2), had a significant impact on the percentage of ET dissolved after 10 min (%Q10min), as shown in Table 1 and Fig. 3E. It is clear that %Q10min significantly changed with the type of jellifying agent used. The pectin-based OMJs showed the highest %Q10min compared with all the other prepared jellies. This might be due to the greater hydrophilic nature of pectin when compared with all the other polymers used as jellifying agents (Pathare et al. 2013). This resulted in faster hydration of the pectin-based OMJs. Additionally, this might be attributed to pectin ionization at the pH of the used dissolution medium (pH 6.8), which is greater than its pKa value (3.5) (Opanasopit et al. 2008). As a result of pectin ionization, negative charges were formed on the polymer backbone. Due to the repulsion of the negative charges, the polymer uncoiled into an extended structure, and because of the counter ion diffusion within the polymer matrix, an extra osmotic pressure difference was generated across the matrix resulting in high water uptake. As a result, the polymer swelled, leading to a higher ET diffusion rate from the OMJs (Sujjaareevath et al. 1998). These findings are supported by Bais et al., who worked on lorazepam fast-dissolving films and found an enhanced drug dissolution rate from pectin films, where approximately 98 % of the lorazepam dissolved in just 4 min (Bais et al., 2016).

Moreover, the percentage of ET dissolved after 10 min significantly changed with a change in the jellifying agent percentage (X2), where a lower jellifying agent percentage resulted in a higher %Q10min. As the jellifying agent percentage decreases, a higher dissolution rate was achieved as releasing the drug is less retarded by the polymer matrix. These findings agree with Zhou et al., who stated that the amount of vitamin C released from the prepared chewable gummy jelly was significantly decreased by increasing the jellifying agent (gelatin) concentration from 6 % to 12 %. This was attributed to the difficulty separating vitamin C molecules from the more compact three-dimensional structure of gelatin molecules (Zhou et al., 2022).

3.5. Selection of the optimized ET oral medicated jelly

It is almost impossible to optimize all the investigated factors concurrently as the optimum condition of one response could adversely impact another one (Elsayed et al. 2019). The optimized ET OMJ was (J2) that had the maximum desirability value (0.917)
and contained 4% pectin, as illustrated in Fig. 3F. It collectively had minimal stickiness and maximal viscosity, firmness, consistency, and percentage of ET dissolved after 10 min (%Q10min). The predicted values for the optimized OMJ (J2) were in reasonable agreement with the observed values in all the dependent variables, as shown in Table 2. This indicates the appropriateness of the utilized design for the statistical analysis and evaluation of the different formulation variables. The optimized OMJ (J2) was subjected to further comparative dissolution study with the market product, stability study, and in vivo clinical studies.

3.6. Characterization of the optimized ET OMJ

3.6.1. Comparative dissolution study of optimized ET OMJ (J2) and the market tablet

The comparative dissolution study clarified a significant increase (greater than 4-fold) in ET dissolution rate and extent from the optimized OMJ (J2) in comparison with the market tablet (Vascon tablet) with an $f_2$ value of 10. More than 96% of ET dissolved within 10 min from the optimized OMJ (J2), while only 22.35% dissolved from the market tablet, as illustrated in Fig. 5. The release $T_{90}$ values in the case of the optimized OMJ (J2) and the market tablet were 3.71 min and 55.28 min, respectively. These results ensure the success of the optimum ET OMJ (J2), prepared with pectin, in enhancing the dissolution rate compared with the market tablet. The increased dissolution rate of ET from J2 might result from pectin’s high hydrophilic nature, which led to the fast hydration of the optimized OMJ (Pathare et al. 2013). Moreover, this might be attributed to pectin ionization at pH 6.8, which resulted in high water uptake, polymer swelling, and, consequently, diffusion of the drug from the formulation at a higher rate than the market tablet (Opanasopit et al. 2008; Suja-arrevelth et al. 1998).

3.6.2. Stability studies

Table 3 presents the stability study results of the optimized OMJ (J2). The appearance of the stored optimized OMJ (J2) remained unchanged. By the end of the 3 and 6 months, no significant change ($p$ greater than 0.05) was observed in the drug content, viscosity, firmness, consistency, stickiness, or %Q10 min of the stored optimized OMJ in comparison with the freshly prepared one.

3.7. Clinical studies

3.7.1. In vivo palatability and disintegration time studies

The texture evaluation outcomes revealed that 87.5% of the participants reported that the optimized OMJ (J2) was consistent, non-sticky, and easy to handle. The taste evaluation results revealed that 100% of the participants found the pure ET powder “very bitter”. On the other hand, the taste evaluation results of the optimized OMJ showed that 12.5% of the volunteers stated an “acceptable” response, 37.5% stated a “pleasant” response, and 50% stated a “very pleasant” response. These results indicate the success of masking the bitterness of ET with the presence of the added sweetening and flavoring agents (Almurisi et al. 2020). There was a significant improvement in the aftertaste from the optimized OMJ compared with ET pure drug.

The average in vivo disintegration time of the optimized OMJ (J2) equaled 49.63 ± 4.21 secs. This rapid disintegration might be attributed to the presence of citric acid in the optimized OMJ, which stimulates the secretion of the saliva in the buccal cavity, boosting the optimized OMJ disintegration (Irfan et al. 2015).

