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Original article

In vitro and *in vivo* characterization of domperidone-loaded fast dissolving buccal films

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ABSTRACT

The delivery of drugs via fast dissolving films is an effective alternative for drugs with low bioavailability when administered by other routes. This is the case of domperidone (DMP) an anti-emetic drug with low water solubility and vulnerable to extensive first-pass effect. To overcome these limitations, in this work, we designed and produced fast dissolving muco-adhesive buccal films of domperidone using varying amount polyvinylpyrrolidone (PVP K-90) using the solvent casting method. Films loaded with more than 10% of drug were not homogenous and opaque as indicated by white patches of drug in the film matrix. Formulation of DMP in the film form resulted in conversion of the drug from crystalline state to the semi-crystalline state as indicated by X-ray powder diffraction analysis. Moreover, about 40% of drug loaded within the films was released during the first five minutes compared to only about only 6.5% of pure drug in drug dissolution assays *in vitro*. *In vivo* pharmacokinetics analysis revealed that the DMP-loaded film had higher maximum plasma concentration (C_{max}) and shorter time to reach C_{max} (T_{max}) than a commercially available tablet formulation. In conclusion, the produced DMP buccal film formulation showed high absorption rate, rapid onset of action, and improved bioavailability compared with the conventional tablet. Our findings may support the development of novel dosage forms for the transmucosal delivery of DMP for convenient, rapid, and effective treatment of nausea and vomiting.

1. Introduction

The buccal delivery of drugs has recently emerged as an effective and safe alternative over other conventional routes of drug administration. Buccal administration easily release the loaded drug into the buccal cavity for either local or systemic effects. This route of administration is especially suitable in pediatric and geriatric contexts, where patients often struggle to ingest traditional oral solid dosage forms. Moreover, the buccal route is very convenient for drugs that are inactivated in the gastric environment, drugs that irritate the gastrointestinal tract, and during nausea and vomiting episodes (Arya et al., 2010; Rao et al., 2013; Reddy et al., 2013; Almeida et al., 2015; Aboutaleb et al., 2016; Chougule, 2017; Junmahasathien et al., 2018). Various buccal dosage forms are now commercially available, including muco-adhesive films and tablets, oral disintegrating tablets, hydrogels, and fast dissolving films.

Fast dissolving buccal films are thin oral strips composed of hydrophilic polymers. They rapidly dissolve in the saliva without the need of water, releasing the loaded drug immediately in the oral cavity and offering a very rapid onset of action (Almeida et al., 2015; Chougule, 2017). Ideally, these films should be highly water soluble, have good mechanical properties, present compatibility with the loaded drug, and possess certain muco-adhesive properties. Different polymers, such as hydroxypropyl methylcellulose, methylcellulose, polyethylene glycol (PEG), pullulan, polyvinylpyrrolidone (PVP), gelatin, and maltodextrin, have been

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successfully used in the preparation of fast dissolving films (Arya et al., 2010; Pathare et al., 2013; Teodorescu and Bercea, 2015).

Domperidone (DMP) is an anti-emetic drug that stimulates the motility of the stomach and bowel, which speeds up the passage of food through the stomach into the intestine, helping in the treatment of nausea and vomiting. Additionally, DMP keeps the cardiac sphincter properly closed, so that the stomach content do not leak back up into the esophagus. These effects are mainly attributed to its antagonistic action on dopamine D_2 receptors at the chemoreceptor trigger zone (Patil et al., 2016; Gunda et al., 2016; Sadozai et al., 2013). However, DMP is poorly soluble in water (1 mg/mL) and its oral bioavailability is in the range of 15–17% of the administered dose. Such a low oral bioavailability stems from its low aqueous solubility, extensive first pass effect, and efflux mediated by transporters in the small intestine (Helmy and El Bedaiwy, 2014; Athukuri and Neerati, 2017). Therefore, the buccal delivery of DMP might be used as an alternative route to overcome the disadvantages of its oral administration. Transmucosal delivery of DMP is expected to (i) accelerate the onset of action, due to rapid absorption, (ii) enhance bioavailability, due to avoidance of first pass effect, and (iii) allow self-administration, improving patient compliance. Moreover, it might also benefit pediatric and geriatric patients suffering from nausea and vomiting (Alipour et al., 2015; Nagendrakumar et al., 2015; Aboutaleb et al., 2016; Ali et al., 2016; Chonkar et al., 2016; Kadam et al., 2017; Bala and Sharma, 2018).

