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Research article

Formulation of domperidone in gastro-retentive floating tablets

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Abstract

The aim of this work was to enhance the oral bioavailability of water-insoluble, weakly-basic, anti-emetic drug; Domperidone (DMP), which has a poor oral bioavailability (13-17%). Adsorption of drug onto the surface of Aerosil 200 was achieved by solvent evaporation method to enhance the drug dissolution rate. Then, the adsorbates were formulated into gastro-retentive floating tablets to retain the drug in the acidic medium of stomach which is favorable for the drug dissolution. Different drug: adsorbent ratios were prepared and tested for their *in-vitro* dissolution rate to select the best ratio for the final formulation. Different concentrations of several polymers were used in the preparation of tablets matrices together with sodium bicarbonate to induce the floating effect via reaction with gastric HCl. Drug-excipient compatibility studies were performed using Fourier-transform Infrared Spectroscopy (FT-IR) and Differential Scanning Calorimetry (DSC) which confirmed the absence of incompatibilities between the drug and the used excipients. The tablets were prepared by direct compression technique and evaluated for their weight uniformity, drug content, friability, hardness, thickness, floating properties, *in-vitro* dissolution rate and kinetics of drug release. Formulae F7 (containing 30% w/w sodium alginate) and F8 (containing 40% w/w sodium alginate) showed the best results and thus; they were selected for *in-vivo* studies in rabbits. The selected formulae showed marked enhancement of domperidone bioavailability compared with the commercial conventional immediate-release tablets; Motinorm®, with relative bioavailability values of 298.26±11.53% and 315.04±13.39% for F7 and F8, respectively and proved that the selected formulae successfully controlled the drug release.

Key words: Domperidone, adsorbates, floating tablets, dissolution, bioavailability.

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1. Introduction

Poor bioavailability is a critical challenge that faces effective oral delivery of many drugs. Improvement of drug dissolution rate can effectively improve the absorption of poorly water-soluble drugs and consequently, leads to enhancement of their oral bioavailability [1]. Adsorption of drugs onto the surface of adsorbents like silica leads to increase in the effective surface area of drug and thus; improves the

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dissolution rate [2]. For weakly-basic drugs, gastro-retentive floating dosage forms have presented a promising approach for the improvement of oral bioavailability of these drugs. Floating drug delivery systems (FDDS) are hydrodynamically- balanced systems (HBS) having a bulk density lower than gastric contents and thus; they remain buoyant in the stomach and retain the drug in the acidic medium favoring the drug release [3]. Moreover, while the system is floating on the gastric contents, the drug is released at a controlled rate over prolonged time period [4]. Domperidone (DMP) is 5-chloro-1-[1-[3-(2, 3-dihydro-2-oxo-1H benz imidazol-1-yl)-propyl] 4-piperidinyl]-1, 3-dihydro-2H-benzimidazol-2-one. It is a dopamine (D_2) receptor antagonist. DMP is used for the treatment and prevention of acute nausea and vomiting of any cause; especially cytotoxic therapy and radiotherapy [5]. According to biopharmaceutical classification system (BCS), DMP is classified under class-II drugs (poorly-soluble and highly-permeable). It is practically insoluble in water (1 part in 50,000 part of water) and has a pka value of 7.9 so; it is a weakly basic drug with a very poor dissolution rate at relatively high pH values [1]. This makes the absorption of drug dissolution rate-limited and lowers the oral bioavailability to 13-17% [6]. So, the dissolution rate of DMP is the most critical factor determining the drug bioavailability and its enhancement is vital. To deal with this challenge, adsorbates of DMP with Aerosil 200 were prepared in different weight ratios using solvent evaporation technique and they were tested for their *in-vitro* dissolution rate to select the best ratio for the final formulation. Then, the adsorbates were incorporated into gastro-retentive floating tablets to combine the advantages of both adsorption and FDDS. Different concentrations of several polymers were used in the preparation of tablets matrices including hydrophilic polymers like hydroxypropylmethyl-cellulose (HPMC 15000) and sodium alginate (Na Alg) and hydrophobic polymers like Ethylcellulose (EC), Eudragit RL 100, Eudragit RS 100 and Eudragit RLPO. Drug-excipient compatibility studies were performed using Fourier- transform Infrared Spectroscopy (FT-IR) and Differential Scanning Calorimetry (DSC) to confirm the absence of incompatibilities between the drug and the used excipients. The tablets were prepared by direct compression technique and evaluated for their weight uniformity, drug content, friability, hardness, thickness, diameter, floating properties, *in-vitro* dissolution rate and kinetics of drug release. The best formulae were selected for further *in-vivo* studies in rabbits.

