

Original Research Article

# Bioequivalence study of buccal formulations of two prokinetic agents versus the conventional oral tablets.

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## Abstract

This study was to investigate the efficiency of buccal dosage forms to deliver poor orally absorbed drugs. Two buccal gel formulations containing two gastrokinetic drugs with low oral bioavailability; domperidone and mosapride citrate; were tested against their market products. Twenty-four volunteers were enrolled in this study divided into two groups in a single dose, two treatment and two periods cross over design. Both buccal formulations achieved high relative bioavailabilities ( $F_{rel}$ ) compared to the market products where buccal gel of domperidone achieved  $F_{rel}$  of 202% and buccal gel of mosapride citrate achieved 162%. The study reveals the importance of the buccal route for administration of poorly absorbed drugs from the gastrointestinal tract.

**Keywords:** Prokinetic, buccal, transcutol, penetration, area under the plasma concentration – time profile, elimination rate constant.

## Introduction

Prokinetic agents are currently being investigated as potential therapies for motility disorders of the lower gastrointestinal tract. Cholinergic agonists such as bethanechol are known to improve postoperative ileus but are limited because of side effects. Dopamine antagonists such as domperidone appear to have maximal prokinetic effect in the proximal gastrointestinal tract and are effective for such conditions as gastroparesis and gastroesophageal reflux, but they appear to have little physiologic effect in the colon or in colonic motility disorders. Cisapride and its derivatives appear to hold the most promise for patients with colonic motility disorders. [1].

Domperidone is a selective peripheral dopamine antagonist at the D2 receptor and it is used in the prevention and symptomatic relief of acute nausea and vomiting. The buccal delivery of domperidone could therefore be convenient to avoid oral administration. The passive delivery of domperidone through the skin was previously investigated by Blanes and co-workers, 1990 [2]; Calpena and co-workers 1994 [3]; and Hadgraft and coworkers, 1995 [4]. Although absorption is rapid, the systemic bioavailability of domperidone is only about 15% in fasting subjects given an oral dose; this increased when domperidone is given after food. The low bioavailability is thought to be due to first-pass hepatic and intestinal metabolism. The bioavailability of rectal domperidone is similar to that after oral doses, although peak plasma concentrations are only about one-third that of an oral dose and occur after about an hour, compared with 30 minutes after an oral dose [5].

Mosapride citrate is 5-HT<sub>4</sub> receptor agonist and 5-HT<sub>3</sub> receptor antagonist. Displays no activity at D<sub>2</sub>, 1, 2, 5-HT<sub>1</sub> and 5-HT<sub>2</sub> receptors. Gastroprokinetic agent; increases gastric emptying in rats and stimulates gastric motor activity in conscious dogs. Masahiko Fujisawa and coworkers found it has an effect reducing the gastro-intestinal damage induced by NSAIDs[6]. Mosapride citrate is a novel agent that has not been yet evaluated for both percutaneous and mucosal delivery. Oral bioavailability was 8% of the dose in dogs and 14% in monkeys, suggesting the extensive first-pass metabolism of mosapride[7].

Buccal drug delivery offers several advantages over the peroral route. These advantages include avoidance of presystemic drug elimination within the gastrointestinal tract and/or during the hepatic first-pass metabolism, and independence from the potential variability of absorption caused by the gastric emptying rate, or the presence of food in the upper region of the gastrointestinal tract [8]. In addition, the buccal mucosa is relatively permeable with a rich blood supply and has a substantial resistance to irritation or damage [8-10]. Other important advantage is the facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation and versatility in designing as multidirectional or unidirectional release systems for local or systemic actions [11]. The permeability of the buccal mucosa is four to 4,000 times greater than the permeability across skin. As a result, a faster onset of action for several drugs is observed [12]. A shorter turnover time in the oral mucosa (14 days) as opposed to skin (27 days) ensures a faster recovery of the oral mucosa [13].

The aim of this study to compare the bioavailability of two buccal gel formulations containing each of the prokinetic drug against the

conventional oral tablet formulations present in the Egyptian market.

## Materials and Methods

### Test and reference products

The test and reference products for both domperidone and mosapride citrate are shown in tables (1, 2).