The objective of this study was to prepare and characterize fast dissolving buccal films containing DMP, which may be suitable for the treatment of nauseous and vomiting patients. We hypothesized that solvent casting of DMP with PVP would improve its solubility and absorption from the buccal cavity, resulting in rapid action and improved bioavailability. To do so, we prepared films using the solvent casting method with PVP as film forming material and ethyl alcohol as casting solvent. PVP perform dual duties, it will act as film forming matrix and in the same time the polymer will convert the drug from the low water solubility form (crystalline form) to more water soluble form (amorphous form). According, there will be no need to improve the solubility of drug before incorporation into the film form. Then, we characterized the films with respect to their physiochemical properties, *in vitro* drug dissolution, and *in vivo* pharmacokinetics.

2. Materials and methods

2.1. Materials

Domperidone was kindly provided by Sedico Pharmaceuticals (Cairo, Egypt). Polyvinyl pyrrolidone K-90 (PVP K-90) and PEG 400 were purchased from Fluka Chemical (Neu-Ulm, Germany). Ethyl alcohol and tween 80 were purchased from El-Nasr Pharmaceutical Chemicals (Cairo, Egypt). All other chemicals and reagents were of pharmaceutical grade.

2.2. Preparation of fast dissolving films

Domperidone-loaded fast dissolving films were prepared using the solvent casting method as previously reported –(Sharma et al., 2018). Briefly, PVP K-90, DMP, and other excipients were accurately weighed and dissolved in 50 mL of ethanol followed by stirring for 30 min at room temperature. Then, the alcoholic solution was poured into a clean ceramic-coated mold and the solvent was allowed to evaporate at room temperature under laminar air flow. After complete evaporation of the solvent, the produced dry films were carefully removed and visually inspected for defects and air bubbles. Finally, the prepared films were packed in aluminum foil and stored in a desiccator until further use. To determine maximum loading capacity, films containing increasing amounts of the drug namely 5%, 10% and 15% w/w of the dried film weight have been prepared (Senthilkumar and Vijaya, 2015; Ali et al., 2016). We designed ten different DMP-containing fast dissolving oral film formulations, where citric acid was used as saliva stimulating agent, PEG 400 as plasticizer, and tween 80 as drug dispersant (Table 1).

2.3. Fourier-Transform infrared spectroscopy (FT-IR)

Interactions between the drug and polymer components are likely to occur due to their intimate contact. Thus, Fourier-transform infrared spectroscopy (FT-IR) was used to detect chemical interactions and assess the compatibility of DMP with the excipients. The spectra of the samples (pure DMP, pure PVP K-90, physical mixture, and the F6 DMP film) at a range of 4,000–400 cm^{-1} were recorded with an FT-IR spectrophotometer (IR-470, Shimadzu, Kyoto, Japan) using the KBr disc method (Kadam et al., 2017).

2.4. Powder X-Ray diffraction (XRD)

Powder X-ray diffraction patterns were obtained analyzing pure DMP, pure PVP K-90, physical mixture, and the F6 DMP film. Each sample was scanned in a Bragg-Brentano diffractometer (PW1050, Philips, Amsterdam, Netherlands) over a 2θ range from 40 to 600 at a scanning rate of 0.06/min (Zayed, 2014).

2.5. Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) images of pure DMP and the surface of the F6 film, as well as transverse sections of the F6 film were obtained in a scanning electron microscope (JSM-6400, Jeol, Tokyo, Japan). Samples were coated with gold using ion sputtering at 15 kV prior to analysis (El-Feky et al., 2018).

2.6. Surface pH

The pH of the produced films was determined by dissolving pieces (6 cm^2) of each film in 10 mL distilled water. Films were completely dissolved and the pH was measured using a pH meter (Jenway, Felsted, UK) by placing the electrode on the surface of the dissolved film solution (Ali et al., 2016). The mean value of three readings was recorded.

2.7. Mechanical properties

The understanding of the mechanical properties of rapid dissolving films is fundamental since they are exposed to intense mechanical stresses during preparation, packing, and sticking to the oral mucosa (Sharma et al., 2015). Therefore, we assessed film thickness, tensile strength, elongation, and folding endurance of the prepared films.

2.7.1. Film thickness

The thickness of each film was measured using an electronic digital micrometer (MIME Technology Europe, Maastricht, Netherlands). Ten randomly selected film pieces of each formulation were tested for their thickness. Thickness was measured at 5 separate points of each film and the average thickness was calculated (Alipour et al., 2015).