2. Materials and Methods

Materials

Domperidone was supplied as a gift sample by "Pharco, for pharmaceutical and chemical industry", Egypt. Aerosil 200, Magnesium stearate and sodium bicarbonate were purchased from "El-Nasr pharmaceuticals and chemicals Co.", Egypt. Micro-crystalline cellulose (Avicel) PH 101 grade was purchased from "Evans Chem. Co.", Egypt. Sodium alginate was purchased from "The general chemical & pharmaceutical Co. Ltd", Sudbury Middlesex, England. HPMC 15000 was purchased from "El-Gomhouria Co.", Cairo, Egypt. Eudragit RL 100, Eudragit RS 100 and Eudragit RLPO were purchased from "RÖhm pharma, GMBH", Darmstadt, Germany. Ethylcellulose was purchased from "El-Nile Co., for pharmaceutical and chemical industry", Egypt. Methanol and acetonitrile (HPLC grade) were purchased

from "Merck-Schuchardt", Germany. Acetophenone and triethylamine were purchased from "Fluka", Buchs, Switzerland.

Motinorm® tablets were supplied by "Glaxo Smith Kline", Egypt. Adult male Newzeland rabbits (average body weight = 2 kg) were obtained from the animal house, Faculty of Medicine, Assiut University, Assiut, Egypt. Heparine was used in the form of Cal-Heparine® ampoules which were supplied by "Amoun", Egypt. All other used chemicals and reagents were of analytical grade and were used as received.

Methods

Drug-excipient compatibility studies

Fourier-transform infrared (FT-IR) studies

A qualitative FT-IR analysis was performed for drug, excipients and their physical mixtures (1:1 w/w) to check for possible incompatibilities. Samples of 1-2 mg were mixed with potassium bromide (IR grade) and compressed into discs in a compressor unit under vacuum and then scanned from 4000 to 400 cm^{-1} using FT-IR spectrometer (Shimadzu IR-470, Japan), with an empty pellet holder as a reference.

Differential Scanning Calorimetry (DSC) studies

DSC studies were performed for drug, excipients and their physical mixtures (1:1 w/w) to investigate the drug-excipient compatibility. DSC thermograms were obtained by using a shimadzu DSC-50 (Japan) equipped with a software computer program. Samples of about 5 mg were placed in an aluminum pan of 50 µl capacity and 0.1 mm thickness, press-sealed with aluminum cover of 0.1 mm thickness. An empty pan sealed in the same way was used as a reference. Samples were heated from 30 °C to 300 °C at a rate of 10 °C min^{-1} and nitrogen flow of 25 ml/min. Indium was used as a standard for calibrating temperature. Thermograms obtained were analyzed using TA-50 program to determine temperature and heat of fusion (ΔH) for each peak.

Preparation of domperidone adsorbates

Adsorbates of DMP with Aerosil 200 in weight ratios of 1:1, 1:3 and 1:5 (w/w) drug: adsorbent were prepared by solvent evaporation method. The desired amount of drug was dissolved in methanol. The accurately weighed adsorbent was dispersed in minimum amount of methanol and then added to the solution of drug with sufficient stirring. The solvents were removed under reduced pressure at 40 °C till constant weight was obtained. The prepared samples were pulverized, sieved to obtain a particle size range of 125-250 µm and stored in a dessicator over calcium chloride till used.

In-vitro dissolution rate study of DMP from the prepared adsorbates

USP dissolution apparatus II (paddle type) (Erweka, Germany) was used at a rotation speed of 100 r.p.m. Powdered samples of adsorbates equivalent to 20 mg of domperidone were added to the dissolution medium (900 ml buffer solution with pH 1.2, kept at 37±0.5 °C). Pure drug was sieved to obtain a size range of 125-250 µm and treated similarly. At time intervals of 5, 15, 30, 45, 60, 90 and 120 minutes, samples (5 ml) of the solution were withdrawn with a volumetric pipette, using cotton plug as a filter and replaced with an equal volume of fresh dissolution medium equilibrated at 37°C. The samples were analyzed spectrophotometrically at λ_{max} of 284 nm. Each experiment was performed in triplicate, and the mean recordings were used for calculations. The adsorbates of

DMP with Aerosil 200 in a weight ratio of 1:5 (w/w) showed the highest dissolution rate and thus; this ratio was selected for being used in the formulation of floating tablets.

