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Metoclopramide hydrochloride loaded oral wafers for postoperative care of children: in vitro and in vivo evaluation

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ABSTRACT

The present study focused on the formulation of metoclopramide HCl (MET HCl) loaded oral wafers (OWs) as a fast dissolving dosage form without drinking water to produce a prompt improvement of emesis. OWs were prepared by casting technique using Hydroxypropyl Methylcellulose (HPMC) as a film forming agent and plasticizers like propylene glycol (PG), polyethylene glycol (PEG) 400 and polyethylene glycol 600. The prepared formulations were visually inspected and subjected to evaluation parameters such as thickness, weight variation, drug content, folding endurance, surface pH, tensile strength, mucoadhesiveness, percentage of moisture absorption, percentage of moisture loss and *in vitro* release study. G3 batch was selected for further investigations e.g. DSC, FTIR and *in vivo* evaluation. The bioavailability of MET HCl loaded OWs was assessed by measuring the plasma concentrations of MET HCl in different studied rabbit's groups' .All wafers were transparent, smooth, uniform and flexible. G3 batch (300 mg HPMC, 20% PEG 400) showed the highest tensile strength, percent elongation, mucoadhesiveness and faster drug release. The pharmacokinetic data of MET HCl loaded OWs preparation (G3 batch) showed a significant higher C_{max}, AUC_{0-24} and lower T_{max} ($p<0.001$) than oral plain MET HCl solution. It could be concluded that MET HCl loaded OWs is a promising fast-release preparation with enhanced rate and extent of drug absorption hence, higher therapeutic efficiency against vomiting and nausea in pediatrics, especially postoperatively can be expected.

Keywords: Metoclopramide HCl, Oral wafers, Postoperative, Nausea, Vomiting, Pediatrics

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INTRODUCTION

Antiemetics play an important role in the quality of the life of patients in different pathological conditions, particularly during and after chemotherapy, due to that they control the adverse effects of the medical treatment, as well as during the period following a surgical operation. The most common routes of administration of antiemetics are oral or intravenous, but these routes are not suitable for pediatric patients according to the problems associated with acute vomiting or invasiveness of parenteral route[1]

Metoclopramide hydrochloride (MET HCl) is an effective antiemetic for preventing different types of emesis. It is a potent dopamine (D2) receptor antagonist, has short half-life of about (3-4 h) due to first pass metabolism which necessitates frequent oral administration and this makes it unsuitable for pediatric use. So, it was necessary to design a novel buccal drug delivery system; OWs are fast dissolving films that are intended for buccal administration[2] They enhance patient acceptability by rapid disintegration and improving the effectiveness of medicinal agents. They dissolve in minutes after their contact with saliva without the need of chewing or water[3, 4] They are characterized by a rapid absorption and an instant bioavailability of drugs because of the high blood flow and the permeability of buccal mucosa that is almost 4,000 times higher than that of the skin[5] . This novel formulation will be useful to meet the current demands of the industry such as enhanced solubility, stability; biological half-life and bioavailability of therapeutic agents[6] OWs are prepared using hydrophilic polymers like HPMC leading to a rapid dissolution on contact with the saliva [3]. Plasticizers are also included in the wafers preparation to increases the spreadability and the flexibility of the wafers [7].

The fundamental goal of this research study was to formulate MET HCl into a new dosage form, as OWs, making it suitable for pediatric administration.

MATERIALS AND METHOD

Materials

Metoclopramide HCl and Hydroxypropyl methylcellulose (HPMC K15M) were kindly supplied by Egyptian International Pharmaceuticals Industries Company. Polyethylene glycol (PEG) 400, PEG 600, propylene glycol (PG) and acetonitrile were kindly supplied by Sigma Pharmaceuticals. Ortho phosphoric acid (OPA) and triethylamine (TEA) were purchased from El-Gomhorea Chemical Company, Egypt.

Methods

Preparation of MET HCl Oral Wafers

OWs of 20 mg drug were prepared by the solvent-casting technique[8] The weighed quantity of HPMC (300 mg) was sprinkled over 7 ml of water in a beaker over a magnetic stirrer. The appropriate quantity of propylene glycol (PG) or Polyethylene glycol (PEG) 400 or PEG 600 as plasticizers was added in different concentrations to adjust the elasticity of the prepared wafers. A homogenous casting solution was obtained by continuous stirring of the polymeric solution; the drug (20 mg) was added and dissolved by stirring. The solution was allowed to stand overnight to remove the suspended air bubbles. The casting solution was poured into a petri-plate having a surface area of 23.75 cm, the plates were kept in a hot air oven at 40˚C for about 3-4 h. The wafers were removed after drying by peeling. These films were wrapped in an aluminum foil for further use[9].The composition of the successfully prepared OWs was illustrated in Table 1.

Table 1: Composition of successfully prepared Oral Wafers.

Formula code	METHCl (mg)	HPMC (mg)	Plasticizer	Plasticizer (%)
G1	20	300	PEG 400	10
G2	20	300	PEG 400	15
G3	20	300	PEG 400	20
G4	20	300	PG	10
G5	20	300	PG	15
G6	20	300	PG	20
G7	20	300	PEG 600	10
G8	20	300	PEG 600	15
G9	20	300	PEG 600	20

Characterization of OWs

MET HCl loaded wafers were formulated using HPMC and different plasticizers at different concentrations. The prepared formulations were visually inspected and subjected to evaluation parameters such as thickness, weight variation, drug content, folding endurance, surface pH, tensile strength, mucoadhesiveness, percentage of moisture absorption and percentage of moisture loss, DSC, FTIR in addition to the in vitro and in vivo studies.

