Research Article

Effervescent Mouth Dissolving Tablets of Domperidone: Formulation, Characterization and Pharmacokinetic Evaluation

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ABSTRACT

Difficulties of swallowing and first-pass metabolism are of the major limitations of oral medicaments resulting in patient non-compliance and poor oral bioavailability. These drawbacks can be avoided by the administration of alternative dosage forms e.g. mouth dissolving tablets (MDTs) that dissolve upon contact with saliva and consequently allowing systemic drug absorption via buccal mucosa. This study aimed to prepare MDTs containing ternary solid dispersion of domperidone/polyvinyl pyrrolidone K30/pluronic F-127. MDTs were prepared using different excipients where powdered blends were evaluated to investigate their flow properties followed by physical characterization of the directly compressed tablets. Formula (F_6) containing 40% w/w effervescent base as a disintegration-aiding agent and 5% w/w Avicel PH-102 as a binder achieved the best results according to the standard specifications. Stability studies that were conducted to this formula recommended that precautions must be taken to avoid the negative impacts of the inappropriate manufacturing and storage conditions on the physical properties of MDTs. Moreover, pharmacokinetic study in human volunteers was conducted on formula (F_6) showing that drug bioavailability was improved up to 164.84% relative to the convenient oral tablets which means that the administration of MDTs via buccal route had the ability to bypass the first-pass metabolism.

Keywords: Ternary solid dispersion; mouth dissolving tablets; glycine; effervescent base; Avicel PH-102; polyethylene glycol 4000; gelatin; human volunteers.

INTRODUCTION

There are different routes of drug administration. Each route has its own purposes, advantages and limitations. It should be known that the speed in which the administered medicaments are absorbed, is a function of both the route of administration and the dosage form.[1] Oral solid dosage forms e.g. swallowed tablets and capsules, are widely used all over the world since they are preferred to the patient and the clinician alike, self and easily administered, easily manufactured and physicochemically stable.[2-4] Despite the advantages of oral route, it has some disadvantages that make it unsuitable for some drugs that e.g. are subjected to hepatic metabolism which affects their bioavailability, irritate gastric mucosa such as NSAIDs, undergo degradation at the acidic pH of the gastric juice and that have slow onset of action which is unsuitable for emergencies.[3,5] To attain the advantages of oral route with avoidance of its limitations, alternative dosage forms can be formulated to dissolve upon contact with salivary secretion without any fluid intake and thus the dissolved drug is directly absorbed to the systemic circulation via buccal mucosa.[6] These dosage forms are called mouth dissolving tablets (MDTs).

Domperidone (DMP) is a weak base antidopaminergic antiemetic drug with a good solubility in acidic pH.[7] In order to formulate DMP as MDTs, it should have an acceptable solubility in saliva that has pH range of 5.5-7.0.[8] Therefore and as a primary step, it is necessary to enhance the solubility and dissolution rate of DMP in phosphate buffer pH 6.8 that could simulate the pH of saliva. Solid dispersion technique is one of the physical modifications that can be used to enhance the solubility and dissolution rate of poorly water-soluble drugs using different polymers.

In order to formulate MDTs, the most effective excipients are binders and disintegrants that should be selected rightly to maintain tablets physical strength, achieve fast disintegration of tablets and consequently fast dissolution and absorption of the active substances.[5]

The present work aimed to prepare MDTs containing ternary solid dispersion (SD) of DMP/polyvinyl pyrrolidone K30 (PVP K30)/pluronic F-127 (PL F-127), which was prepared by solvent evaporation method. MDTs were prepared by direct compression technique. Different types of binders were used in one concentration (5% w/w) e.g. polyethylene glycol 4000 (PEG 4000), microcrystalline cellulose PH-102 (Avicel PH-102) and gelatin. Disintegration-aiding agents such as glycine amino acid and effervescent base were incorporated in three different concentrations; 10, 20 and 40% w/w for each. Before tableting, powder blends were evaluated for angle of repose, Carr's index and Hausner ratio to investigate their flow properties. MDTs were characterized physically through different parameters e.g. physical appearance, content uniformity, uniformity of weight, thickness, diameter, hardness, friability, moisture content, dispersion time, *in-vitro* disintegration time, *in-vivo* disintegration time and in-vitro dissolution studies. To investigate the effect of manufacturing and storage

conditions on the physical properties of MDTs, the best formula was subjected to stability studies. In addition, pharmacokinetic study were performed by evaluating different pharmacokinetic parameters to investigate drug bioavailability compared to convenient oral tablets.

MATERIALS AND METHODS

Materials

Domperidone was given as a gift from Delta Pharma Company for Pharmaceutical Industries, Cairo, Egypt. Dichloromethane was purchased from Fisher Scientific UK LTD, Leicestershire, UK. Polyvinylpyrrolidone K30 was supplied by Himedia laboratories PVT, LTD, Mumbai, India. Anhydrous calcium chloride and pluronic F-127 were obtained from sigma-aldrich Inc, Missouri, USA. Polyethylene glycol 4000 was purchased from Scharlau Chemie, S.A, Barcelona, Spain. Microcrystalline cellulose PH-102 was supplied by Alandalus Import and Export, Kaliobeya, Egypt. Fructose was purchased from Safety Misr Co., Cairo, Egypt. Glycine, gelatin, mannitol, menthol, magnesium stearate, talc powder, methanol AR, monobasic potassium hydrogen phosphate, sodium hydroxide pellets, sodium bicarbonate, citric acid, tartaric acid and sodium lauryl sulfate were obtained from EL Gomhouria Co, Cairo, Egypt. Methanol (HPLC grade) and acetonitrile (HPLC grade) were purchased from Riedel-de Haën Gmbh, Hanover, Germany All other ingredients were of analytical grade.