2.7.2. Tensile strength and elongation

The tensile strength and percent elongation were determined using a tensile tester (Model 1128, Instron, Norwood, MA, USA). Briefly, a piece of film of a known width and thickness was placed

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Table 1
Composition of the prepared films containing domperidone.

Formulation	Component (%, w/w)				
	PVP K-90	PEG 400	DMP	Citric acid	Tween 80
F1	93.00	–	5	2	–
F2	83.00	10.0	5	2	–
F3	88.00	–	10	2	–
F4	78.00	10.0	10	2	–
F5	72.50	12.5	10	2	–
F6	70.00	15.0	10	2	–
F7	65.00	15.0	15	2	–
F8	63.00	15.0	15	2	2.00
F9	64.25	15.0	15	2	0.75
F10	64.50	15.0	15	2	0.50

PVP, polyvinylpyrrolidone. PEG, polyethylene glycol. DMP, domperidone.

in the grips of the tensile tester. The long axis of the film was aligned with the tensometer grips drawing an imaginary line joining the points of attachment of the grips. Grips were evenly and firmly tightened to a degree that prevented slippage of the film during the test, but did not crush the sample. The tensile strength is the maximum stress applied right before the film sample breaks. It is calculated from the applied load at rupture and the cross-sectional area of fractured film applying the following equation (Eq. (1)) (Sharma et al., 2015):

$$Tensil\ \ strength = \frac{load\ \ at\ \ failure(N)}{film\ \ thickness\ \ (mm) \times film\ \ width\ \ (cm)} \quad (1)$$

Elongation as a function of the applied load was recorded at the moment of rupture. Elongation is the increase in length produced in the gage length of the sample by a tensile load. It is usually measured at the moment of film rupture (percent elongation at rupture) and can be calculated using the following equation (Eq. (2)) (Bhattarai and Gupta, 2015):

$$Percent\ \ elonagation = \frac{L - Lo}{Lo} \times 100 \quad (2)$$

where L_o is the original distance between the two grips of the tensometer and L is the distance between the two grips at the moment of film rupture.

2.7.3. Folding endurance

Folding endurance was determined by repeatedly twisting the film, at the same point, up and down until it was teared or broken. The number of times that the film could be twisted up and down without breaking is the value of folding endurance. Three randomly selected film pieces of each formulation were tested (Sarangi et al., 2017).

2.8. Water sorption

Due to the hydrophilic and hygroscopic nature of the film-forming polymer (PVP), water sorption may be an issue for packaging and storage. Water sorption increases film weight, decreases drug stability, and increases disintegration time of the film. To assess water sorption, three pieces of each film were weighted. Then, the film pieces were secured in a pinch, left at room temperature, and reweighed every five minutes until there was no increase in weight (Tomar et al., 2012).

2.9. Weight variation and drug content

Films were assessed for weight variation by individually weighing three film pieces (6 cm^2) of each formulation using a digital balance (Bala and Sharma, 2018). To analyze drug content, a piece of 6 cm^2 (2 cm × 3 cm) was used for formula containing 5% w/w of the drug (F1 and F2) and a piece of 3 cm^2 (2 cm × 1.5 cm) was used for determination of drug content for formula containing 10% of the drug (F3 – F6). Each film piece was dissolved in 100 mL of ethanol and the absorbance was measured spectrophotometrically at 284 nm (Aboutaleb et al., 2016; Bhikshapathi et al., 2014; Alim et al., 2015; Javali et al., 2017).

2.10. In vitro disintegration time and drug release

The drop method was used to investigate the *in vitro* disintegration of the prepared films. Briefly, three film pieces (6 cm^2) of each prepared formulation were fixed on the top of conical flasks and one drop of phosphate buffer (pH 6.8) was placed on the surface of the film. The time required for the drop to pass through the film was recorded (Maher et al., 2016). The *in vitro* release of DMP from the films, as well as the dissolution of pure DMP, was assessed using USP Drug Dissolution Apparatus II (Paddle type). Aliquots (10 mg) of pure DMP and the equivalent piece of each film were accurately weighed and placed in individual dissolution vessels containing 500 mL of phosphate buffer (pH 6.8) kept at 37 ± 0.5 °C and stirred at 50 rpm. At appropriate time intervals (1, 2, 3, 4, 5, 10, 15, 20, 25 and 30 min), 5 mL of the dissolution medium were withdrawn and replaced with an equal volume of fresh buffer to keep the volume of the dissolution medium. The withdrawn samples were filtered and the drug content was determined spectrophotometrically at 284 nm. All experiments were carried out in triplicate and the results are presented as mean values of the three experiments over time. Then, we used the dissolution data to calculate model independent parameters to compare the profiles of different formulations (Bhikshapathi et al., 2014; Chen et al., 2014; Zayed, 2014; Alipour et al., 2015; Simionato et al., 2018).