**Table 1: Test formulations used in the study**

Composition	Db	Mb
Solvent system	Transcutol P: water (40:60%)	Propylene Glycol :Water (40:60%)
Drug	3.5 mg /ml (domperidone)	2.5 mg/ml (mosapride citrate)
Polymer concentration	2% Chitosan	2% Xanthan gum
Other excipients	0.05% menthol 0.05% Saccharin sodium	0.05% menthol 0.05% Saccharin sodium

**Table 2: Market products used in the study**

Product	Motilium®	Fluxipride®
Content	10 mg domperidone	5 mg mosapride citrate
Batch Number	BFE1452	1031100
Expiry date	5/2016	10/2013

### Study Design

The study was approved by the Research Ethical Committee of BeniSuef University, Egypt. The study was assigned in fasted state with single-dose, two-treatment, two-period, and two-sequence crossover study. Volunteers were randomly allocated to two groups of equal number. Group 1 was administered with domperidone test product followed by the reference product whereas Group 2 started with mosapride citrate test product followed by the reference product. Each volunteer received both products with 1-week washout period.

### Volunteers

Twenty-four healthy Egyptian male volunteers, aged between 18-24 years old with normal body mass index were participated in the study. All volunteers were in good health condition based on medical history. No drug or smoking was allowed 1 month before the study period to avoid the effect of inducing or inhibiting hepatic metabolizing enzymes and risk of drug interaction. The method and condition of the study were clearly informed to all volunteers and a signed informed consent was obtained from all volunteers before entering the study.

### Dosage and drug administration

Test products of domperidone and mosapride citrate were administered as a single dose equivalent to 5 and 2.5mg respectively were spread in the cavity between the gums and the upper and lower lips using an applicator. The reference products (Motilium® 10mg and Fluxipride® 5mg tablets respectively) were administered as a single dose of 10 and 5mg respectively with a cup of water.

In both periods, volunteers were instructed to avoid drinking or eating for 4 hours after the administration. After 4 hours, volunteers

were served with standard meal after over night fasting and were allowed to take liquids.

### Organoleptic characteristics

Volunteers were invited to refer about possible irritation, bad taste, dry mouth or excessive salivation and all other parameters able to influence patient usability. All the parameters observed were tabulated.

### Blood samples collection

A 5ml blood samples were collected at predose (0h) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12 and 24 hr after dose.

### Sample Preparation and HPLC Conditions

Blood samples were centrifuged for 10min at 3000 rpm and the plasma was taken and immediately kept at -20°C until assay.

For domperidone samples; 0.5ml plasma was mixed with 100ul of 2 M NaOH plus 30 ul of 230ng/ml solution of simvastatin as internal standard. Samples were then mixed in vortex mixer for 10 seconds. 6 ml of ethyl acetate were then added to the mixture and vortex again for 45 seconds. The samples were then centrifuged for 10 min at 5000 rpm at 10°C. Afterwards, samples were transferred to be evaporated under vacuum until dryness. The dry residue are then reconstituted with 50ul mobile phase, vortex for 30 seconds then loaded into the LC/MS system to be injected.

The prepared samples were analyzed using a LC/MS system consisting of a reverse phase C-18 column (Luna, Phenomenex, 5 um, 50mm X 4.6 mm). The system consisted of a binary pump (Shimadzu, LC-20AD binary pump, Japan), a degasser (Shimadzu, DGU- 20A, Japan) and an autosampler (Shimadzu, SiL- 20A, Japan). Detection was performed by an Applied BiosystemsSciex API-3200 detector (Applied BiosystemsSciex, Ontario, Canada) using Turbo-Ion Spray for ion production. The mobile phase was



methanol: acetonitrile: water (10:70:20 v/v) containing 0.1% formic acid, with a flow rate of 1mL/min. The calibration curve of this method was constructed between the concentrations of 0.5-40ng/ml and the  $r^2$  of the fitted line was 0.994.

For mosapride citrate samples; 1ml plasma was mixed with 6 ml of tertiary butyl methyl ether plus 100  $\mu$ l of 250ng/ml solution of itopride as internal standard and mixed in vortex mixer for 45 seconds. The samples were then centrifuged for 10 min at 5000 rpm at 10°C. Afterwards, 5ml of the decantant of samples were transferred to be evaporated under vacuum at 45°C until dryness. The dry residue are then reconstituted with 250ul mobile phase, vortex for 30 seconds then loaded into the LC/MS system to be injected.