Formulation of DMP gastro-retentive floating tablets

Gastro-retentive floating tablets of DMP were prepared by the direct compression technique using the formulae shown in tables (1-3). Polymers were incorporated in different concentrations of the final tablet weight (500 mg). Eudragit RL100 and Eudragit RS100 were supplied as crystalline beads and needed to be ground using vibrating uniball mill (VEB Leuchten bau-KM1, Germany) while the rest of polymers were used as received. Fixed dose of DMP (20 mg) was incorporated into all tablets by incorporating a fixed amount (120 mg) of DMP-Aerosil 200 adsorbates in weight ratio of 1:5 (w/w) which was equivalent to 20 mg of DMP. Sodium bicarbonate in a concentration of 9% (w/w) of the final tablet weight was used to induce the floating effect via generation of carbon dioxide upon reaction with gastric HCl. Magnesium stearate (Mg St) was used as a lubricant in a concentration of 1% (w/w). Microcrystalline cellulose (Avicel PH101) was used as a diluent. All powders were sieved to obtain a size range of 125-250 µm and mixed by trituration in a glass mortar with pestle to obtain uniform mixture. The blended powders were compressed into tablets weighing 500 mg using a single punch tablet machine (Erweka, Germany) having a die set of 13 mm diameter.

Table 1. Composition of formulated floating tablets of DMP containing different concentrations of hydroxypropylmethylcellulose (HPMC 15000) (hydrophilic polymer).

Formula No.	Adsorbates (mg)	Avicel PH 101 (mg)	Sodium bicarbonate (mg)	MgSt (mg)	HPMC 15000	
					mg	% (w/w)(*)
F1	120	***280***	***45***	***5***	***50***	***10***
F2	120	***230***	***45***	***5***	***100***	***20***
F3	120	***180***	***45***	***5***	***150***	***30***
F4	120	***130***	***45***	***5***	***200***	***40***

(*) The percent of polymer is expressed as a percent of the total tablet weight (500 mg).

Table 2: Composition of formulated floating tablets of DMP containing different concentrations of sodium alginate (Na Alg) (hydrophilic polymer).

Formula No.	Adsorbates (mg)	Avicel PH 101 (mg)	Sodium bicarbonate (mg)	MgSt (mg)	Na Alg	
					mg	% (w/w)(*)
F5	120	***280***	***45***	***5***	***50***	***10***
F6	120	***230***	***45***	***5***	***100***	***20***
F7	120	***180***	***45***	***5***	***150***	***30***
F8	120	***130***	***45***	***5***	***200***	***40***

(*) The percent of polymer is expressed as a percent of the total tablet weight (500 mg).

Table 3. Composition of formulated floating tablets of DMP containing 40% (w/w) of different hydrophobic polymers.

Formula No.	Adsorbates (mg)	Avicel PH 101 (mg)	Sodium bicarbonate (mg)	MgSt (mg)	Polymer (mg)(*)			
					Ethylcellulose	Eudragit RL100	Eudragit RS100	Eudragit RLPO
F9	120	***130***	***45***	***5***	200	-	-	-
F10	120	***130***	***45***	***5***	-	200	-	-
F11	120	***130***	***45***	***5***	-	-	200	-
F12	120	***130***	***45***	***5***	-	-	-	200

(*) The used amount of each polymer represents 40% (w/w) of the total tablet weight (500 mg).

Physical evaluation of the prepared floating tablets

Uniformity of tablets weight

According to European pharmacopoeia 2014, twenty randomly-selected tablets from each formula were individually weighed. The average weight was determined and the standard deviation was calculated. For tablets weighing more than 250 mg, tablet weight should not deviate from claimed value by more than 5% [7].

Uniformity of drug content

The European pharmacopoeia 2014 method was adopted. Ten tablets were randomly selected from each formula and assayed individually. A pre-weighed tablet was powdered, transferred into a 100 ml volumetric flask and the volume was completed to 100 ml with methanol. The contents of flask were stirred continuously and filtered. After suitable dilution with buffer solution (pH 1.2), the solution was assayed spectrophotometrically at 284 nm. Drug content was expressed as a percentage of label claim and should be 100±15% [7].

Tablet friability

According to European pharmacopoeia 2014, the friability of the prepared tablets was evaluated by calculating the percentage loss in the weight of 20 tablets from each formula after the revolution in a friabilator (Erweka, Germany), at 25 r.p.m., for 4 minutes. The tablets were brushed gently to remove the adhered powder. The percentage of weight loss was calculated using the following equation:

Weight loss (%) = ((weight of tablets before testing – weight of tablets after testing)/ weight of tablets before testing) X 100.

The percentage of weight loss should not exceed 1% [7].

Tablet hardness

The hardness of the prepared tablets was determined by means of the Erweka hardness tester (Erweka, Germany). For each batch, the hardness of 10 tablets was determined and expressed as average ± standard deviation [3].

Thickness and diameter of the prepared tablets

The thickness and the diameter of randomly-selected 20 tablets from each formula were measured by means of a

micrometer (Mitutoyo Co., Japan). The average thickness and diameter were determined [3].