Phase solubility studies

The effect of PVP K30 and PL F-127 on the solubility of DMP was investigated according to the phase solubility technique.[9]

An excess amount of DMP (75 mg) was added to 20 ml PVP K30 solutions ranging in concentration from 1% to 5% w/v prepared in 0.2 M phosphate buffer solution (pH 6.8) in a series of 50 ml stoppered glass bottles. The obtained suspensions were shaken at 25±0.5° C for 7 days in a thermostatically controlled shaking water bath (Julabo SW 20C, Allentown, USA). DMP content was assayed spectrophotometrically at wavelength of 284 nm using UV/VIS spectrophotometer (UV- 1650 PC, Shimadzu Corporation, Kyoto, Japan) and the regression equation of the standard curve that was developed in the same medium.

To investigate the effect of PL F-127 on DMP solubility, the previously mentioned solubility phase study was repeated using phosphate buffer solution (pH 6.8) containing 5% w/v PVP K30 and increasing consecration of PL F-127 ranging from 2% to 4.5% w/v.

Preparation of DMP ternary solid dispersions (SDs) by solvent evaporation method

To prepare SDs of DMP with PVP K30 and PL F-127 in weight ratios of 1:9:0.125, 1:9:0.25 and 1:9:0.5, respectively; an appropriate amount of each polymer was added to a solution of DMP in methanol-dichloromethane (1:1 v/v). The solution was stirred at room temperature for 2 hours using magnetic stirrer (1200, Jenway, Staffordshire, UK) and then poured into an open tray located in a closed hood for at least 12 hours to allow slow evaporation of solvent.[10] After drying overnight, the solid residue was scratched, dried in a vacuum oven for 24 hours at room temperature, pulverized and sieved through USP mesh sieve no. 45 (TX, Tongxin, Henan, China). Powdered samples were stored in closed containers and kept away from light and humidity in a desiccator containing anhydrous calcium chloride as a dehydrating agent until further evaluation.

Preparation of physical mixtures (PMs)

PMs were prepared by simple trituration of DMP and polymers with their respective weight ratios in a porcelain mortar for 5 minutes. PMs obtained were then sieved through USP mesh sieve no. 45, kept in closed containers and stored as mentioned before until further evaluation.[11]

In-vitro dissolution studies

In-vitro dissolution studies of plain DMP and its different systems were performed in 500 ml of phosphate buffer (pH 6.8) using dissolution USP apparatus II (rotating paddle) rotating at 100 rpm and maintained 37±0.5° C. At predetermined time intervals, aliquots of dissolution medium were withdrawn through 0.45 µm syringe filters and analyzed spectrophotometrically. Withdrawn samples were replaced by freshly prepared medium to keep the volume constant and all the determinations were carried out in triplicate.

The dissolution profiles were evaluated by means of four parameters: i) initial dissolution rate that was calculated as percent of the drug dissolved over the first 15 minutes per minute (IDR_{15} %/min), ii) percentage of the drug dissolved after 2 minutes (PD_2), iii) Percentage of the drug dissolved after 10 minutes (PD_{10}) and iv) dissolution efficiency parameter after sixty minutes (DE_{60}%) (Data of PD_2 only shown).[12-14]

Kinetic studies

To survey more precisely the mechanism of drug release from the prepared SDs and PMs, in-vitro dissolution data were fitted to zero order, first order and Higuchi kinetic equations.[15]

Fourier-transform infrared spectroscopy (FTIR)

FTIR spectra of the selected SD and PM were performed using FTIR spectrophotometer (FTIR 4100, JASCO, Essex, UK) compared to their individual components. Potassium bromide disc technique was used at 6-8 tons, 13 mm die size, 400-4000 cm^{-1} scanning range and resolution of 1 cm^{-1}.

Differential scanning calorimetry (DSC)

DSC analysis was carried out using differential scanning calorimeter (DSC-50, Shimadzu Corporation, Kyoto, Japan). Samples (1.5-2.5 mg) were heated in a hermetically sealed aluminum pans at 30-300° C and

constant rate of 10° C/min under a nitrogen purge of 30 ml/min.

Powder X-ray diffraction (PXRD)

PXRD patterns were obtained using X-ray powder diffractometer (XGEN 4000, Scintage Inc., California, USA) supplied with CuKα radiation. Diffractograms were run at a scanning rate of 1.8 degree min^{-1} and the scanning scope was over a range of 2θ angle from 0 to 80° at room temperature.

A relationship was established between some representative peak heights in the diffraction patterns of ternary systems and those of a reference substance (i.e. plain drug). This relationship was translated into a specific equation that calculates the relative degree of crystallinity (RDC) in order to monitor the change in crystallinity at a designated 2θ value as shown in Equation (1):

$$RDC = I_{sam}/I_{ref}, \quad (1)$$

Where I_{sam} is the peak height of the sample under investigation at certain angle and I_{ref} is the peak height at the same angle for the reference substance (i.e. plain drug) with the highest intensity.[16,17]

Scanning Electron Microscopy (SEM)

SEM was carried out using electron microanalyzer (JXA-840A, JEOL Electron Probe Microanalyzer, Tokyo, Japan) to assess the microscopic surface morphology of the optimized ternary SD and its PM compared to pure DMP. The samples were mounted on a double-sided adhesive tape. Gold coating was applied on the surface of particles before examination to render it electroconductive.

Evaluation of flow properties of dry blends

Dry blends of MDTs were prepared according to % w/w presented in Table 2. In order to investigate the flow properties of dry blends, measurements of angle of repose (α), Carr's index (CI) and Hausner ratio (HR) were adopted.[18]

To measure the angle of repose (α), fixed height cone method was applied where drug-excipient blend was allowed to flow through a funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated according to Equation (2):

$$\alpha = Tan^{-1} height / (0.5 \times base) \quad (2)$$

Where α is the angle of repose, ***height*** is the height of the pile and ***base*** is the diameter of formed cone.