The prepared samples were analyzed using a LC/MS system consisting of a reverse phase C-18 column (Luna, Phenomenex, 5  $\mu$ m, 50mm X 4.6 mm). The system consisted of a binary pump (Shimadzu, LC-20AD binary pump, Japan), a degasser (Shimadzu, DGU- 20A, Japan) and an autosampler (Shimadzu, SiL- 20A, Japan). Detection was performed by an Applied BiosystemsSciex API-3200 detector (Applied BiosystemsSciex, Ontario, Canada) using Turbo-Ion Spray for ion production. The mobile phase was Acetonitrile:water (80:20% v/v) containing 0.1% formic acid, with a flow rate of 1mL/min. The calibration curve of this method was constructed between the concentrations of 0.5- 40ng/ml and the  $r^2$  of the fitted line was 0.989.

## Statistical Methods and Data Analysis

### Pharmacokinetic Analysis

Maximum plasma concentration ( $C_{max}$ ) and time to reach the peak concentration ( $t_{max}$ ) were obtained directly from the plasma concentration-time profiles. The area under the plasma concentration-time profile from time zero to infinity ( $AUC_{0-}$ ) and half-life ( $t_{1/2}$ ) were determined regarding noncompartmental analysis. The slope of the terminal log-linear portion of the plasma concentration-time profile was determined by least square regression to find an elimination rate constant ( $K_e$ ). The area under the plasma concentration-time profile from time zero to the last

quantifiable point ( $AUC_{0-t}$ ) was calculated using the trapezoidal rule and the area from the last quantifiable point to infinity ( $AUC_{t-}$ ) was determined as  $C_t/K_e$ . The  $AUC_{0-}$  was the sum of  $AUC_{0-t} + AUC_{t-}$ . Relative bioavailability ( $F_{rel}$ ) referred to the following equation:

$$\text{Relative bioavailability} = \frac{\left(\frac{AUC_{\text{of buccal gel}}}{\text{Dose of buccal gel}}\right)}{\left(\frac{AUC_{\text{of oral tablet}}}{\text{Dose of oral tablet}}\right)}$$

The PK parameters were generated using WinNonlin® non-compartmental analysis version 6 (Pharsight Corp., Palo Alto, California) using linear trapezoidal method.

### Statistical Analysis

One way analysis of variance (ANOVA) was done to determine the statistical deference of  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-}$  which represented the extent and rate of drug absorption. All the statistical analysis was done with the level of significance of  $p < 0.05$  using IBM™SPSS statistical analysis for Windows®.

## Results and Discussion

### Volunteers' safety

Twenty four healthy Egyptian volunteers participated in the study. Their mean values of age, weight, height and body mass index were  $28.61 \pm 6.63$  year,  $62.23 \pm 5.00$  Kg,  $1.69 \pm 0.04$  m and  $22.38 \pm 1.65$  Kg/m<sup>2</sup>, respectively.

The dose regimen was well tolerated in all volunteers. There was no complaint on the therapy or presence of signs and symptoms of overdosage.

Both test products showed good residence time of 4 hr. After application and during the entire residence, the gels did not cause any appreciable alteration, without producing dry mouth or excessive salivation. In addition, gel formulations did not cause irritation or burning sensation (see table 3). Volunteers reported that formula Mb was so sweet like market food products due to the presence of propylene glycol and saccharin sodium which are common ingredients in these products.

**Table 3: In vivo evaluation of organoleptic properties and acceptability**

Formula	Irritation	Pain	Taste <sup>a</sup>	Dry mouth	Excessive salivation	Other
Db	No	No	++	No	No	----
Mb	No	No	+++	No	No	----

<sup>a</sup> Taste: good +++, acceptable ++, bad +.

### Pharmacokinetics and Bioequivalence

The *in vivo* pharmacokinetic parameters of domperidone test and market products in table (4) and the plasma concentration – time profiles in figure(1) show that the oral market product exhibited a normal extravascular profile with a maximum plasma concentration ( $C_{max}$ ), time for maximum concentration ( $t_{max}$ ), area under the

plasma concentration – time profile ( $AUC_{0-t}$ ), ( $AUC_{0-}$ ) and elimination rate constant  $K_{el}$  of  $4.99 \pm 0.499$  ng/ml,  $2 \pm 0.5$  hr,  $31.7 \pm 2.4$ ,  $40.54 \pm 3.02$  ng.hr/ml and  $0.0534 \pm 0.0092$  hr<sup>-1</sup> respectively. The pharmacokinetics values in this study were lower than the values reported by previous studies [14, 15].