Floating properties of the prepared tablets

The USP dissolution apparatus (type II) (Erweka, Germany) was used for determining the floating lag time and total floating time. The glass vessels of the apparatus were filled with 900 ml of buffer (pH 1.2) maintained at 37±0.5°C and rotated at 100 r.p.m. The time taken by each formula to start floating is called floating lag time, where the time for each formula during which it remains buoyant over the solution is the total floating time [3].

***In-vitro* dissolution rate of DMP from the prepared floating tablets**

USP dissolution apparatus II (paddle type) (Erweka, Germany) was used at a rotation speed of 100 r.p.m. Each of the tested tablets was added to the dissolution medium (900 ml buffer solution with pH 1.2, kept at 37±0.5°C). At time intervals of 0.083, 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours, samples (5 ml) of the solution were withdrawn with a volumetric pipette, using cotton plug as a filter and replaced with an equal volume of fresh dissolution medium equilibrated at 37°C. The samples were analyzed spectrophotometrically at λ_{max} of 284 nm. Each experiment was performed in triplicate, and the mean recordings were used for calculations.

Kinetic Analysis of the drug release data

The mechanism of drug release from each formulation was determined by linear regression analysis according to zero-order, first-order and Higuchi-diffusion models. The correlation coefficient (r) values were calculated for each model. The highest value of the calculated correlation coefficients assigned the mechanism of the drug release from the prepared tablets. The drug release data were fitted to the following equations: [8].

Zero-order model: $M_t / M_\infty = K_0 t$.

First-order model: $M_t / M_\infty = e^{-K1t}$

Higuchi-diffusion model: $M_t / M_\infty = k_H t^{½}$.

Where (M_t / M_∞) is the fractional release of the drug at time t, k_0 = zero-order rate constant, k_1 = first-order rate constant, k_H = Higuchi rate constant and t = time of release.

Then, the release data were analyzed using the equation proposed by Korsemeyer and Peppas:[8]

$$M_t / M_\infty = Kt^n$$

Where M_t / M_∞ is the fractional release of the drug at time t, K is the release rate constant and n is the diffusional exponent that characterizes the type of release mechanism during the dissolution process. In case of tablets (cylindrical sample) , n= 0.45 for Fickian diffusion; while in case of non-Fickian release, the value of n falls between 0.45 and 0.89; for zero order release (case II transport), n= 0.89 and for supercase II transport, n > 0.89.

***In-vivo* studies on the selected formulae**

Treatment of animals

On basis of the previously mentioned tests, formulae F7 (containing 30% w/w Na Alg) and F8 (containing 40% w/w Na Alg) showed the best results and thus; they were selected for *in-vivo* studies in rabbits in comparison with the commercial conventional immediate-release tablets; Motinorm®. The protocol of study was approved by Medical Ethics Committee, faculty of medicine, Assiut university, Egypt (IRB no: IRB00008718). 24 healthy adult male Newzeland rabbits weighing 1.8-2.2 Kg (average body weight= 2 Kg) were used

and housed at room temperature. Food was withheld for 24 hours before the experiment, but the rabbits had free access to tap water. A specific equation was used to calculate the rabbit drug dose equivalent to human dose based on body surface area ratio between rabbit and man [9]. The rabbits were divided into 4 groups, each consisted of 6 rabbits. The first group was considered as a control and received no dosage forms. The 2nd, 3rd and 4th groups were given an oral dose of 1.1 mg/kg of DMP (equivalent to 20 mg per tablet human dose) from Motinorm®, Formula F7 and formula F8 tablets, respectively using a stomach tube. Blood samples of about 1-2 ml were withdrawn via an indwelling catheter in the marginal ear vein into a 5 ml screw-capped heparinized centrifuge tubes at the following time points: pre-dose, 0.083, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24 hours following drug administration. The samples were centrifuged at 5000 r.p.m for 15 minutes. The supernatant was removed and transferred into a new screw-capped centrifuge tube. This separated plasma was stored at -20°C until analysis.

Assay of drug in plasma

The HPLC method developed by Sivakumar *et al.* [10] was adopted. The mobile phase was a filtered and degassed mixture of methanol, acetonitrile and triethylamine solution (10 mM, pH 7.0 ± 0.05 adjusted with 85% phosphoric acid) in a ratio of 20:33:47 (v/v). To 0.1 ml of each plasma sample, 0.5 µg of Acetophenone as an internal standard (0.1 ml of a 5 µg/ml standard solution in the mobile phase) and 2 ml of acetonitrile were added. The extraction was carried out by vortexing the samples for 10 minutes followed by centrifugation at 5000 r.p.m for another 10 minutes. After precipitation of plasma proteins, the organic layer was separated and then, transferred into a Pyrex conical tube. The solvent was evaporated and the solid residues were reconstituted into 100 µl of mobile phase. Then, 20 µl sample was injected directly into HPLC column (Venusil x BP C-18 column, 250 x 4.60 mm, 5 µm). The mobile phase flow rate was 1 ml/min and UV detection was performed at 285 nm. Chromatograms were recorded and the peak areas were calculated using Young Lin Autochrom-3000 software. All analysis was performed at room temperature, the assay was done in triplicates and the mean was considered.