2.11. In vivo pharmacokinetics

In vivo pharmacokinetic studies were carried out to determine the rate and extent of buccal drug absorption from the F6 film and a commercial DMP tablet. The study protocol was approved by the Animal Care and Use Committee, Al-Azhar University at Assiut. Nine healthy male white New Zealand rabbits with an average body weight of 2.25 kg were divided into three groups of six rabbits. The first group was the negative control group, which received saline solution. For the groups administering oral DMP dose, the animal dose was calculated based on the human dose using the conversion factor (Reagan-Shaw et al., 2008). The second group was the positive control group, were administered calculated animal dose of DMP commercial tablets equivalent to 0.52 mg DMP equivalent to human dose. The third group received formula F6 film, in which pieces of film equivalent to 0.52 mg DMP

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(equivalent to human dose) were placed in the inner side wall of mouth cavity. Care was taken to assure that the films were attached to the buccal mucosa. Blood samples (2 mL) were withdrawn from the ocular vein at 5, 10, 15, 30, 60, 120, 240, and 360 min post administration. Plasma was obtained centrifuging blood samples at 5,000 rpm for 10 min (Thermo Fisher Centrifuge, Waltham, MA, USA) and kept at −20 °C until analysis.

Domperidone plasma concentrations were determined using a previously reported HPLC method (Shazly et al., 2018; Singh et al., 2010). Briefly, samples were injected into a HPLC system (Waters, Milford, MA, USA) attached to an auto sampler and a photodiode array detector (PDA). A reverse phase C_{18} column (RP-C_{18}, 150 mm × 4.6 mm, Phenomenex, Torrance, CA, USA) was used. The mobile phase was a mixture of phosphate buffer:acetonitrile: methanol (40:30:30, v/v). Flow rate was maintained at 1.5 mL/min, and the PDA was set at 284 nm. Curves showing DMP plasma concentration over time were constructed and different pharmacokinetics parameters, such as area under the curve (AUC), T_{max}, C_{max}, and absorption rate constant (K_a), were calculated (Shazly et al., 2018; Khan et al., 2016).

2.12. Statistical analysis

Statistical analysis was carried out using Minitab 15 Statistical Software (Minitab, State College, PA, USA). Student's *t*-test was used to compare the *in vitro* DMP release from film formulations to that from the free DMP form. Moreover, *t*-test was used to detect differences in the *in vivo* drug performance between the F6 film and the commercial tablet. Data are presented as mean ± standard deviation (SD, n = 3).

3. Results and discussion

After solvent casting, films had smooth surfaces and were dry, thin, flexible, transparent, and free from bubbles. Dry films were easily removed from the ceramic mold (casting container), probably because of the presence of plasticizer (PEG 400). Under visual inspection, films F1–F6 were homogenous (Fig. 1A). However, when drug loading exceed 10% (w/w), as in films F7–F10, the films were not transparent, even when tween 80 was used as a dispersing agent (Fig. 1B). This indicates that the amount of polymer was insufficient to convert the DMP from the crystalline state to the amorphous state and form a solid solution. Thus, some of DMP was precipitated as white crystals (Fig. 1B). Since this artifact could greatly affect the physical properties and biological performance of the prepared film, films containing more than 10% DMP were not tested in *in vitro* release assays and *in vivo* pharmacokinetic studies.

3.1. Fourier-transform infrared spectroscopy (FTIR)

The spectrum of pure DMP is characterized by FT-IR peaks at 3,390, 3,080, 2,915, 1,697, and 1,400–1,600 cm^{-1}. The spectrum of the F6 film exhibited all main peaks present in pure DMP, pure polymer, and physical mixture. These observations strongly indicate the absence of any chemical interaction between the drug and excipients used during film preparation (Balakrishna et al., 2016).