Apparent bulk volume was determined by pouring a weighed quantity of blend (100 g) into a graduated cylinder (250 ml). The volume of this weight was measured and bulk density was calculated (ρ_{bulk}). Tapped volume was also determined by tapping the cylinder contained the powdered blend until no further volume changes occur and tapped density was calculated (ρ_{tap}). Carr's Index (CI) was then calculated as presented in Equation (3):

$$CI = 100 \times (\rho_{tap} - \rho_{bulk})/\rho_{tap} \quad (3)$$

Where ρ_{tap} is tapped density and ρ_{bulk} is bulk density. In addition, Hausner ratio (HR) was calculated using Equation (4):

$$HR = \rho_{tap}/\rho_{bulk} \quad (4)$$

Preparation of MDTs

MDTs were prepared with final weight of 250 mg for each tablet (Table 2). The powdered mixtures were weighed individually and directly compressed with 13 mm flat face surface punches using hydraulic press single tablet punching machine (Shanghai, China). The prepared tablets were stored in well closed containers and kept in a desiccator containing anhydrous calcium chloride as a dehydrating agent until being characterized.

Evaluation of the physical properties of MDTs

Content uniformity was determined by dissolving each of 10 tablets in 50 ml of phosphate buffer (pH 6.8). The solution was filtered and assayed spectrophotometrically at 284 nm with respect to standard calibration curve of DMP. The corresponding concentrations were determined where the tablets must contain 85-115% of the average content.[18]

Weight variation of the prepared MDTs was determined by weighting 20 tablets individually then the average mass was calculated. Not more than two of the individual weights deviate from the average weight by more than 5% and none should deviate by more than twice the percentage.[18]

Hardness was measured using tablet tester (Dr. Schleuniger's Pharmaton, 8M, Thun, Switzerland). The mean breaking strength of each formula was determined.[18]

Friability of MDTs was determined using table friability tester (Pharma test, PTF10ER, Hainburg, Germany). The percentage loss of weights were calculated and taken as a measure of tablet friability.[18]

Moisture content of MDTs was determined in triplicate for each formula using Karl Fischer titration apparatus (787 KF titrino, Metrohm, Herisau, Switzerland) and the average values were tabulated. This test was repeated during stability studies to investigate the effect of elevated temperature and humidity on the physical parameters of the selected formula compared to the freshly prepared tablets.

In-vitro disintegration test was carried out using tablet disintegration tester (Dr. Schleuniger's Pharmaton, DTG-3, Thun, Switzerland). Six tablets of each formula was immersed in 500 ml phosphate buffer pH 6.8 maintained at 37±0.5° C. Time till complete disintegration was recorded and the average value was calculated.

In-vivo disintegration time was measured using three volunteers. Each volunteer rinsed his mouth using 100 ml water and placed the tablet between gum and cheek until

completely disintegrated in saliva. After complete disintegration, the remains were spat out and the mouth was washed with water. The experiment was carried out in triplicate for each formula and the time required to feel no tablet fragments was measured with a stopwatch.[19]

Dispersion time was measured by dropping a tablet in a glass cylinder containing 6 ml of phosphate buffer (pH 6.8) at 37 ± 0.5° C where three tablets were randomly selected for each formula and the average dispersion time was determined.[20]

In-vitro dissolution studies of MDTs compared to the convenient oral tablets were performed as previously done for the dissolution of SDs. Apparatus I (rotating basket) was used for tablets containing effervescent base to avoid their floating,[21] while apparatus II (rotating paddle) was used for other formulae.

Stability studies

Accelerated stability study at 40±2° C and 75±5% relative humidity (RH) and *long term stability study* at 25±2° C and 60±5% RH were performed on the best formula. Physical appearance, content uniformity, friability, moisture content, dispersion time, in-vitro disintegration time, in-vivo disintegration time and in-vitro dissolution studies were re-evaluated after 1, 3 and 6 months for accelerated stability study and after 3, 6 and 12 months for long term stability study compared to the freshly prepared formula.[22]

Pharmacokinetic study on healthy volunteers

Subject selection: Six healthy volunteers of 25-35 years, 64-75 kg and 165-185 cm in height participated in this study. None of subjects had any history of drug abuse, alcohol abuse, gastrointestinal, neurological, cardiovascular, renal or hepatic disease. Physical examinations, clinical investigations and laboratory tests were determined one month prior to the beginning of the study and within 24 hours prior to the start of the study showed normal findings. The protocol of this study was approved by Cairo University, Protection of Human Subjects Committee (PHSC) in accordance with the "Ethical Principles for Medical Research Involving Human Subjects" enunciated in the Declaration of Helsinki,[23] adopted in Helsinki in 1964 and amended in Seoul, South Korea, October (2008). Volunteers were requested to avoid medications for one week prior to and during the study and to become fasted for 12 hours before the study and 4 hours after dosing. They remained under controlled dietary and liquid intake until the end of the study. Moreover, they were watched medically during the period of study.

Study design: The study was performed as a non-blind, two-period, randomized and crossover design consisting of two groups. In group I, half the number of volunteers received (F_6) formula where they were asked to administer the formula by placing it between gum and check until completely dissolved in saliva, while in group II, the rest of volunteers were asked to ingest one of the convenient oral tablets by the aid of 200 ml of water. Venous blood samples were collected at 0, 10, 20, 30, 40, 50 minutes and then after 1, 2, 4, 8, 12, 24 and 48 hours. Blood samples were centrifuged within one hour of collection at 4500 rpm for 15 minutes using bench centrifuge (Rotofix 32A, Hettich Instruments LP, Tuttlingen, Germany) and the plasma was separated and frozen at -20°C until being assayed.