Pharmacokinetic analysis of data

Pharmacokinetic parameters were determined from plasma concentration-time curve as the following: [11, 12]

The maximum plasma concentration (C_{max}) and the time to attain the peak concentration (T_{max}) were obtained directly from the curve. The absorption rate constant (K_{abs}) was obtained by the method of residuals. The elimination rate constant ($K_{el.}$) was calculated from the terminal linear portion of the semi-logarithmic plot of plasma concentration versus time curve using linear regression analysis. The apparent half-lives of absorption and elimination ($t_{½}$) were obtained by dividing 0.693 by the corresponding rate constant. The area under plasma concentration-time curve from zero to end time (AUC_{0-t}) and the area under first moment curve from zero to end time ($AUMC_{0-t}$) were calculated by using linear trapezoidal rule. AUC and AUMC from zero-time to infinity ($AUC_{0-\infty}$ and $AUMC_{0-\infty}$) were calculated by the following equations:

$$AUC_{(0-\infty)} = AUC_{(0-t)} + (C_t / K_{el.})$$

$$AUMC_{(0-\infty)} = AUMC_{(0-t)} + t.C_t/K_{el.} + C_t/K_{el.}^2$$

Where, C_t is the last measurable concentration at the end time point (t), K_{el} is the elimination rate constant of drug. The mean residence time of the drug in the body (MRT) was calculated using the following equation: MRT = $AUMC_{(0-\infty)}$ / $AUC_{(0-\infty)}$. Total clearance of the drug (Cl_T) was calculated as dose divided by $AUC_{(0-\infty)}$. The apparent volume of distribution (V_d) was obtained by extrapolation method. Relative bioavailability F_R (%) was obtained from the comparison of the AUC of each of the tested formula divided by that for the commercial tablets (Motinorm®) by using the following equation:

$$F_R\,(\%) = \frac{AUC_{0-\infty}\ (\text{tested formula})}{AUC_{0-\infty}\ (\text{commercial product})} \times 100$$

The data were presented as mean values ± SD. Student's t-test was performed for data derived from the pharmacokinetic parameters in order to investigate the statistical significance ($p < 0.05$) of the difference between each of the tested floating formulations and the commercial Motinorm® tablets using a statistical computer package (SPSS version 13.0).

3. Results and Discussion

Drug-excipient compatibility studies

Fourier-transform infrared (FT-IR) studies

Figure (1) shows the FT-IR spectra of DMP-HPMC 15000 system as a representative example. Domperidone (trace A) showed characteristic peaks at 1697 cm^{-1} (C=O stretching vibration), 3300-3500 cm^{-1} (N-H stretching vibration), 3000-3100 cm^{-1} (aromatic =C-H stretching vibration), 2850-3000 cm^{-1} (sp^3 –C-H vibration) and several bands at 1400-1600 cm^{-1}(aromatic C=C stretching vibration). HPMC 15000 (trace B) showed characteristic peaks at 3200-3600 cm^{-1} (broad peak for O-H stretching vibration) and 2850-3000 cm^{-1} (sp^3 –C-H vibration). Physical mixture (trace C) showed the same characteristic peaks of both DMP and HPMC 15000 with no significant changes indicating the absence of any chemical interaction between them. Similar results were obtained with the rest of excipients confirming the absence of chemical incompatibilities between drug and the used excipients.

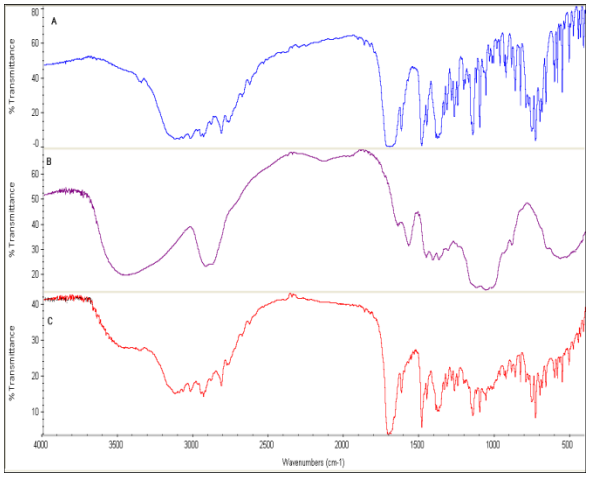


Figure 1. FT-IR spectra of DMP (A), HPMC 15000 (B) and 1:1 (w/w) physical mixture of them (C).