Physical appearance

OWs were physically inspected for the color, clarity and surface textur[6]

Film thickness

A digital micrometer (Schwyz, China) was used to determine the thickness of the prepared OWs at three different places on each formulation and the mean values of the three readings and the standard deviations were calculated[10]

Weight variation

This test ensures the uniformity of the formed films. Three small pieces of each formulation were

cut randomly and weighed individually using a digital balance and the mean values were calculated[11]

Drug content

Thin piece of each formula (1cm^2) was dissolved in 100 ml phosphate buffer (pH 6.8) for 24 h in thermostatic shaker water bath (Julabo SW-20C, Germany) at 100 rpm and 37 ± 1^{o}C

Folding endurance

Folding endurance was determined by repeated folding of the tested wafer at the same place till it breaks. The number of times the film could be folded at the same place without breaking is the value of the folding endurance [12]

Surface pH

The surface pH of the prepared OWs was determined to investigate the side effects which may occur due to the change in pH, since an acidic or alkaline pH may cause irritant effects to the buccal mucosa. The film was placed in a Petri dish, moistened with distilled water. The pH was determined by bringing the electrode of the pH meter in contact with the formulation for 1 min[13]

Tensile strength and % Elongation[14]

The OWs should have sufficient strength to resist the mechanical damage during the production, handling and application. Universal tensile strength apparatus (Hounsfield, Slinfold and Horsham, U.K) was used to measure the tensile strength of the OWs. The maximal force applied to the film, that resulted in its tearing, gives the tensile strength of the film[7], and is calculated by the formula:

$$\text{Tensile strength (N/mm}^2\text{)} = \frac{\text{breaking force (N)}}{\text{Cross sectional area(mm2)}}$$ [15]

The value of the OW elongation shows the change occurred in the film length after applying the force, which is calculated according to the formula below.

$$\text{Elongation at break (\%)} = \frac{\text{increase in length at breaking point (mm)}}{\text{original length (mm)}} * 100$$ [16]

Three random samples were selected from each batch for this test and average values were reported.

Determination of the mucoadhesive force

Mucoadhesion is the state where a certain material binds to a mucosal surface via interfacial forces and is held together for longer time[17] The mucoadhesion occurs in two steps. Firstly, the contact stage, where a contact occurs between the mucoadhesive substance and the mucus membrane. Secondly, the consolidation stage, where physicochemical interactions occur leading to strong connection that results in a prolonged adhesion[18].The mucoadhesiveness was evaluated by measuring the force required to separate the film formulation from mucin disc in between two vials

using a specific balanc[19] The apparatus (Figure 1) consists of a two-arm balance, one side of which contained a plastic jar and the other side contained two glass vials. One of the vials was attached to the base of the stage, and the other was attached to the arm of the balance by a thick thread. Two mucin discs (E) were secured to the two glass vials (C) separately using cyanoacrylate adhesive and a rubber band. A circular piece of the film was added on the mucin disc between these two vials and the height of the vial adjusted, so the film could adhere to the surface of both vials.

Then, a constant weight was applied on the upper vial for 2 min, after which it was removed, and the upper vial was connected to the balance. Water was added slowly at a constant rate to a plastic jar placed (a rate of 13–15 drops per min) until the both vials were separated. The mucoadhesive strength, expressed as the detachment stress in dynes/cm^2 was determined using the following equation:

Detachment stress (dynes/cm2) = $\frac{m.gr}{A}$ [20]

Where (m) is the weight of water in gram that detached the two vials, (gr) is the acceleration due to gravity as 980 cm/s^2, (A) in cm^2 is the area of the mucin exposed and is equal to πr^2 (r is the radius of the exposed mucin).

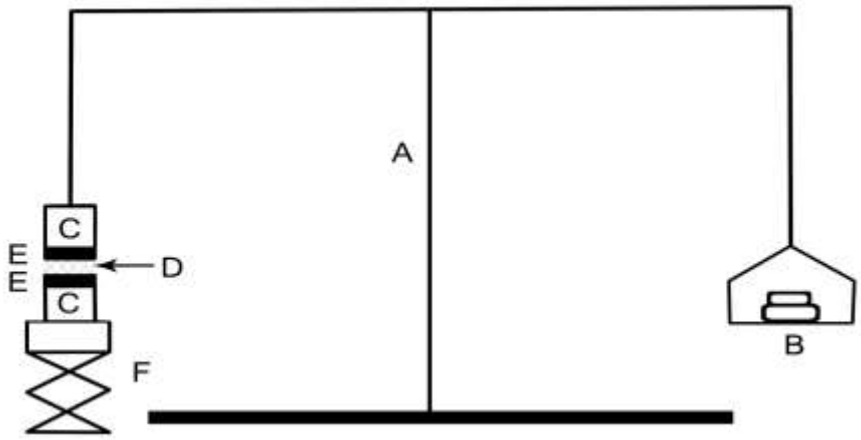

Figure 1: Modified chemical balance for measuring mucoadhesive force (A): modified balance, (B): plastic jar, (C): glass vial, (D): gel formulation, (E): mucin. (F): height-adjustable pan.

Percent moisture absorption [21]

The percent moisture absorption (PMA) test was carried out to check the physical stability of the OWs at high humidity. Three 1cm^2 strips were cut out, weighed and placed in desiccators containing saturated solution of potassium chloride, which gives a humidity of about 79.5% for 10 days. The wafers were removed daily, weighed until constant weight was obtained. PMA was calculated using the following formula[22]PMA = $\frac{(Wt - W0)}{W0}$ x100

Where

W_t = weight of the film at time t W_0 = weight of the film at zero time.