Assay method: Chromatographic separation was performed with a reversed phase C_{18} column (VWR L-2350 250 x 4.6 mm) on High performance liquid chromatography (VWR HITACHI ELITE LaChrom, Tokyo, Japan) coupled with UV detector (VWR L-2400, Tokyo, Japan) having a detection wavelength of 280 nm.

Mobile phase consisted of 50% acetonitrile (HPLC grade) and 50% of 0.05 mM potassium hydrogen orthophosphate adjusted at pH 6.8 with 0.2 M sodium hydroxide. Mobile phase was filtered using 0.45 µm millipore filters (0.45 µm PTFE, Sartorius Stedium biotech, Goettingen, Germany) and then was degassed in a bath sonicator (LeelaSonic-200, Leela Electronis, Maharashtra, India) for 15 minutes. Mobile phase was delivered at flow rate of 1 ml/min and all samples were assayed at ambient temperature. The validation of this chromatographic bioanalytical method was performed in order to evaluate its specificity, recovery, linearity, accuracy, precision, limit of detection (LOD) and limit of quantitation (LOQ).[24]

Pharmacokinetic and statistical analysis: For the assessment of DMP pharmacokinetics, all plasma concentrations data were analyzed using Wagner-Nelson Method. Pharmacokinetic parameters of the buccally absorbed drug compared to the convenient oral tablets included: Maximum peak plasma concentration C_{max} (ng/ml) and its time T_{max} (hr), area under the curve ($AUC_{(0-48)}$ and $AUC_{(0-\infty)}$), mean residence time (MRT), terminal elimination half-life ($t_{1/2\ el}$), terminal elimination rate constant (k_{el}) and relative bioavailability (F value). All data were reported as mean of six replicates. For comparing between two groups, independent-samples T test was applied using SPSS® computer software program (version 16.0, SPSS Inc., Chicago, USA).

RESULTS AND DISCUSSION

Phase solubility studies

Figure 1 shows the effect of polymers (PVP K30 alone, and PVP K30 with PI F-127) on drug solubility in phosphate buffer pH 6.8 at 25±0.5° C. Determination coefficient (R^2) was 0.9875 for phase solubility diagram of DMP in the presence of PVP K30. The intrinsic solubility of DMP was found to be 10.73 µg/ml and linearly increased up to 23.64 µg/ml as the concentration of PVP K30 was increased suggesting the features of an A_L-type diagram where DMP solubility increased by 2.20 folds at 5% w/v PVP K30. The increment of drug solubility can be explained by solubilization effect of PVP K30, its influence on drug wettability and the formation of soluble

complexes between hydrophobic drug and hydrophilic polymer.[25,26]

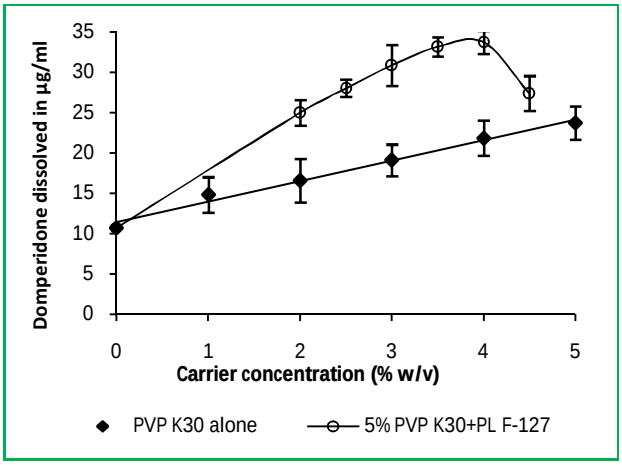

Figure 1: Phase solubility diagrams of domperidone in phosphate buffer pH 6.8 at 25±0.5° C in the presence of in the presence of increasing concentrations of PVP K30 and PL F-127.

Phase solubility diagram obtained for DMP in 5% w/v PVP K30 solutions and increased concentrations of PL F-127 is also shown in Figure 1. The addition of other polymer resulted in increasing drug solubility up to 33.70 µg/ml in the presence of both 5% w/v PVP K30 and 4% w/v PL F-127. This might be attributed to the higher improvement of drug wettability and dispersibility compared to the effect of single polymer. Furthermore, the addition of PL F-127 reduced the interfacial tension between the hydrophobic drug and dissolution medium resulting in enhancing the wettability of drug particles.[27] Higher concentration of PL F-127 led to a decrement of drug solubility due to increased viscosity of the diffusion boundary layer adjacent to the dissolving surface.[28] Pervious expectation was confirmed by the in-vitro dissolution data of ternary systems. The apparent stability constant of the resulted complexes could not be calculated since the exact drug/polymer stoichiometric ratio was not known.[29]

In-vitro dissolution studies

Dissolution rates of ternary systems were significantly enhanced by increasing the concentration of PL F-127 ($p<0.05$) reaching maximum PD_2 at weight ratio of 1:9:0.25 DMP/PVP K30/P F-127 (Figure 2, Table 1) where PD_2 values were 25.41±1.51 and 100.08±1.66 for PM and SD, respectively. This result might be attributed to the ability of pluronic to improve wettability, dispersibility and to reduce interfacial tension between the hydrophobic drug and dissolution medium.[27]

Higher concentration of PL F-127 led to a significant decrement of PD_2 ($p<0.05$) which might be related to the gelling property of pluronic at higher concentration that increases the viscosity of the diffusion boundary layer adjacent to the dissolving surface.[28]