3.7.2. In vivo pharmacokinetic study in healthy human volunteers

3.7.2.1. Liquid Chromatography/Tandem mass spectrometry method for the assay of etilefrine in human plasma. There were no significant interferences noticed with etilefrine or rosuvastatin (IS) in the chromatographed human plasma utilizing in preparing the calibration standards and the quality control samples. The detected retention time of etilefrine was 0.46 min, while the retention time of rosuvastatin was 0.63 min, as shown in Supplementary Fig. S2. The linear relationship between ET concentrations and the peak area ratio of ET/rosuvastatin is illustrated in Supplementary Fig. S3. The exhibited linearity was high (0.9983). The lower limit of quantitation (LLOQ) for ET was 1 ng/ml.

3.7.2.2. Bioequivalence assessment. All the participants tolerated the drug and the procedures implemented in the study well. The mean plasma concentrations versus time for ET from the optimized OMJ (J2) compared to the market tablet was graphically illustrated in Fig. 6. Table 4 shows the ET pharmacokinetic parameters calculated for both treatments.

3.7.2.3. Statistical analysis of etilefrine pharmacokinetic parameters. $C_{\text{max}}$ value of the optimized OMJ (J2) was significantly increased with (1.70 folds) than that of the market tablet ($p$-value ≤ 0.05). The values $AUC_{0-12}$ and $AUC_{0-\infty}$ of the optimized OMJ (J2) were significantly increased with (1.5-fold) and (1.54-fold), respectively, than the market tablet ($p$-values < 0.05). These findings reveal that ET absorption extent was significantly increased from the optimized OMJ than from the market tablet. The $T_{\text{max}}$ value of ET from the optimized OMJ was significantly lower than that of the market tablet ($p$-value < 0.05). This could be because of disintegrating the optimized OMJ (J2) and rapidly dissolving ET in the saliva, resulting in the immediate absorption of the drug from the optimized OMJ through the buccal mucosa and higher ET plasma concentration being reached more quickly. Concerning the mechanism of transporting ET through the buccal mucosa, the uptake process was concentration-dependent by simple diffusion (Abd El Azim et al. 2015). The relative bioavailability of the optimized OMJ compared with the market tablet was 154.55%. These aforementioned results fulfill the aim of this work in increasing the bioavailability of etilefrine.

This improvement in ET bioavailability could be because of the buccal administration that avoid the drug metabolism by bypassing the first-pass effect.

These findings are supported by Onishi and Sakata who developed etilefrine buccal aqueous droplets and etilefrine buccal fast dissolving films. They stated that upon in vivo investigation in rats, ET buccal aqueous droplets and buccal fast dissolving films showed a significantly higher bioavailability (2.3- and 1.15-fold), respectively, than the intragastric administration. They attributed this to that the buccal route offered an efficient approach to bypass
The liver metabolism of etilefrine (Onishi and Sakata 2018; Onishi and Sakata 2021). These findings are also in harmony with the results of Sakata and Onishi who developed ET buccal fast dissolving tablets. They stated that upon in vivo investigation in rats, ET buccal fast dissolving tablets achieved higher bioavailability (2.6-fold) than the intragastric administration. They attributed this also to rapid absorption of PX through the buccal mucosa and escaping large amounts of it from being metabolized in liver, achieving a higher bioavailability (Elshafeey and El-Dahmy 2021).

Moreover, this increase in ET bioavailability may also be because of the extended residence time of ET on the buccal mucosal surface as well as on the gastrointestinal tract surface because of the adhesiveness properties of pectin, which allows the drug particles to adhere to the absorption sites for a longer period, increasing the absorption extent and the drug plasma level. These findings are supported by Thirawong et al., who reported that pectin has strong mucoadhesive properties on the buccal and gastrointestinal tract mucosa (Thirawong et al. 2007).

### 4. Conclusion

Conclusively, the newly formulated etilefrine OMJs, prepared by the heat and congealing method, exhibits several advantages over the market tablet, such as offering a palatable easily taken dosage form, rapid dissolution in saliva, and rapid absorption through the buccal mucosa, avoiding the first-pass effect and increasing the drug bioavailability. The optimized OMJ (J2) fulfilled all the desired textural properties, where it showed the least stickiness and the highest firmness and consistency, hence, it was easily removed from the container and easily handled and administered at the application site. More than 96 % of ET dissolved within 10 min from the optimized OMJ, while only 22.35 % dissolved from the market tablet. The bioavailability assessment study in human volunteers revealed that the optimized OMJ (J2) had significantly higher Cmax (1.7 folds) when compared with the market tablet with a relative bioavailability of 154.55 %. Therefore, OMJs can be considered a promising dosage form that can enhance the bioavailability of drugs undergoing first-pass effect and can easily be accepted by pediatric and geriatric patients, as well as those with dysphagia.

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### Informed Consent Statement

CRediT authorship contribution statement

Ahmed Hassen Elshafeey: Conceptualization, Methodology, Formal analysis, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision. Rania Moataz El-Dahmy: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2022.07.004.

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