Percent moisture loss (Moisture Vapor Transmission) [21]

PML test was performed to check the integrity of the OWs at dry conditions. Three $1cm^2$ strips were cut out and weighed then kept in desiccators containing anhydrous calcium chloride for 3 days; the films were removed and weighed again. The average PML was determined using following formula:

$$\text{Moisture loss} = \frac{(W0 - Wt)}{W0} \times 100$$

Where

W_0 = initial weight

W_t = final weight

***In vitro* release studies**

The in vitro release of OWs was performed using a cellophane membrane over a diffusion cell .The cellophane membrane was soaked overnight in a buffer solution (pH 6.8), then stretched over an open end of a glass tube 3 cm diameter and made water-tight by rubber band. The formulated wafers were cut into size of 2 cm^2 and placed over the cellophane membranes. The tubes were then immersed in a 250 ml beaker containing 100 ml buffer (pH 6.8). The tubes were adjusted, so the membranes were below the surface of the release medium. Then, the beakers were transferred to shaker water bath adjusted at 37 ± 1°C and 100 rpm. 3ml samples were withdrawn at different time intervals (15, 30, 45, 60, 90, 120, 180 and 240 min) from the receptor medium and replaced by equal volumes of PBS (pH 6.8) maintained at the same conditions. Samples were measured at 273 nm. [23]

Kinetic analysis of the release data

The in vitro release data of MET HCl from fast dissolving films were analyzed according to zero-order, first order, Higuchi, Korsmeyer–Peppas model and Hixson–Crowell cube root law. The model which produces the highest correlation was used for the assessment of the drug release rates[24]

Instrumental analysis

Fourier transform infrared spectroscopy (FTIR**)** was performed on a Perkin-Elmer 1600 FTIR spectrophotometer using KBr disk method. The scanning range was 450-4000 cm^{-1} and the resolution was 1 cm^{-1}. Differential Scanning Calorimetry (DSC) thermograms were recorded on a Shimadzu-DSC 50. Samples (2mg) were heated in hermetically sealed aluminum pans over the

temperature range of 30-400ºC at a constant rate of 10ºC/min under a nitrogen purge (30 ml/min).

Stability study

The optimized wafer (G3) was packed in an aluminum foil and stored for a short term accelerated stability study at room temperature and refrigerator temperature. The wafers were analyzed after (2 weeks and 3 months for the drug release and the other parameters at the end of the period.

***In vivo* studies**

Quantification of Metoclopramide HCl in Plasma

The mobile phase consists of acetonitrile: water (25: 75), with 0.06% triethylamine and pH adjusted to 4 with orthophosphoric acid. A stock solution of MET HCl was prepared at a concentration 1000 µg/ml. Calibration curve was established in the plasma by adding different volumes of standard MET HCl solution to the drug free plasma. Then, 1 ml of acetonitrile was added to the above mixture for the extraction of MET HCl from plasma[25] The mixture was mixed by vortex for 30 s and then centrifuged at 6000 rpm for 15 min. 20 µl of the supernatant was automatically injected into the HPLC system for analysis. Calibration curve was constructed by plotting the area under the curve against the concentrations of MET HCl.

Pharmacokinetic Study

White male rabbits (weighing 2-2.5 kg) were used for the bioavailability studies. Animals were housed in the standardized conditions at the animal house of the Faculty of Pharmacy, Zagazig University, Egypt. All animals were kept under constant temperature (25 ± 2ºC). All animal procedures were performed in accordance with the approved protocol for use of experimental animals set by the Ethical committee of animal handling in Zagazig University "ECAHAZU"), Faculty of Pharmacy, Zagazig University, Egypt.(Approval number: P7-12-2017).

Rabbits were divided into three groups. The first group received water (Negative control). The second group received pure MET HCl (Plain), while the third group was given the prepared MET HCl oral wafer (G3). The formulations were administered at equivalent amount of 7.5 mg of MET HCl/kg. Blood samples (about 2.5 ml) were withdrawn from the sinus orbital into heparinized tubes at 0.5, 1, 2, 3, 4, 6 h after administration. The blood samples were centrifuged immediately at 4000 rpm for 10 min to obtain plasma samples which were immediately stored at −20°C for HPLC analysis. The concentration of MET HCl in the plasma samples was calculated from the calibration curve. The pharmacokinetic calculations were performed on each individual set of data, using the pharmacokinetic software PK solver using a non- compartmental method. The pharmacokinetic parameters including the maximum plasma concentration (C_{max}, ng/ml), the time required to reach

maximum plasma concentration (T_{max}, h) and the area under the plasma concentration time curve from time 0 to 24 h (AUC_{0-t}, $ng.ml^{-1}h$).

Statistical analysis

One way analysis of variance (ANOVA) was employed to assess the significance of the difference between the formulation and the plain drug at level ($p< 0.05$) using GraphPad Prism version 5.02.

RESULTS AND DISCUSSION

Characterization of MET HCl loaded oral wafers

Physical characteristics such as homogeneity, color, transparency and surface of the formed wafers were visually inspected. All wafers were transparent, smooth, uniform and flexible (Figure 2).

Figure 2: Photographic image of G3 oral wafer

As shown in Table 2, the thickness of the selected oral wafers ranged from 0.11 ± 0.01mm (G1) to 0.16 ± 0.01mm (G3) with low standard deviation which indicated that there was a non-significant difference in thickness and ensured the uniformity of the prepared films.

The weight of the prepared MET HCl films ranged between 0.223 ± 0.07 mg (G7) to 0.256 ± 0.01 mg (G3), which indicated that all the formulations exhibited uniform weight with low standard deviation values as noticed in Table 2.

The measurement of the drug content of the selected wafers was done to ensure that the drug is uniformly distributed in the formula. The drug content ranged between 95 ± 0.22% (G8) to 99.8 ± 0.07% (G1) which indicated that the drug was uniformly distributed within the films as in Table 2.

Folding endurance for the prepared oral wafers was found to be in the range of 102 ± 1.3 (G1) to 190 ± 3.5 (G6), which indicated that the wafers had an accepted flexibility, also with high physical strength[26] Results are shown in Table 2.

Table 2: Thickness, Weight, Drug content, Folding endurance and Surface pH of the prepared oral wafers.