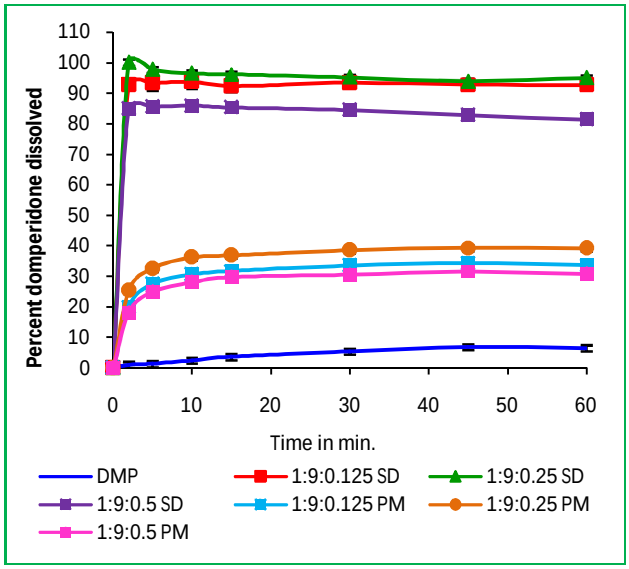

Figure 2: Dissolution profiles of domperidone from different domperidone/PVP K30/PL F-127 systems (SD: Solid dispersion and PM: Physical mixture) in phosphate buffer pH 6.8 at 37±0.5° C.

Table 1: Dissolution parameters of domperidone in phosphate buffer pH 6.8 from different domperidone/PVP K30/PL F-127 systems (mean±SD, n=3).

DMP powder		PD_2 (%)
		1.07±0.23
PM	1:9:0.125	20.08±0.64
	1:9:0.25	25.41±1.51
	1:9:0.5	18.14±1.42
SD	1:9:0.125	92.71±1.45
	1:9:0.25	100.08±1.66
	1:9:0.5	84.98±0.46

One-way ANOVA statistical analysis of PD_2 of different SDs revealed that ternary SD of 1:9:0.25 DMP/PVP K30/PL F-127 exhibited the most significantly improved PD_2 compared to other SDs ($p<0.05$). Therefore, this ternary SD was selected to be physicochemically characterized by FTIR, DSC, PXRD and SEM analysis.

Kinetic studies

Comparing R^2 of different models of release kinetics (zero order, first order and Higuchi model) indicated that the release of DMP from the investigated PMs and SDs approached Higuchi model i.e. diffusion was the release mechanism of the drug from all systems (Data are not shown).

Fourier-transform infrared spectroscopy (FTIR)

In order to study drug/polymer interaction, FTIR analysis was employed. As presented in Figure 3(I), FTIR spectrum of pure drug was characterized by N-H stretching at (3119.3 cm^{-1}) and C = O stretching at (1714.01 cm^{-1}) for the presence of -CO-NH group. Drug spectrum also showed aromatic C-H stretching at (3022.87 cm^{-1}), asymmetric C-H stretching at (2939.95 cm^{-1}), symmetric C-H stretching at (2820.38 cm^{-1}), N-H deformation at

(1697.05 cm^{-1}) and C = C at (1622.02 cm^{-1}). The characteristic absorption band at (734.75 cm^{-1}) with strong stretching intensity might be attributed to the presence of C-Cl bond. The spectrum of PVP K30 showed C-H stretching band at (2953 cm^{-1}) and C=O band at (1666.2 cm-1). A very broad endothermic band at (3048-3750 cm^{-1}) was attributed to the presence of water confirming the broad endotherm detected later in DSC study. FTIR spectrum of PL F-127 was characterized by principal absorption peaks of aliphatic C-H stretching at (2886.92 cm^{-1}), in-plane O-H bend at (1355.71 cm^{-1}) and C-O stretching at (1110.8 cm^{-1}).

FTIR spectra of the optimized ternary systems showed the disappearance of N-H stretching peak of DMP with slight shifting of PVP carbonyl band from (1666.20 cm^{-1}) to (1664.27 cm^{-1}) and (1662.34 cm^{-1}) for PM and SD, respectively. This might indicate an intermolecular hydrogen bonding between =NH group of DMP and C=O band of PVP in the drug-polymer systems.[30,31]

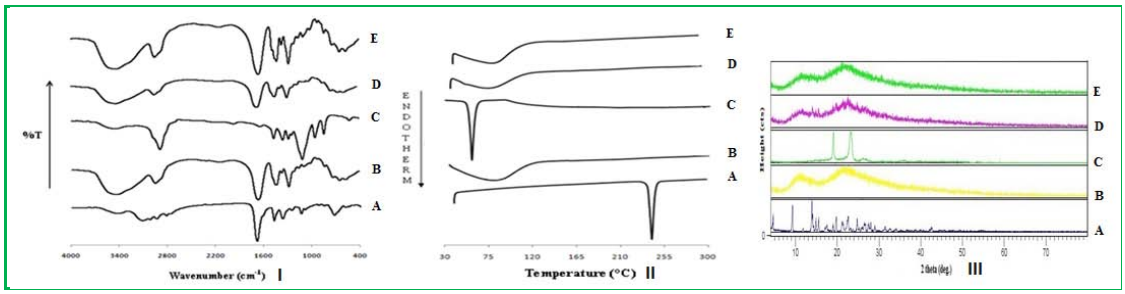

Figure 3: FTIR spectra (I), DSC thermograms (II) and PXRD patterns (III) of (**A**) Pure domperidone, (**B**) PVP K30, (**C**) PL F-127, (**D**) PM of 1:9:0.25 domperidone/PVP K30/PL F-127 and (**E**) SD of 1:9:0.25 domperidone/PVP K30/PL F-127.