3.2. X-ray powder diffraction (XRD)

The diffraction pattern of pure DMP is characterized by sharp intense peaks in 2θ range from 5 to 45 (Fig. 2A), indicating high drug crystallinity. However, the diffractogram of PVP K-90 (Fig. 2B) shows diffused shadow peaks, indicating the amorphous nature of the polymer. On the other hand, the diffraction pattern of the drug polymer physical mixture (Fig. 2C) shows the combination of the characteristic peaks of pure DMP and the diffused peaks of polymer. In the case of F6 film, the sharp intense peaks of pure DMP were absent (Fig. 2D). Conversely, a single sharp intense peak in 2θ range from 25 to 30 was evident, which suggests the transformation of the drug from the stable crystalline form to the highly energetic semi-crystalline form. Such transformation is in agreement with several previous studies (Maher et al., 2016; Chen et al., 2014; Suksaeree et al., 2017; Christina, 2014).

3.3. Scanning electron microscopy (SEM)

The SEM of pure DMP revealed particles with smooth surfaces and micrometer-sized rod-shaped structures (Fig. 3A), indicating the high crystalline nature of the drug. For the F6 film, the surface of film was nearly smooth without any evident drug particles (Fig. 3B). Few pores can be seen on the film surface, which could be formed during the solvent evaporation step of the casting method. Moreover, the SEM image of the F6 film transverse section indicated the formation of a homogenous layer with uniform thickness (Fig. 3C). Moreover, even at high SEM magnification, it is very difficult to detect any drug particles inside the film (Fig. 3D). This further indicates the conversion of the drug from the crystalline state to the semi-crystalline and/or molecular form. This finding is in accordance with XRD patterns of the pure DMP and the DMP-containing film. Such a reduction in drug crystallinity is

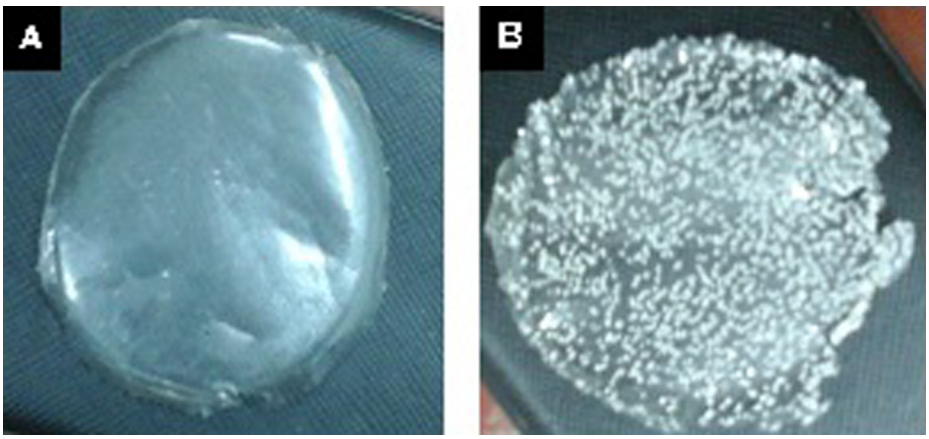

Fig. 1. Representative images of films loaded with (A) 10% (w/w) or (B) 15% (w/w) domperidone.

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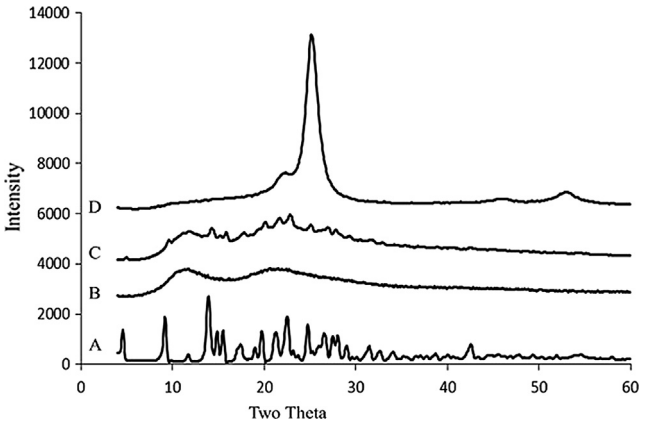

Fig. 2. X-ray powder diffraction patterns of pure domperidone (A), pure polymer (B), physical mixture (C), and the F6 film (D).

expected to improve its dissolution rate (Prem Kumar et al., 2014; Raghavendra and Prem Kumar, 2017).

3.4. Surface pH

The surface pH of the prepared films ranged from 6.5 to 6.8. This range is close to neutrality and compatible to the buccal pH. Therefore, the prepared films are expected to not cause any irritation to buccal mucosa (Kumria et al., 2016).