Formula Code	Thickness (mm)± SD	Weight (g) ±SD	Drug content (%)±SD	Folding endurance±SD	Surface PH±SD
G1	0.11 ± 0.01	0.232±0.024	99.8 ± 0.07	102 ± 1.3	6.59 ± 0.31
G2	0.14 ± 0.03	0.248 ± 0.01	99.6 ± 0.12	148 ± 2.41	6.63 ± 0.19
G3	0.16 ± 0.01	0.256 ± 0.01	98.9 ± 0.05	187 ± 0.81	6.96 ± 0.21
G4	0.12 ± 0.08	0.223±0.052	98.8 ± 0.09	165 ± 2.55	6.98 ± 0.65
G5	0.14 ± 0.05	0.234±0.012	98 ± 0.21	176 ± 1.34	6.62 ± 0.57
G6	0.142 ± 0.03	0.24 ± 0.01	97.9 ± 0.34	190 ± 3.5	6.22 ± 0.61
G7	0.125 ± 0.01	0.223 ± 0.07	96.9 ± 0.14	119 ± 0.97	6.9 ± 0.1
G8	0.145 ± 0.04	0.234±0.031	95 ± 0.22	139 ± 4.11	6.1 ± 0.22
G9	0.15 ± 0.02	0.236 ± 0.06	96.1 ± 0.8	178 ± 5.5	6.34 ± 0.49

* Data are expressed as mean+ standard deviation of the mean (SD, n=3)

The surface pH of all formulations was between 6.1 ± 0.22 (G8) and 6.98 ± 0.65 (G4), as shown in Table 2. The pH values indicate that the pH is near to that of the saliva which ranged from (6-7.5) [27], so it would not cause irritation.

Tensile strength and percent elongation refer to the elasticity and strength of the prepared wafers. Soft and tough wafers are preferable as they have the highest tensile strength and percent elongation. Data recorded in Table 3 shows that as the concentration of plasticizer increased from 10 to 20 % the tensile strength increased from 15.02 ± 0.27 to 21.21 ± 0.44 for OWs containing PEG 400 as plasticizer, from 10.323 ± 0.13 to 17.26 ± 0.29 for PG plasticizer and from 9.87 ± 0.31 to 15.84 ± 0.42 for PEG 600 plasticizer. This in a good agreement with that mentioned by **Panchal et al., 2012[28]** who found that as the plasticizers concentration increased, the tensile strength also increased. The results of the percentage elongation studies are shown in Table 3, this test is used to study the flexibility of the prepared wafers, it was observed that the % elongation increased by increasing the plasticizers concentrations from 10 to 20 %, in case of PEG 400 plasticized polymer, % elongation increased from 21.4 ± 0.2 to 41.51 ± 0.63, from 25.8 ± 0.3 to 35.9 ± 0.28 for PG plasticized polymer, and from 29.95 ± 0.35 to 40.11 ± 0.24 for PEG 600 plasticized polymer. The increasing in OWs elongation may be attributed to the fact that plasticizers decrease the intermolecular bonds between the polymer matrices and replace them with hydrogen bonds formed between plasticizer and polymer molecules. Such reconstruction of the polymer chains enhances the flexibility of wafer[29]

Generally results revealed that all the selected formulations showed a good tensile strength and percent elongation.

As the concentration of the plasticizer increased from 10 to 20 %, the mucoadhesiveness also increased from 25.2 ± 0.01 to 32.6 ± 0.23 for PEG 400 plasticized polymer, from 20.6 ± 0.4 to 25.6 ± 0.22 for PG plasticized polymer and from 23.6 ± 0.31 to 26.7 ± 0.18 for PEG 600 plasticized polymer, Table 3. This could be attributed to that OWs are hydrophilic in nature, undergo swelling and form a chain interaction with the mucin[30]

The films were evaluated for PMA and results were shown in Table 4.

Table 3: Tensile strength, % elongation and mucoadhesiveness of the prepared oral wafers.

Formula Code	Tensile strength(N/mm^2) ±SD	Elongation (%) ± SD	Mucoadhesive force ($*10^3 Dyne/cm^2$) ± SD
G1	15.02 ± 0.27	21.4 ± 0.2	25.2 ± 0.01
G2	19.19 ± 0.19	34.91 ± 0.31	28.1 ± 0.14
G3	21.21 ± 0.44	41.51 ± 0.63	32.6 ± 0.23
G4	10.323 ± 0.13	25.8 ± 0.3	20.6 ± 0.4
G5	13.5 ± 0.22	31.89 ± 0.17	22.1 ± 0.08
G6	17.26 ± 0.29	35.9 ± 0.28	25.6 ± 0.22
G7	9.87 ± 0.31	29.95 ± 0.35	23.6 ± 0.31
G8	12.71 ± 0.38	38.56 ± 0.51	24.8 ± 0.7
G9	15.84 ± 0.42	40.11 ± 0.24	26.7 ± 0.18

* Data are expressed as mean± standard deviation of the mean (SD), n=3

The swelling behavior of the polymer is reported to be important for its bioadhesive character because it is necessary to initiate the intimate contact of the wafer with the mucosal surface. PMA was correlated with the capacity of the excipients to absorb water in vapor form, as the polymer used was hydrophilic [30]. The moisture absorption was found to be not too high and within the acceptable limits. The little moisture content helps the formulations to be stable and prevents them from being completely dried or being brittle product[31] Moisture absorption increased with an increase in the plasticizer concentrations [29]. This result may be due to that hydroxyl groups in the used plasticizers have strong affinity with water molecules; enabling OWs to easily retain water [32]. PML ranged from 3.75 ± 1.40 to 7.52 ± 0.90 Table 4. The small moisture loss helps the films to remain stable, flexible and avoid drying[21]

Table 4: Percent moisture absorption and percent moisture loss of the prepared oral wafers.