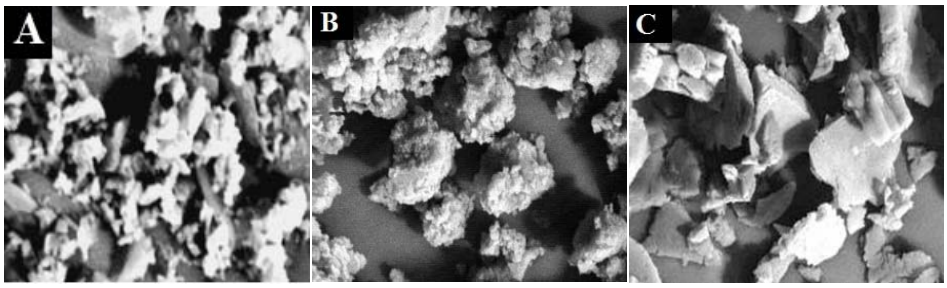

Figure 4: SEM microphotographs of (**A**) Pure domperidone, (**B**) PM of 1:9:0.25 domperidone/PVP K30/PL F-127 and (**C**) SD of 1:9:0.25 domperidone/PVP K30/PL F-127.

Differential scanning calorimetry (DSC)

Figure 3(II) shows the thermal profiles of SD, PM and their individual components. DSC thermogram of DMP presented a sharp endothermic peak at 243.43° C corresponding to its melting point. A broad endothermic peak corresponding to PVP K30 was observed at 80.15° C that might be attributed to the loss of water from of the hygroscopic polymer. Pluronic F-127 had an endothermic peak at 57.39° C related to its melting point. DSC thermograms of SD and PM showed a disappearance of drug peak suggesting the dissolution of DMP microcrystals within the molten polymer due to heating during DSC characterization.[32] In addition, the absence of DMP endotherm in SD might be ascribed to the transformation of the crystalline drug into an amorphous state. This amorphousness might be due to the hydrogen bonding between drug and polymer and/or drug entrapment in polymer matrix during solvent evaporation as the solvent was removed the drug molecules lost their mobility and entrapped in polymer without any crystal structure.[26,32]

Powder X-ray diffraction (PXRD)

Figure 3(III) shows PXRD patterns of DMP solid systems. The diffraction spectrum of pure DMP showed the crystalline nature of the drug as demonstrated by numerous sharp, highly intense and less diffused peaks. These peaks were observed at 2θ of 9.22°, 11.77°, 13.90°, 14.88°, 15.53°, 19.00°, 19.75°, 22.58°, 24.76°, 28.98°, 31.47° and 42.61° in finger print regions referring to drug crystallinity. A hollow pattern with no diffraction peaks was recorded for PVP K30 indicating its amorphous state. The diffraction spectrum of PL F-127 showed two characteristic peaks at 2θ of 19.07° and 23.24° indicating its crystalline nature.

PXRD patterns of the ternary PM and SD exhibited 'halo' shaped diffractograms characteristic of amorphous material since the reflexes did not return to the base line. Furthermore, broadening of DMP peaks and reduction of their intensities were observed suggesting the conversion of crystalline DMP to partially disordered molecules.[26]

Characteristic drug peak at 22.58° 2θ was used for calculating RDC of DMP, ternary PM and SD. Based on RDC values, when pure DMP was considered as a

reference sample, a significant decrement in crystallinity of the ternary systems was observed ($p<0.05$). RDC values were 1, 0.17 and 0.14 for pure DMP, PM and SD, respectively indicating the amorphousness of ternary systems as previously investigated by PXRD patterns.

Scanning electron microscopy (SEM)

SEM micrographs revealing the surface morphology of the samples at 1000X are shown in Figure 4. SEM micrograph of pure DMP showed crystalline particles of rather irregular shape and size (Figure 4A), while SEM micrograph of PM revealed more identified cotton-shaped powder with crystalline dusts of DMP deposited on the surface (Figure 4B). Ternary SD appeared in the form of irregular particles in which the original crystalline morphology of DMP disappeared and small lumps of amorphous pieces of irregular size were present (Figure 4C). This result could be attributed to the dispersion of the drug in polymer matrix confirming the findings based on FTIR, DSC and PXRD analysis. These changes might be responsible for the increased dissolution rate of DMP.

Evaluation of flow properties of dry blends

As shown in Table 2, angle of repose, Hausner ratio and Carr's index were found to be in the range of 48.19° - 34.21°, 1.11 - 1.20 and 9.52% - 23.81%, respectively. It is clearly observed the consistency of the measured flow parameters, where the best flow behavior was accomplished by F_6 with angle of repose of 34.21° indicating good flowability, Hausner ratio of 1.11 and Carr's index of 9.52% indicating excellent flowability compared to other formulae.

Table 2: Composition and flow characterization of domperidone mouth dissolving tablets (F_1-F_8)

Composition % w/w	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Avicel PH-102	5	5	5	5	5	5	—	—
Glycine	10	20	40	—	—	—	—	—
Effervescent base	—	—	—	10	20	40	40	40
PEG 4000	—	—	—	—	—	—	5	—
Gelatin	—	—	—	—	—	—	—	5
Flow properties								
Angle of repose (α)	46.56	47.39	47.39	46.78	48.19	34.21	43.97	45.85
Hausner ratio (HR)	1.19	1.20	1.18	1.31	1.18	1.11	1.12	1.13
Carr's index (CI) %	15.79	16.67	15.43	23.81	15.00	9.52	10.53	11.11

Evaluation of the physical properties of MDTs

The *physical appearance* of the prepared MDTs was characterized by white color, round and flat-faced shape. It was observed that none of the prepared tablets deviated from the stated limit of *weight variation* (250.10±2.81 - 251.60±2.75 mg) indicating uniform weighting and die filling. All the assayed MDTs were within the pharmacopoeial limit of *content uniformity* (98.18±0.81% - 101.25±0.40%.) evidencing proper trituration. *Friability* of the tested tablets ranged from 0.10 to 0.63 % with no breaking, capping or cracking during the test. *Hardness* ranged from 3.4±0.10 to 4.7±0.26 Kp. Friability and hardness data revealed good mechanical strength that can withstand the mechanical and physical stresses during handling, packaging and transportation processes. In addition, *moisture content* was found to be 5.08±0.01-9.32±0.22%.