3.5. Mechanical properties of films

3.5.1. Thickness

The thickness of the produced DMP films ranged from 19.66 ± 0.417 μm to 21.66 ± 0.928 μm (Table 2), which indicates a uniform thickness among the prepared formulations. This uniform thickness of DMP films may assure uniform distribution of the drug and polymer inside the film, leading to the uniformity in weight and drug content (uniform dosing).

Table 2
Mechanical characterization of domperidone oral films.

Formulation	Thickness (μm)	Tensile strength (MPa)	Elongation (%)
F1	20.33 ± 1.247	57.58	26.44
F2	21.66 ± 0.942	60.33	22.49
F3	21.33 ± 0.41	40.28	46.00
F4	20.33 ± 0.371	38.58	73.33
F5	20.00 ± 0.816	38.19	114.66
F6	19.66 ± 0.417	30.07	144.53
F7	21.66 ± 0.928	22.52	288.66
F8	21.00 ± 0.00	15.72	295.00
F9	21.66 ± 0.414	35.60	142.00
F10	20.66 ± 0.471	12.27	275.00

Data are presented as mean ± SD (n = 3).

3.5.2. Tensile strength and elongation

Tensile strength analyses showed that films without plasticizers were hard and easily teared upon applying the stress (Table 2). On the other hand, the addition of plasticizers greatly increased the elasticity of the films, resulting in the enhancement of their physicomechanical properties. Regarding percent elongation, the results showed that the increase in the concentration of plasticizer (PEG 400) led to an increase in the elasticity and percent elongation of the films (Table 2); the percent elongation increased from 22.49% (F2) to 295.00% (F8) as the concentration of PEG 400 increased.

3.5.3. Folding endurance

Folding endurance values of the produced films were higher than 16 folds, indicating good strength and elasticity, which can attributed to the use of the plasticizer.

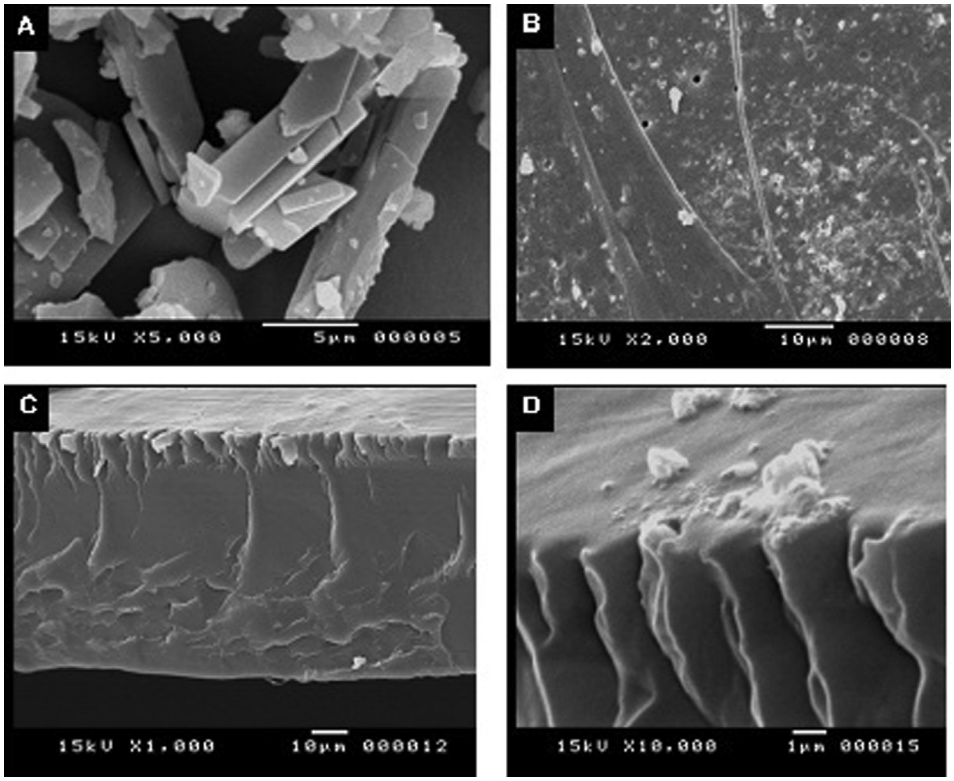

Fig. 3. Representative scanning electron microscopy images of pure domperidone (A), the surface of the F6 film (B), and transverse sections of the F6 film (C and D).

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Table 3
Weight variation, content uniformity, water sorption, *in vitro* disintegration time, and surface pH of domperidone oral films.