Formula code	Moisture loss after 3 days± SD	Percent moisture absorption after 10 days ± SD*
G1	5.26 ± 0.30	5.51 ± 0.11
G2	7.25 ± 0.52	7.11 ± 0.30
G3	7.52 ± 0.90	7.53 ± 0.21
G4	3.75 ± 1.40	4.25 ± 0.62
G5	4.87 ± 1.10	4.65 ± 0.16
G6	6.97 ± 0.32	7.88 ± 0.27
G7	4.52 ± 0.20	6.52 ± 0.77

G8	5.69 ± 0.91	10.3 ± 0.29
G9	6.66 ± 0.11	11.4 ± 0.67

* Data are expressed as mean ± standard deviation of the mean (SD), n=3

***In vitro* release**

The in vitro drug release studies were carried out for all the formulations in PBS (pH 6.8). As shown in Figure (3-5), all the prepared formulations showed fast release of MET HCl over 4 h. It was observed that the release of MET HCl increased by increasing the concentration of the plasticizers used [28, 33, 34]. Increasing PEG 400 concentration from 10 to 20 % lead to an increase in the amount of the drug released from 78.26 ± 3.841 to 87.93 ± 2.003 after 4 h. By using PG as a plasticizer, an increase in the amount of the drug release from 56.07 ± 1.484 to 73.27 ± 2.05 was obtained. Similar behavior was observed with PEG 600. This may be due to that the used plasticizers are water soluble which diffuse out from the films, making pores through which the distribution of the liquid happens to enable the film breaking down, improving the release profile of the drug [35]

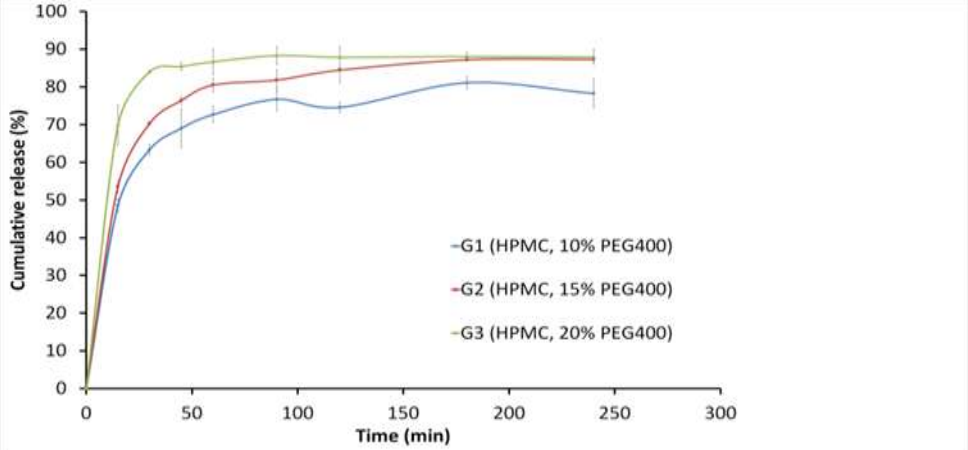

Figure 3: In vitro release data of MET HCl from HPMC (polymer) containing PEG 400 as plasticizer

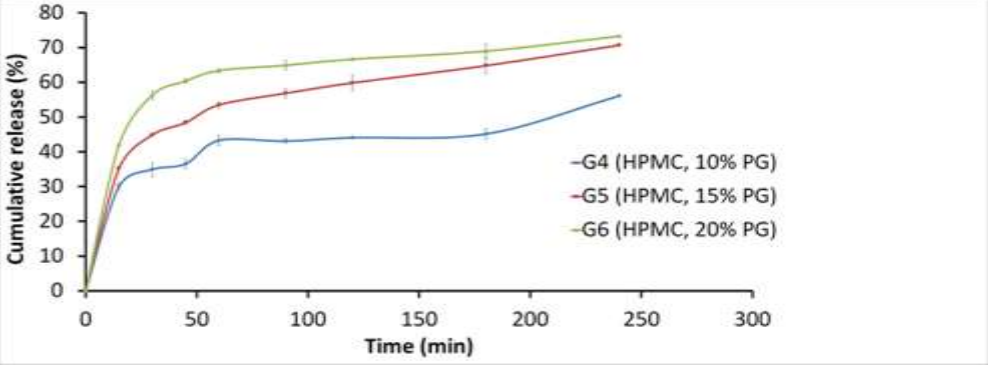

Figure 4: In vitro release data of MET HCl from HPMC (polymer) containing PG as plasticizer

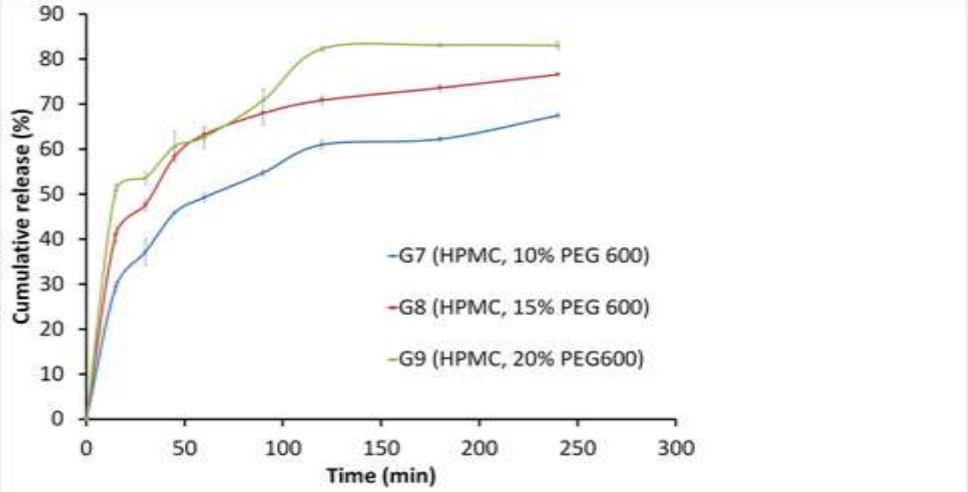

Figure 5: In vitro release data of MET HCl from HPMC (polymer) containing PEG 600 as plasticizer

Kinetic analysis of the release data

From the obtained results it was found that the best fitted model showing the highest determination coefficient (R2) was Korsmeyer-Pepas which means predominant release mechanism is controlled by diffusion [34]