The  $AUC_{0-24}$  and  $AUC_{0-}$  of the gel test formula (Db) were higher ( $34.16 \pm 4.2$  and  $41.62 \pm 5.2$  ng.hr/ml respectively) than those of the

oral tablet product ( $31.7 \pm 2.42$  and  $40.54 \pm 3.02$  ng.hr/ml respectively) ( $p > 0.05$  in case of AUC<sub>0-</sub>). The relative bioavailability *Frel* of the test product to the oral product was 202%. In addition, the plasma drug concentration profile of the buccal gel showed a concentration region with a steady state drug concentration of 2ng/ml for duration of 5 hrs.

The steady state pattern of domperidone plasma concentration could be attributed by looking into the buccal gel formulation. The presence of high concentration of transcutool P in the formula may lead to drug accumulation in the buccal mucosal tissue as a sustained release depot from which the drug is slowly absorbed over extended period. The effect of transcutool P on creating drug

depots in skin as another biological barrier was discussed in many research articles [16, 17].

Transcutol is a hygroscopic liquid that is freely miscible with both polar and non-polar solvents. Transcutol has been recognized as a potential transdermal permeation enhancer due to its non-toxicity, biocompatibility with skin and mucous membranes and superb

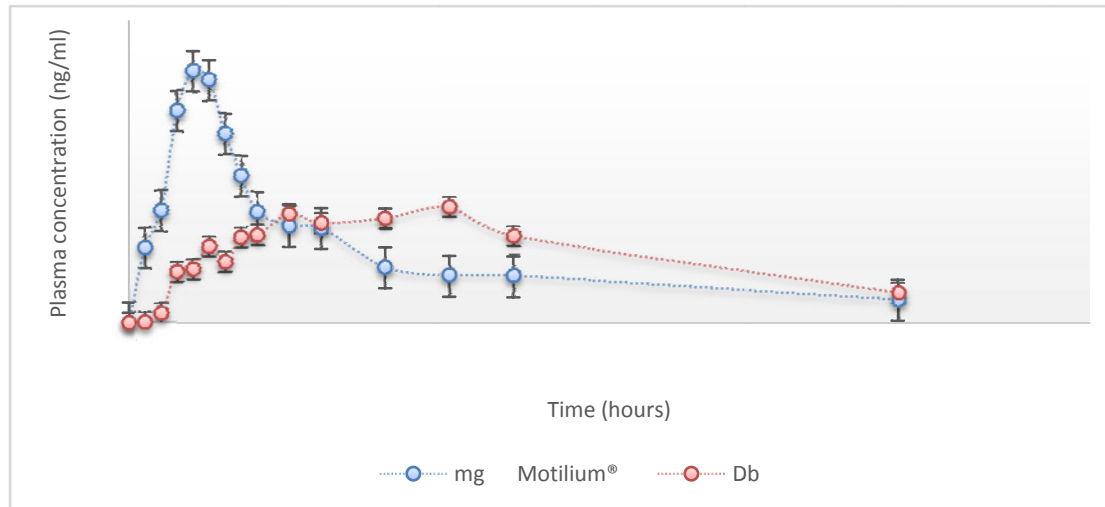


Figure 1: Domperidone plasma concentration versus time profile obtained after single dose of Motilium Tab.(10mg/body) and domperidone buccal gel formula D29 (5mg/body) (mean±SD, n=12)

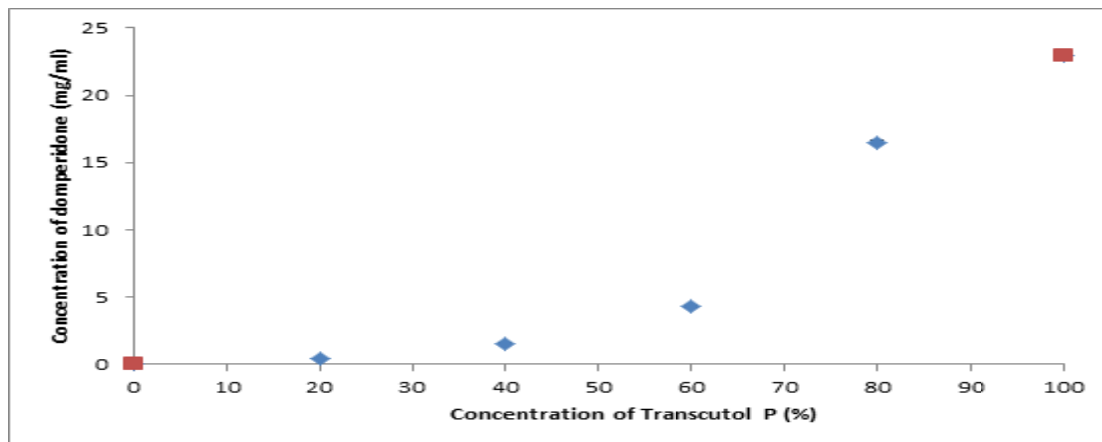


Figure 2: Solubility of domperidone in different binary systems (n=3)