Formulation	Weight Variation (%)	Content Uniformity (%)	Water Sorption (%)	Disintegration Time (s)	Surface pH
F1	100.33 ± 1.247	97.58 ± 0.462	2.44	160	6.7
F2	101.66 ± 0.942	100.33 ± 0.825	2.49	165	6.8
F3	101.33 ± 0.4 ± 1	100.28 ± 1.002	1.46	158	6.65
F4	100.33 ± 0.371	98.58 ± 1.023	3.33	155	6.7
F5	100.00 ± 0.816	98.19 ± 0.956	4.66	157	6.5
F6	99.66 ± 0.417	100.07 ± 0.556	4.53	160	6.7
F7	101.66 ± 0.928	102.52 ± 0.968	3.66	162	6.6
F8	101.00 ± 0.00	100.72 ± 0.843	2.95	160	6.7
F9	101.66 ± 0.414	98.60 ± 0.517	1.42	160	6.7
F10	100.66 ± 0.471	102.27 ± 0.836	2.75	165	6.8

Data are presented as mean ± SD (n = 3).

3.6. Water sorption

Minimal water sorption was observed for all the prepared DMP film formulations (Table 3), which indicated low hygroscopic ability of the films.

3.7 wt. variation and drug content uniformity

All DMP films passed weight variation test where the percent of weight variation in the range of 100% ±1.5 (Table 3) (Londhe and Umalkar, 2012).

3.8. In vitro disintegration

The *in vitro* disintegration time of the film formulations was within the 155–165 s range. This could be attributed to the high hydrophilicity of the excipients. This result may be an indicator of a fast dissolution of the film and rapid release of the entrapped drug during buccal administration (Kumar et al., 2014).

3.9. In vitro drug release

The *in vitro* release of pure DMP reached 12% after 30 min (Fig. 4). Such a low releases is related to its low solubility and high crystallinity, confirmed by XRD and SEM data (Figs. 2 and 3). On the other hand, the rate of drug release from films F1–F6 was significantly higher than that of the pure drug (Fig. 4). Such an enhanced drug release from films confirms the conversion of DMP from its poorly soluble crystalline state to a semi-crystalline state that is highly soluble in water. Moreover, the addition of plasticizers and the PVP matrix improve the water solubility and consequently the release rate from films (Raimi-Abraham et al., 2015).

Based on model independent parameters of dissolution profiles, film F6 had the highest dissolution efficiency (DE), the highest relative dissolution rate (RDR), and the shortest mean dissolution time (MDT, Table 4). The similarity factor (*f2*) between dissolution profile of pure drug and that of all tested formulation was <50, whereas the dissimilarity (difference) factor (*f1*) of the films was higher than 15. These findings indicate that a much higher dissolution of DMP is obtained from DMP-loaded films than that from the

Table 4
Model-independent parameters of domperidone dissolution from different film formulations.

Formulation	Dissolution Parameters					
	DE (%)	RDR	PD_{30}	MDT	*f2*	*f1*
Pure drug	8.74	1.00	11.51	7.20	–	–
F1	62.62	6.68	95.40	10.27	16	614
F2	64.92	6.98	97.79	9.81	15	665
F3	66.56	7.33	99.29	9.35	14	696
F4	69.31	8.23	100.00	8.53	13	740
F5	75.46	9.56	100.00	6.76	11	805
F6	81.26	10.50	100.00	5.12	9	866

DE, dissolution efficiency. RDR, relative dissolution rate. PD_{30}, percent dissolved in 30 min. MDT, mean dissolution time. *f2*, similarity factor. *f1*, difference factor.

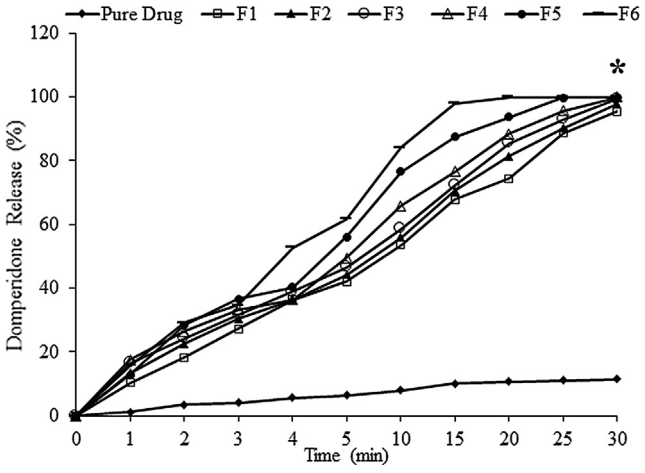

Fig. 4. *In vitro* domperidone dissolution from different film formulations. Data are presented as mean ± SD (n = 3). The asterisk denotes significant differences (p < 0.05) between any film formulation (F1, F2, F3, F4, F5, and F6) and the free form of domperidone.