Instrumental analysis

Fourier transform infrared spectroscopy (FTIR) was performed to investigate the possible type of interaction between Metoclopramide HCl and different components as shown figure 6**.** It was observed that the characteristic absorption bands of Metoclopramide HCl traced at 3390 cm^{-1}, 3306 cm^{-1} and 3194 cm^{-1} (N^{+}-H stretching), 1538 cm^{-1} (C=C aromatic), 1596 (N^{+}-H bending), 1634 cm^{-1} (C=O), 2976 cm^{-1} and 2937 cm^{-1} (CH aliphatic), 1262 cm^{-1} (C-O) and 1075 cm^{-1} (para-disubstituted). In case of the selected formula (G3) containing 300 mg HPMC as polymer and 20 % PEG 400 as plasticizer, all the characteristic bands of the drug and polymers were obviously distinct except for a decrease in the (N^{+}-H stretching) bands of drug which may be due to reduction in the intensity and position due to intermolecular hydrogen bond between (N^{+}-H stretching) of drug and hydroxyl group of polymer. Also, it is obvious that there was an increase in the (OH) of HPMC due to intermolecular hydrogen bond. This reflected that there were little interactions between the drug and the polymer.

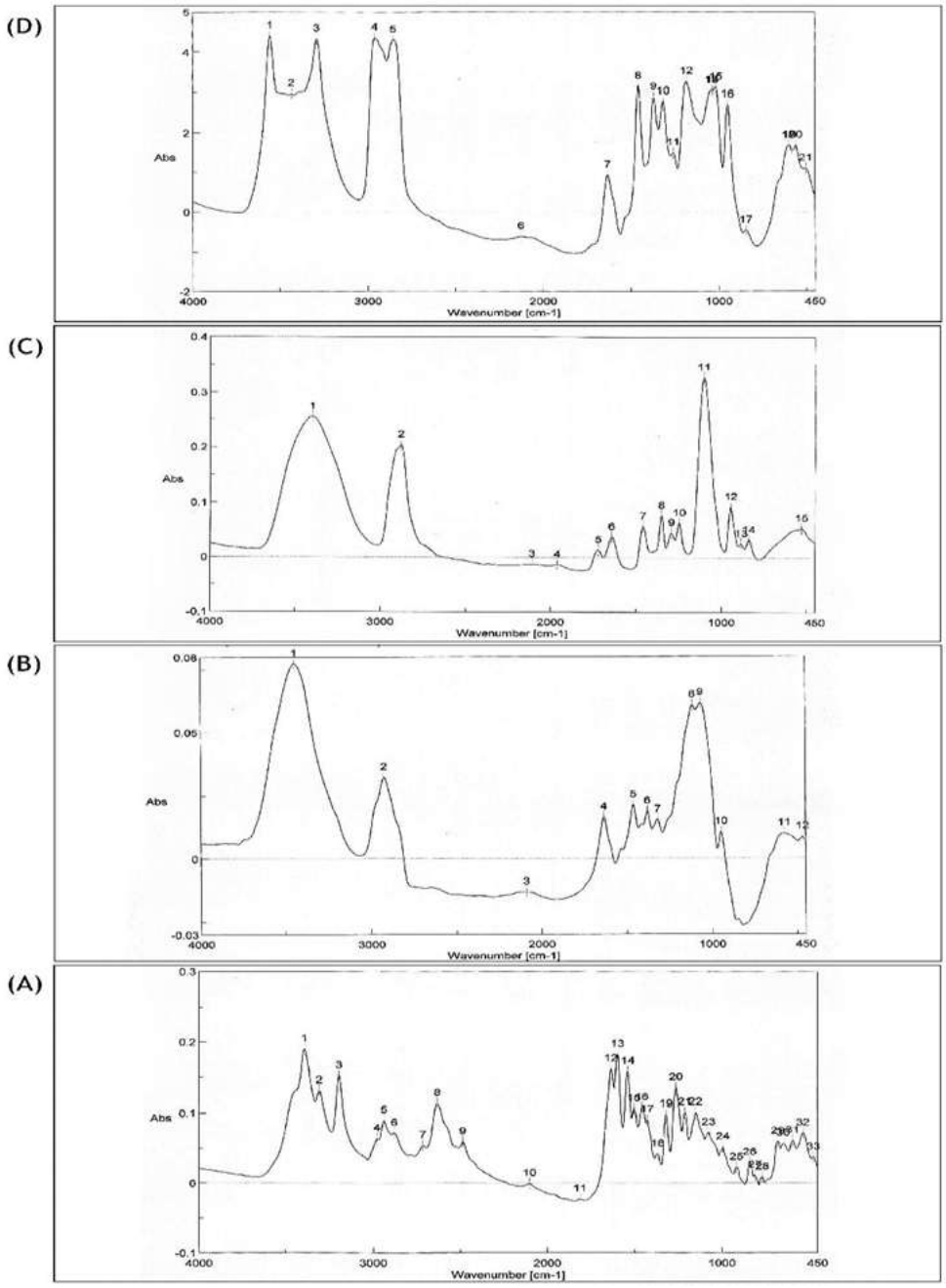

Figure 6: FTIR spectra of Metoclopramide HCl film A) Pure drug, B) Pure HPMC, C) Pure PEG 400, D) Film (G3)

In order to get further evidence on the possible interaction and complex formation, differential scanning calorimetry (DSC) studies were performed on OWs containing drug as well as the individual components of it. DSC thermograms in figure 7, showed a distinct peak at 183^{o}C indicating the pure drug. Notably, a significant shift of drug peak was observed upon formulating the drug within the wafer indicating the presence of interaction between drug and the polymers as described before in FTIR.