Differential Scanning Calorimetry (DSC) studies

Figure (2) shows DSC thermograms of DMP-HPMC 15000 system as a representative example. DMP (trace A) showed a sharp melting endothermic peak at 252.49°C with a fusion enthalpy (ΔH) of (-94.37 J/g). This indicated that the drug was present in a pure crystalline state. HPMC 15000 showed a broad endothermic peak at 100°C which can be attributed to vaporization of the adsorbed moisture [13]. Physical mixture showed no significant shift in the position of DMP melting endothermic peak, but with reduction in the intensity and fusion enthalpy (ΔH = -68.81 J/g) due to dilution effect. The results confirmed the absence of incompatibilities between drug

and HPMC 15000. Similar results were obtained with the rest of excipients confirming the suitability of their use in the formulations.

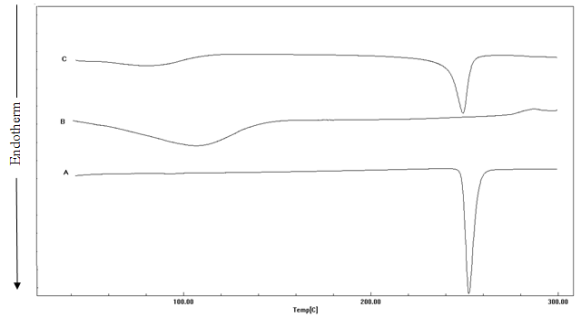


Figure 2. DSC thermograms of DMP (A), HPMC 15000 (B) and 1:1 (w/w) physical mixture of them (C).

In-vitro dissolution rate study of DMP from the prepared adsorbates

Figure (3) shows the release profiles of DMP from the different drug adsorbates with Aerosil 200 in comparison with the pure drug. It was obvious that all adsorbates showed higher dissolution rate than the pure drug due to drug deposition on more extensive surface area in case of adsorbates. Increasing the amount of adsorbent in mixture increased the dissolution rate. Adsorbates of DMP with Aerosil 200 in a weight ratio of 1:5 showed the highest dissolution rate and thus; this ratio was selected for being used in the formulation of floating tablets [2].

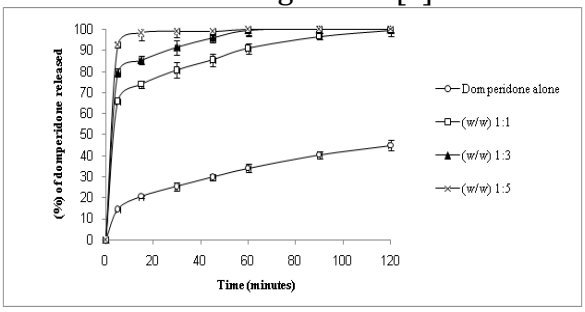


Figure 3. Release profiles of DMP from the different drug adsorbates with Aerosil 200 in comparison with the pure drug.

Physical evaluation of the prepared floating tablets

The results revealed that all prepared tablets had uniform weight (495-506 mg), thickness (3.27-3.62 mm) and diameter (12.92-13.11 mm) and showed acceptable results regarding their drug content and friability according to the previously-mentioned specifications. The tablet hardness ranged from 6.3-9.5 kg/cm^2. So, the tablets were accepted to be used for further studies.

Floating properties of the prepared tablets

Tablets containing Na Alg or HPMC 15000 showed the shortest floating lag time (3-15 minutes) and the longest total floating time (up to 12 hours) among all investigated formulae. This can be attributed to their high swelling properties upon contact with water [13]. Relatively poor floating properties were obtained with the tablets containing hydrophobic polymers (Ethylcellulose and Eudragits) due to their poor swelling properties [13]. In general, increasing the polymer concentration in tablet from 10% to 40%, the floating lag time became shorter and tablets remained buoyant for longer time probably due to the increase in swelling index values which increase by increasing the polymer concentration [13]. Formulae F3 (containing 30% w/w HPMC 15000), F4 (containing 40% w/w HPMC 15000), F7 (containing 30% w/w Na Alg) and F8 (containing 40% w/w Na Alg) showed the best floating properties with floating lag time ranging from 3-7 minutes and total floating time that exceeded 12 hours. The floating process for a tablet containing 40% Na Alg (formula F8) is shown in figure (4) as a representative example.

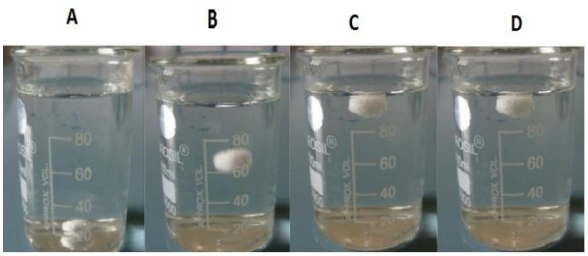


Figure 4. Floating process for a tablet containing 40% Na Alg during lag time (A), the start of floating process (B), during floating time (C) and after 12 hours testing (D).