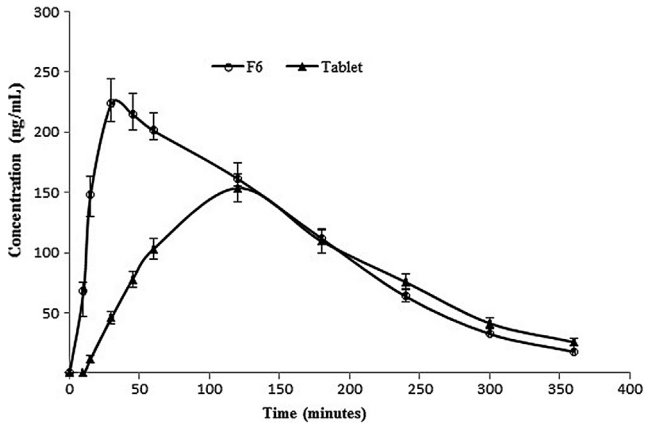

Fig. 5. Domperidone plasma concentration in rabbits after buccal administration of the F6 film (circles) or the commercial oral tablet (triangles). Data are presented as mean ± SD (n = 6). The asterisk denotes a significant difference (p < 0.05) between F6 and the commercial tablet formulation.

Table 5
Domperidone pharmacokinetic parameters after buccal administration of the commercial tablet and the F6 film.

Formulation	Pharmacokinetic Parameter				
	C_{max} (ng/mL)	T_{max} (min)	K_a (min^{-1})	AUC_{0-6} ($ng.hr \cdot mL^{-1}$)	Relative Bioavailability (%)
Commercial tablet	181.74	120	4.17	29,429.72 ± 1226	100.00
F6 film	223.80*	30*	24.51*	38,875.75 ± 1168*	131.89

Data are presented as mean ± SD (n = 3). The asterisks denote significant differences ($p < 0.05$) between F6 and the commercial tablet formulation within the same column. C_{max}, maximum plasma concentration. T_{max}, time to reach maximum plasma concentration. K_a, absorption rate constant. AUC_{0-6}, area under the curve for the first 6 h after administration.

pure drug. Again, this large difference in dissolution rates could be attributed to the decreased drug crystallinity as indicated by XRD data (Zayed, 2014; Raimi-Abraham et al., 2015).

3.10. In vivo pharmacokinetics

We compared the *in vivo* drug performance of the F6 film with that of a conventional oral tablet (Motinorm® tablet). The film produced a significantly higher plasma concentration of DMP than the commercial tablet in the first hour after buccal administration (Fig. 5, Table 5). The maximum plasma concentration (C_{max}), equal to 223.8 ng/mL, was obtained after only 30 min of film administration. Conversely, the C_{max} (181.74 ng/mL) of the oral tablet took 2 h to occur. Drug absorption was higher for the F6 film, as indicated by a significantly higher absorption rate constant (K_a), than for the commercial tablet (Table 5). Moreover, the F6 oral film had a higher area under the curve (AUC) and consequently higher relative DMP bioavailability than the commercial tablet. These findings can be attributed to the rapid drug release, high absorption, and, more importantly, avoidance of hepatic pre-systemic metabolism. Overall, *in vivo* results were in line with *in vitro* data, including drug release, rapid action, and enhanced bioavailability (Kumria et al., 2016; Sayed et al., 2013).

4. Conclusion

In this work, we designed and successfully produced fast dissolving flexible buccal films containing DMP using highly water soluble excipients. No physicochemical interaction was observed as a result of the formulation of the drug in the film form. Incorporation of DMP in fast dissolving films markedly reduced drug crystallinity. As a result, the release and absorption of the drug from the film were much higher than those from either pure drug crystals or a commercially available tablet. Biologically, the film showed short T_{max}, high C_{max}, large absorption rate constant (K_a), and, thus, enhanced relative bioavailability. The formulated fast dissolving oral film stands as a promising dosage form for the transmucosal delivery of DMP for rapid and effective treatment of nausea and vomiting.

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