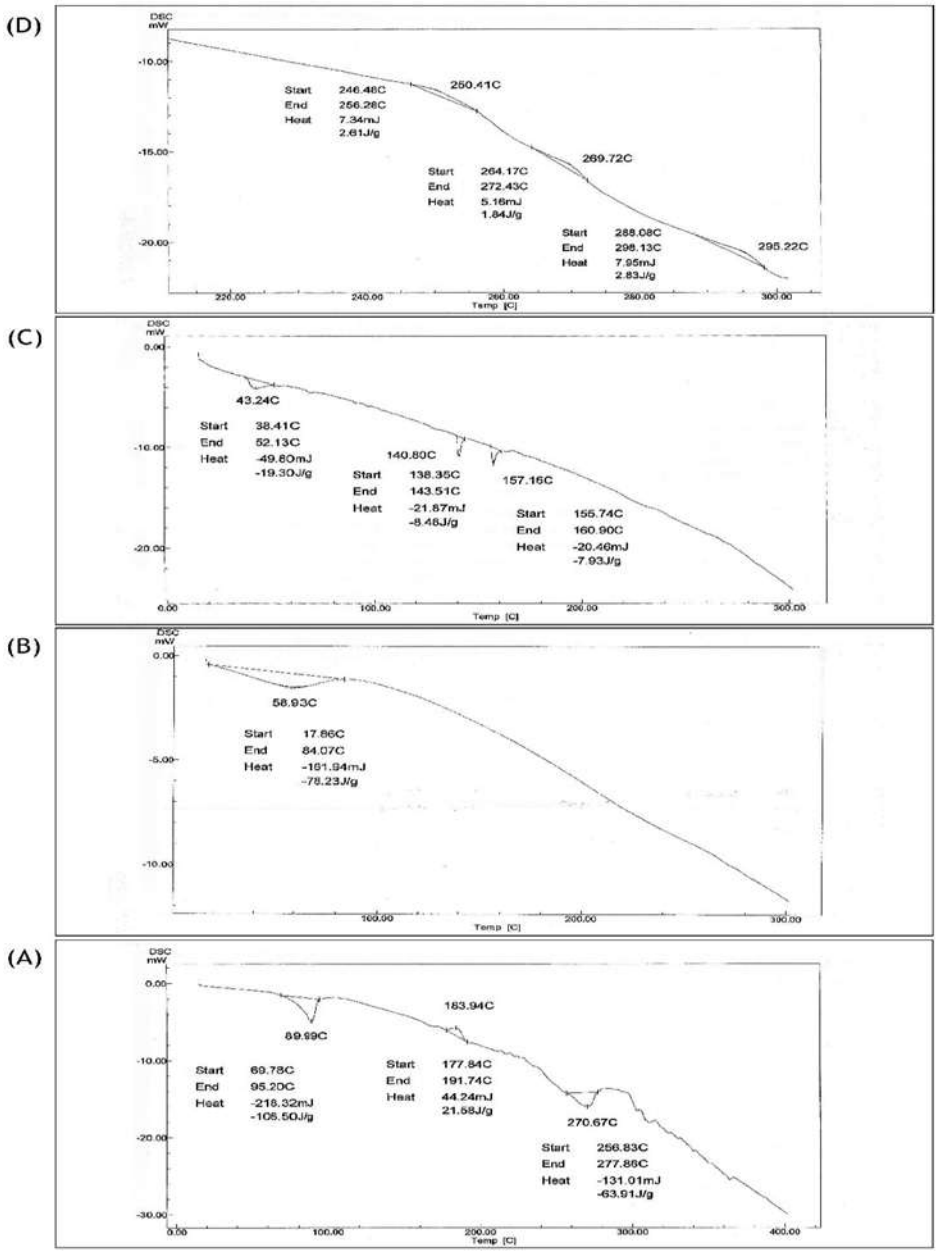

Figure 7: DSC spectra of Metoclopramide HCl film. A) Pure drug, B) Pure HPMC, C) Pure PEG 400, D) Film (G3)

Stability study

Results of the stability study of the optimized OW (G3) are represented in Tables (5 and 6). From the obtained results, it was observed that there was non-significant difference in thickness, weight, drug content, surface pH, tensile strength, % elongation and mucoadhesiveness between the fresh G3 and the stored formulations. In addition to, the marginal difference in the in vitro dissolution properties. From these results, it was concluded that the formulated OW not affected by storage.

***In vivo* studies**

Oral wafers of MET HCl are new dosage forms that are not available in the market and were

prepared to overcome the problems associated with oral route, which might be unsuitable for pediatrics due to difficulty in swallowing especially during the episodes of emesis; also the buccal wafers are non-invasive dosage form which are accepted in pediatrics rather than the parenteral route**.**

Table 5: Stability parameters of stored OW formulation (G3)

Parameters	**Fresh G3**	**Room temperature**		**Refrigeration**	
		After 2 weeks	**After 3 months**	**After 2 Weeks**	**After 3 months**
Thickness	0.16 ± 0.01	0.17 ± 0.02	0.18 ± 0.13	0.17 ± 0.04	0.15 ± 0.01
Weight variation	0.256 ± 0.51	0.25 ± 0.2	0.24 ±0.39	0.261 ± 0.08	0.267 ± 0.11
Drug content	98.9 ± 0.05	97.1 ± 0.31	99.2 ± 0.15	96.8 ± 0.24	96.4 ± 0.19
Surface pH	6.96 ± 0.21	6.4 ± 0.4	6.7 ± 0.22	6.2 ± 0.61	6.9 ± 0.72
Tensile strength	21.21 ± 0.44	20.4 ± 0.3	19.8 ± 0.44	22.2 ± 0.19	21.4 ± 0.31
% Elongation	41.51 ± 0.63	39.8 ± 0.91	38.7 ± 1.01	40.12 ± 0.82	39.43 ± 1.20
Mucoadhesiveness	32.6 ± 0.23	33.2 ± 0.36	33.4 ± 0.4	32.9 ± 0.45	32.7 ± 0.51

* Data are expressed as mean ± standard deviation of the mean (SD), n=3

Table 6: *In-vitro* dissolution data of stored OW formulation (G3).