In-vitro dissolution rate of DMP from the prepared floating tablets

The *in-vitro* dissolution rate studies of the prepared floating tablets revealed that the order of sustaining DMP release from tablets was exhibited by: Eudragit RLPO > Eudragit RS100 > Eudragit RL100 > Ethylcellulose > HPMC 15000 > Na Alg as shown by figure (5). Tablets containing Eudragit RLPO showed more sustaining effect of drug release than those containing Eudragit RS100 or Eudragit RL100 due to the lower content of quaternary ammonium groups in Eudragit RLPO which lead to decrease in the permeability of polymer matrix to aqueous solution and consequently, lead to retardation of drug release [14]. Tablets containing ethylcellulose showed more sustaining effect of drug release than HPMC 15000 and Na Alg due to the hydrophobic nature of ethylcellulose which lead to poor surface wettability and swelling properties decreasing water penetration and causing retardation of drug release [13]. Tablets containing Na Alg showed faster release of DMP than HPMC 15000 due to its higher aqueous solubility and swelling properties resulting in the formation of less compact polymer matrix which upon hydration resulted in the formation of high number of porous channels speeding up the drug release from tablet [13]. In general, increasing the polymer concentration in tablets from 10% to 40% increased the sustaining effect. This can be explained by the increase in the compactness of tablet matrix leading to more retardation of drug release [13] as shown by figure (6) taking Na Alg as a representative example.

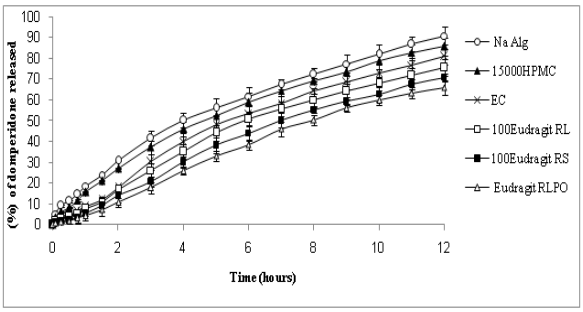


Figure 5. Cumulative percent of DMP released from floating tablets containing 40% (w/w) of different polymers.

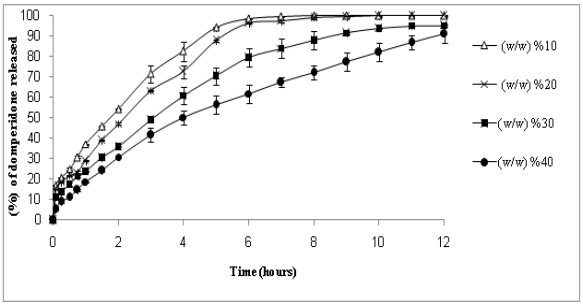


Figure 6. Effect of different concentrations of Na Alg on the DMP release from floating tablets.

Kinetic Analysis of the drug release data from the floating tablets

Kinetic analysis of DMP release data from floating tablets revealed that all prepared tablets showed simplified Higuchi-diffusion model. Analysis of the dissolution data using the equation proposed by Korsemeyer and Peppas gave values of n (release exponent) that lied between 0.45 and 0.89 in all the investigated formulae exhibiting a non-fickian release behavior controlled by a

combination of diffusion and chain relaxation mechanisms [14].

In-vivo studies on the selected formulae of DMP floating tablets

According to the previous results, it was obvious that formulae F7 (containing 30% w/w Na Alg) and F8 (containing 40% w/w Na Alg) showed the best floating properties and release profiles and thus; they were selected for *in-vivo* studies in rabbits in comparison with the commercial conventional immediate-release Motinorm® tablets. The mean plasma levels profiles versus time obtained after oral administration of F7, F8 and Motinorm® are shown in figure (7). Higher peak plasma concentrations (C_{max}) were achieved after administration of F7 and F8 tablets compared with Motinorm® tablets (3.88 ±0.11, 3.95 ±0.08 and 2.10 ±0.12 µg/ml, respectively). Also, higher AUC values were obtained with the floating tablets F7 and F8 compared with Motinorm® tablets (relative bioavailability values were 298.26±11.53% and 315.04±13.39% for F7 and F8, respectively). These results could be attributed to the enhancement in DMP bioavailability resulted from floating tablets that retained the drug in the acidic medium of stomach favoring the drug release and consequently, lead to enhanced absorption and bioavailability of drug [3]. T_{max} and MRT values were prolonged in F7 and F8 compared with the marketed Motinorm® tablets. This delay in T_{max} and MRT could be attributed to the sustaining effect of drug release caused by the sodium alginate matrix in the floating tablets which resulted in slower and more extended drug absorption compared with the marketed immediate-release tablets [13]. The elimination half-lives of DMP were 7.70 ±0.63, 7.59 ±0.54 and 7.48 ±0.28 hours and the apparent volume of distribution values were 0.12 ±0.08, 0.13 ±0.03 and 0.11 ±0.09 L/kg for F7, F8 and Motinorm®, respectively. Pharmacokinetic parameters of the investigated tablets and their statistical significance are listed in tables (4 and 5).