**Table 4: Pharmacokinetics parameters obtained from Domperidone plasma concentration versus time profile obtained after single dose of Motilium Tab.(10mg/body) and domperidone buccal gel formula D29 (5mg/body) (mean±SD, n=12)**

Formulation	Dose (mg)	C <sub>max</sub> (ng/ml)	t <sub>max</sub> (hr)	AUC <sub>0-24</sub> (ng.hr/ml)	AUC <sub>0-</sub> (ng.hr/ml)	Terminal phase slope (hr <sup>-1</sup> )
Market product	10	4.99±0.49	2±0.5	31.7±2.42	40.54±3.02	0.0534±0.0092
Test product (Db)	5	2.15±0.243	5±1	34.16±4.2	41.62±5.2	0.0928±0.039

solubilizing properties. However, transcutool has also been reported to increase the skin accumulation of topically applied compounds without accompanied increase in transdermal permeation[18].

Mixing transcutool with water could eliminate the hygroscopic effect of transcutool alone that resulted in the water back flux and retardation of domperidone thermodynamics in the donor compartment that happened with pure transcutool as single solvent. In addition, these levels of transcutool showed high effect on the drug flux through both membranes due to the synergistic action of water; through its lyotropic action on the mucosal lipids and the solubilizing action of transcutool[19].

Also, the presence of domperidone in the gel formula in a supersaturated state (1.5 degree of saturation) (see figure 2, unpublished data) may aided the accumulation effect of transcutool through increasing the flux of domperidone inside the buccal mucosa. Supersaturated systems have been used as a passive technique for enhancing drug permeation through skin as a biological barrier [20-25]. Though, supersaturated systems are known of their instability and fast loss of its condition through crystallization of the drug. Using polymers as anti-nucleating agents is a very useful tool to keep the supersaturated state of drug solutions and maintain the thermodynamic activity of the drug [26-28]. Using chitosan polymer as an anti-nucleating agent in formula Db maintain the permeation efficiency of domperidone through the buccal mucosa throughout the experiment.

he *in vivo* pharmacokinetic parameters of mosapride citrate in table (5) and the drug plasma concentration – time profiles in figure (3) show that both products; the buccal gel and the market product; exhibit normal extravascular profiles. The maximum plasma concentration (C<sub>max</sub>), time for maximum concentration (t<sub>max</sub>), area under the plasma concentration – time profile (AUC<sub>0-t</sub>), (AUC<sub>0-</sub>) of both products were within the range of previous findings [29-31]. The AUC<sub>0-24</sub> and AUC<sub>0-</sub> of the oral tablet were higher (60.2± 4.3 and 87.5± 24.6 ng.hr/ml, respectively) than those of the buccal gel (Mb) product (59.97± 5.82 and 71.20± 12.9 ng.hr/ml respectively)

(p>0.05). The relative bioavailability  $F_{rel}$  of the test product to the oral product was 162.73%.

The high bioavailability of mosapride citrate from its buccal gel formulation could be attributed to the use of powerful yet safe penetration enhancer such as propylene glycol as co-solvent. Propylene glycol permeation enhancement effect has been discussed in many research articles[25, 32-36]. Since PG can penetrate mucosa, drugs dissolved in PG transport with PG [37]. The actual mechanism by which propylene glycol increases the permeation of topical applied drugs was discussed in research papers. Bendas *et al* suggested that the action of propylene glycol is considered as a “Drag effect”, the drug has high solubility in the solvent so it drag it along its diffusion in the biological membrane [37].

Huth *et al* put a spotlight on the mechanism of PG enhancing effect on the permeation of different substances by mathematical assessment. Covering substances with different solubilities in PG, the study indicated that the fraction of drug penetrating by cotransport increased as the solubility in PG increased. Furthermore, a higher PG content in the vehicle leads to a markedly higher importance of the cotransport pathway [32].

In both experiments, the high bioavailability of both prokinetic drugs was achieved through avoiding the first pass metabolism and utilizing the high permeability of the buccal mucosa.

## Conclusion

The study shows that it is possible to formulate two poorly soluble, poorly absorbed drugs in a buccal gel formula with good relative bioavailability and patient tolerance. This opens the door for further formulations of low bioavailable drugs in form of buccal dosage forms.

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