Time (h)	**Fresh G3**	**Room temperature**		**Refrigeration**	
		After 2 weeks	**After 3 months**	**After 2 Weeks**	**After 3 months**
0	0	0	0	0	0
15	69.927 ± 5.25	67.17 ± 2.14	68.09 ± 1.78	69.7 ± 0.91	70.12 ± 1.12
30	84.03 ± 0.387	79.1 ± 1.23	80.4 ± 2.12	77.14 ± 2.30	78.9 ± 1.14
45	85.425 ± 1.07	81.98 ± 3.11	81.1 ± 1.03	79.2 ± 2.80	80.14 ± 0.14
60	86.66 ± 3.47	83.12 ± 0.18	83.7 ± 0.11	82.9 ± 1.02	84.3 ± 0.44
90	88.308 ± 2.36	85.15 ± 1.12	84.8 ± 0.60	85.9 ± 1.17	85.14 ± 0.91
120	87.87 ± 2.77	86.19 ± 0.18	85.1 ± 2.13	86.23 ± 2.11	86.14 ± 3.16
180	88.06 ± 1.12	87.11 ± 0.74	86.4 ± 1.07	87.89 ± 1.13	87.12 ± 1.11
240	87.936 ± 2.003	84.03 ± 1.22	83.2 ± 0.18	84.8 ± 0.98	88.7 ± 0.76

* Data are expressed as mean ± standard deviation of the mean (SD), n=3

Pharmacokinetic Study

The plasma concentration-time profiles of MET HCl after oral administration and MET HCl loaded OW were shown in figure 8. The mean pharmacokinetic parameters of MET HCl from those different formulations are represented in Table 7. From the obtained results, it was noticed that after the oral administration of the pure drug solution, the peak plasma concentration of MET HCl (C_{max}) was (861.942 ± 17.573 ng/ml) reached after 3 h. In contrast, after administration of the MET HCl loaded oral wafer, the peak plasma concentration (C_{max}) was (1325.083 ± 43.288) reached after 1 h. It was observed that the formulated OW has higher C_{max} and lower T_{max} than the oral formula [36]. The mean AUC_{0-24} was found to be 5319.81 ± 163.46 ng.hr.ml^{-1} for the wafer compared to 3944.86 ± 141.43 ng.hr.ml^{-1} for the plain drug, higher Cmax and an increased AUC

values (in the case of buccal film) signifying an increased rate and extent of MET HCl absorption from the buccal films as compared to the oral plain drug, this increase in the extent of drug absorption from oral wafer formulation may be attributed to the fact that the buccal route of administration bypasses the gastrointestinal tract and the hepatic first pass effect. It can be concluded from this study that buccal films provide a better alternative to oral delivery of MET HCl [37, 38].

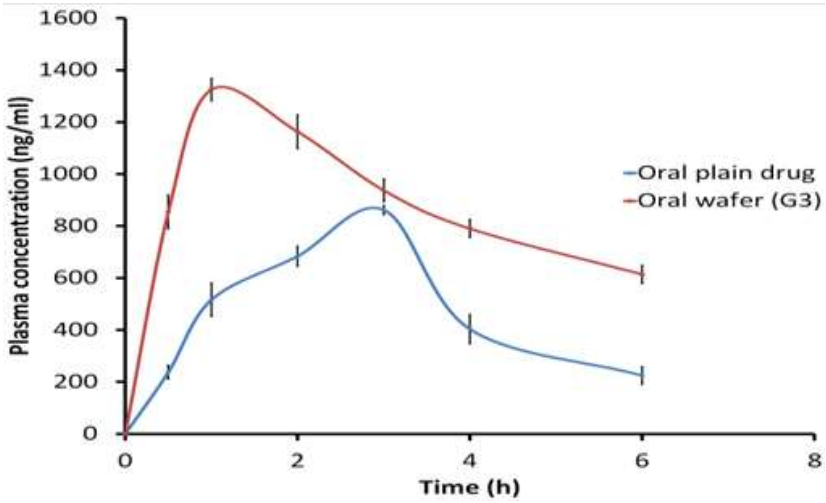

Figure 8: Mean plasma concentrations of Metoclopramide HCl after administration of pure MET HCl and MET HCl loaded wafers (equivalent to 7. 5 mg/kg) to rabbits.

Table 7: Pharmacokinetic parameters after administration of pure MET HCl and MET HCl loaded oral wafer (G3).

Parameters	Pure MET HCl	The selected formula (G3)	P value
C_{max} (ng/ml)	861.942 ± 17.573	1325.083*** ± 43.288	P<0.0001
T_{max} (h)	3.00± 0.09	1.00*** ± 0.1	P<0.0001
K_{el} (h^{-1})	0.1287 ± 0.009	0.149* ± 0.008	0.0432
$t_{1/2}$ (h)	5.4013 ± 0.397	4.642* ± 0.253	0.0491
AUC_{0-24} (ng.h/ml)	3944.86 ± 141.43	5319.81*** ± 163.46	0.0004
$AUC_{0-\infty}$ (ng.h/ml)	4212.749 ± 179.74	9424.63*** ± 271.54	0.6379
$AUMC_{0-\infty}$ (ng.hr^2/ml)	29135.22 ±3555.92	66909.88*** ± 3408.61	0.0002
MRT (h)	6.902 ± 0.61	7.099 ± 0.28	0.0004

* Data are expressed as mean± standard deviation of the mean (SD), n=3

*** Significant at p<0.001.

CONCLUSION

Oral wafers can be used as an excellent substitute for drinking oral medication or injection. Metoclopramide HCl loaded Oral wafers composed of 300 mg HPMC and 20% PEG 400 (G3) was the preparation of choice for the bioavailability study due to its superior tensile strength, percent elongation, mucoadhesiveness and faster drug release. It could be concluded that G3 formulation

lead to a highly significant increase in C_{max}, AUC_{0-24} and lowering in T_{max} compared to the oral plain drug, so enhancement in the rate and the extent of drug absorption from our formulation was achieved; this can be advantageous for effective and fast treatment for emesis and nausea, especially in postoperative care for pediatrics. Clinical trials are recommended for the future work.

CONFLICT OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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