***In-vitro disintegration, in-vivo disintegration and dispersion times* (Table 3)**

Increment of glycine concentration resulted in a decrement of tablets in-vitro disintegration, in-vivo disintegration and dispersion times. This might be owed to the fine wetting nature of amino acids that brought them to act as disintegration accelerators.[33-35] For example, *in-vitro* disintegration times were 6.73±0.21, 6.57±0.16 and 5.42±0.09 minutes for F_1, F_2 and F_3, respectively.

On wetting with buffer solution or saliva, sodium bicarbonate interacted with citric acid and tartaric acid where carbon dioxide (CO_2) was released inside tablets resulting in creation of a pressure within tablets that finally disintegrated. By increasing effervescent base concentration, the measured times were decreased. This might be attributed to the higher amount of CO_2 and higher pressure that were generated at higher concentration of effervescent base.[36,37] For example, in-vivo disintegration times were found to be 6.28±0.97, 5.76±0.67 and 3.54±0.51 minutes for F_4, F_5 and F_6, respectively.

By changing the type of binder from Avicel PH-102 (formula F_6) to PEG 4000 (formula F_7) and gelatin (formula F_8), all the measured times were increased. Although Avicel PH-102 was incorporated as a binder in formula F_6, it is also had good disintegrating properties where it is an insoluble substance and acts by wicking mechanism. Upon contact with saliva or buffer solution, the medium was penetrated into the tablets and replaced the air adsorbed on the particles resulting in weakening the intermolecular bond and breaking the tablets into fine

particles.[38,39] In case of formula F_7, polyethylene glycol 4000 could prolong the measured times which might be due to its binding effect.[40,41] In addition, PEG 4000 is a water-soluble substance causing tablets to dissolve rather than disintegrate even when disintegrating agents are present.[36,38,42] In other meaning, breaking up of formula F_7 was not governed by the disintegration, but it depended on the rate at which the binder dissolved. In case of formula F_8 containing gelatin as a binder, after absorbing buffer solution or saliva, gelatin was swelled, softened and finally had led to tablet disintegration.[36,43] Soluble materials that tend to swell can form viscous plugs.[38] This might lead to prolonged disintegration and dispersion times compared to F_6 and F_7.

All the previously mentioned conceptions might be the reasons that Avicel PH-102 was more efficient in decreasing tablets disintegration and dispersion times compared to other binders. Therefore, F_6 (containing 5% Avicel PH-102) achieved the lowest measured times followed by F_7 (containing 5% PEG 4000) then F_8 (containing 5% gelatin). For example, dispersion times were measured to be 3.42±0.33, 4.70±0.23 and 6.18±0.84 minutes for F_6, F_7 and F_8, respectively.

Table 3: Physical characterization of domperidone mouth dissolving tablets (mean±SD)

Code/Time interval		Dispersion time (min)	*In-vitro* disintegration time (min)	*In-vivo* disintegration time (min)	PD_{10} (%)
F_1		44.20 ± 0.71	6.73 v 0.21	8.55 ± 0.10	6.76 ± 1.27
F_2		41.06 ± 2.58	6.57 ± 0.16	5.58 ± 0.72	57.96 ± 0.12
F_3		39.52 ± 3.55	5.42 ± 0.09	4.76 ± 0.39	51.69 ± 1.86
F_4		19.08 ± 0.08	6.45 ± 0.35	6.28 ± 0.97	84.44 ± 0.53
F_5		8.77 ± 0.08	4.20 ± 0.19	5.76 ± 0.67	77.44 ± 1.44
F_6		3.42±0.33	1.52±0.12	3.45±0.51	101.05±0.53
F_7		4.70 ± 0.23	2.28 ± 0.10	4.38 ± 0.49	97.05 ± 1.51
F_8		6.18 ± 0.84	2.57 ± 0.08	7.126 ± 0.14	86.11 ± 1.62
Accelerated stability study					
F_6	1 month	5.87±0.28	2.75±0.13	5.43±0.08	86.58±0.58
	3 months	14.55±1.89	4.44±0.19	8.16±0.28	72.17±2.31
	6 months	18.14±1.55	5.64±0.43	7.85±0.32	76.85±0.69
Long term stability study					
F_6	1 month	6.28±0.41	2.74±0.10	5.35±0.20	98.98±0.50
	3 months	12.23±0.94	5.85±0.44	6.96±0.28	97.58±0.81
	6 months	18.27±0.98	6.70±0.18	8.89±0.13	97.32±1.73

One-way ANOVA statistical test revealed that formula F_6 accomplished the lowest significant measured times compared to other formulae ($p<0.05$). For example, in-vitro disintegration, in-vivo disintegration and dispersion times were 1.52±0.12, 3.54±0.51 and 3.42±0.33 minutes, respectively.

In-vitro dissolution studies

Tablet disintegration is essential for fast release of active drug, but dissolution is the most important criterion.[39] All formulae attained 97.85±1.59 - 100.85±0.53% while convenient oral tables attained 42.35±2.58% of DMP dissolved after 60 minutes.

Formula F_6 achieved the highest significant percentage of the drug dissolved after 10 minutes (PD_{10}=101.05±0.53%) ($p<0.05$). Furthermore, it was conform to all measured physical parameters and achieved the lowest significant dispersion, in-vitro disintegration and in-vivo disintegration times. Therefore, formula F_6 was subjected to further stability and pharmacokinetic studies.