Table 4. Pharmacokinetic parameters of Formula F7 tablets compared with Motinorm® tablets and statistical significance of the difference between them.

Pharmacokinetic parameter	F7 tablets	Motinorm® tablets	Significance of the difference(*)
C_{max} (µg/ml)	3.88±0.11	2.10±0.12	significant
T_{max} (hours)	4.00±0.32	0.50±0.12	significant
K_{abs} (hours^{-1})	0.35±0.06	3.25±1.90	significant
$t_{½\,(abs)}$ (hours)	1.95±0.37	0.21±0.06	significant
$AUC_{(0\text{-}24\ hr)}$ (µg.hr/ml)	33.32±4.28	11.17±1.61	significant
$AUC_{(0\text{-}\infty)}$ (µg.hr/ml)	33.32±4.28	11.17±1.61	significant
$AUMC_{(0\text{-}24hr)}$ (µg.hr^2/ml)	576.88±24.16	156.39±3.19	significant
$AUMC_{(0\text{-}\infty)}$ (µg.hr^2/ml)	576.88±24.16	156.39±3.19	significant
MRT (hours)	17.31±0.59	14.00±0.57	significant
Cl_T (ml/min.)	1.10±0.09	3.28±0.06	significant

(*) statistically significant when ($p < 0.05$).
Statistically non-significant when ($p > 0.05$).

Table 5. Pharmacokinetic parameters of Formula F8 tablets compared with Motinorm® tablets and statistical significance of the difference between them.

Pharmacokinetic parameter	F8 tablets	Motinorm® tablets	Significance of the difference(*)
C_{max} (µg/ml)	3.95±0.08	2.10±0.12	significant
T_{max} (hours)	4.75±0.45	0.50±0.12	significant
K_{abs} (hours^{-1})	0.30±0.07	3.25±1.90	significant
$t_{½\ (abs)}$ (hours)	2.34±0.22	0.21±0.06	significant
$AUC_{(0\text{-}24\ hr)}$ (µg.hr/ml)	35.19±3.36	11.17±1.61	significant
$AUC_{(0\text{-}\infty)}$ (µg.hr/ml)	35.19±3.36	11.17±1.61	significant
$AUMC_{(0\text{-}24hr)}$ (µg.hr^2/ml)	638.83±20.79	156.39±3.19	significant
$AUMC_{(0\text{-}\infty)}$ (µg.hr^2/ml)	638.83±20.79	156.39±3.19	significant
MRT (hours)	18.15±0.32	14.00±0.57	significant
Cl_T (ml/min.)	1.04±0.08	3.28±0.06	significant

(*) statistically significant when ($p < 0.05$).
Statistically non-significant when ($p > 0.05$).

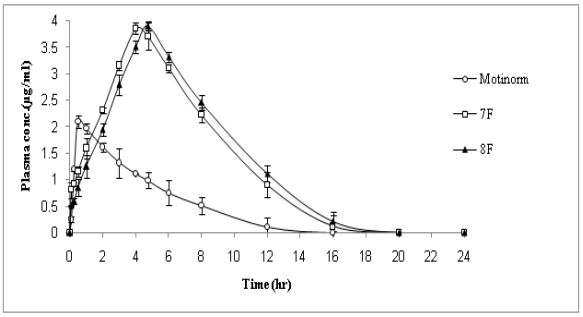


Figure 7. Plasma concentrations of DMP after oral administration of Motinorm®, Formula F7 and formula F8 tablets at a dose level of 1.1 mg/kg

Conclusion

Dissolution rate of DMP was markedly improved through adsorption onto the surface of Aerosil 200. The incorporation of these adsorbates with various polymers into gastro-retentive floating tablets resulted in physically-acceptable tablets with a controlled pattern of drug release over a time period of 12 hours. Increasing the polymer concentration in tablets increased the sustaining effect of drug release. Formulae F7 (containing 30% w/w Na Alg) and F8 (containing 40% w/w Na Alg) showed the best physical properties, floating properties and release profiles and were selected for *in-vivo* studies which revealed a marked enhancement of DMP oral bioavailability in comparison with the commercially-available Motinorm® tablets.

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