Stability studies

Accelerated stability study

Generally, all tested tablets showed a common *physical appearance* of brown discoloration due to what is called Maillard reaction. Maillard reaction is sequence of reactions between drugs containing amino group and carbonyl group of reducing sugars leading to the formation of heterocyclic nitrogen compounds with brown color. Degradation of the drug increased by increasing temperature and upon exposure to sunlight.[44,45]

Content uniformity ranged from 100.18±0.83% to 101.65±0.20% that was still accepted according to the pharmacopoeial range. *Friability* was less than 1% with no evidence of break, capping or cracking ensuring that the mechanical strength of MDTs was still kept. *Moisture content* was found to be 9.97±1.80, 10.03±0.54 and 9.69±0.38% after 1, 2 and 3 months, respectively, showing a significant increment regarding the freshly prepared formula ($p<0.05$). *Dispersion, in-vitro disintegration and in-vivo disintegration times* were

significantly higher than the respective times of the freshly prepared F_6 tablets ($p<0.05$) (Table 3). These increments affected tablets dissolution performances where PD_{10} values were significantly decreased to 72.17±2.31 - 86.58±0.58% ($p<0.05$) (Table 3).

Long term stability study

Changes in *physical appearance* were not observed during the whole period of long term stability study where MDTs kept their white color and round shape. *Content uniformity* and *friability* of MDTs (F_6) after long term stability study agreed with the pharmacopoeial range. Breaks, cracks and capping were not observed. *Moisture content* was increased significantly ($p<0.05$) up to 7.02±0.42, 8.19±0.26 and 8.85±0.49 after 3, 6 and 12 months respectively. Moreover, *dispersion time, in-vitro disintegration time and in-vivo disintegration time* were significantly increased compared to the freshly prepared formula ($p<0.05$). These increments had no significant effect on the dissolution manners of the tested MDTs ($p>0.05$) where PD_{10} values were more than 97% (Table 3).

Based on stability studies, it was indicated that elevated temperature and humidity during manufacturing, storage and transportation processes, had a tremendous effect on tablets physical properties. Accordingly, dry condition, controlled temperature, storing away from light and protection against excessive humidity are necessary to maintain the physical characteristics of dosage form containing sensitive ingredients.

Pharmacokinetic study in healthy volunteers

The bioanalytical method used for quantification of DMP in human plasma was specific where no endogenous compounds appeared to interfere at the same retention time of DMP, accurate, precise and linear in the range of 10-1000 ng/ml (R^2 = 0.9988). Therefore, this bioanalytical method could be used for the estimation of DMP in human plasma.

MDTs (F_6) achieved Cp_{max} of 134.98±18.33 ng/ml after 0.5 hour indicating rapid absorption of a significant larger amount of DMP ($p<0.05$) compared to the convenient oral tablets where their Cp_{max}= 63.38±9.76 ng/ml was attained after 1 hour (Figure 5).

$AUC_{(0-48)}$ values were 1080.51±129.81 and 656.09±129.41 and values of $AUC_{(0-\infty)}$ were 1257.66±185.06 and 693.98±163.02 for MDTs (F_6) and convenient oral tablets, respectively. This might indicate that the amount of the drug absorbed via buccal route was higher than that of oral route as evidenced before.

The main residence times of DMP were 19.24±2.11 and 14.89±2.60, while k_{el} findings were 0.0435±0.0061 and 0.0654±0.0143 hr^{-1} and $t_{1/2}$ values were 16.19±0.90 and 11.07±2.71 hr for MDTs (F_6) and convenient oral tablets, respectively indicating that DMP which was absorbed via buccal route remained in the systemic circulation significantly longer than that absorbed through gastric mucosa ($p<0.05$).

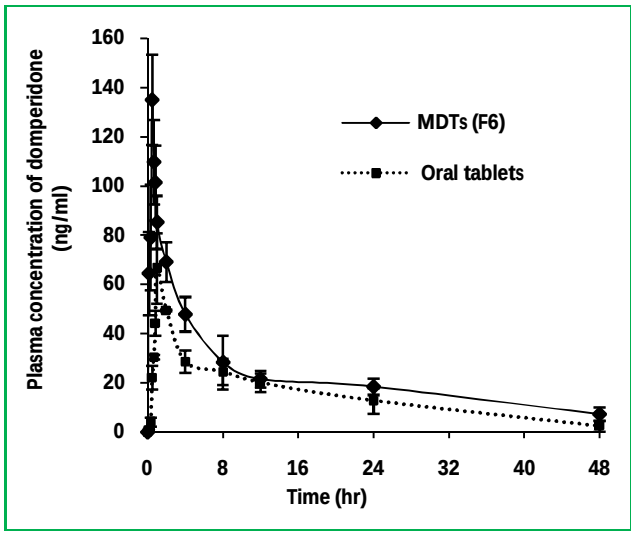

Figure 5: Mean plasma concentration-time profiles of domperidone following administration of mouth dissolving tablets (F_6) and oral tablets.

Statistical analysis of the calculated pharmacokinetic parameters revealed significant differences between MDTs and convenient oral tablets ($p<0.05$). Accordingly, the administration of MDT (F_6) via buccal route attained an improved therapeutic level by bypassing the hepatic metabolic pathway (i.e. first-pass metabolism) as proved by the relative bioavailability (164.84%).

CONCLUSION

It was clearly shown that types of polymers, drug/polymer ratio and tablets excipients affected tremendously drug solubility, tablets disintegration time, tablets dissolution rate and latterly drug bioavailability. Mouth dissolving tablets containing ternary solid dispersion of domperidone/PVP K30/PL F-127, 40% effervescent base and 5% Avicel PH-102 achieved the most optimized results according to the standard specifications. Precautions must be taken throughout the shelf life of dosage forms containing hygroscopic ingredients to keep their appropriate physical properties. Pharmacokinetic study in healthy human volunteers evidenced that the buccal route of administration could be used to introduce the dissolved drug directly into the systemic circulation via buccal mucosa avoiding first-pass metabolism and laterally leading to improvement of drug bioavailability.

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