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Original Article

DESIGN AND EVALUATION OF DOMPERIDONE SUBLINGUAL TABLETS

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ABSTRACT

Objective: The aim of this work was to enhance the bioavailability of poorly soluble, anti-emetic drug; domperidone (DMP) having a poor oral bioavailability (13-17%) due to extensive first pass metabolism. The goal of this study was achieved through solubilization of DMP using solid dispersion technology followed by incorporation of solid dispersions into sublingual tablets to bypass pre-systemic metabolism.

Methods: Solid dispersions of DMP with Pluronic F-68 were prepared in different weight ratios by fusion method and they were evaluated for their *in vitro* dissolution rate to select the best ratio for final formulation. Then, solid dispersions were formulated into sublingual tablets in combination with various soluble excipients. Sublingual tablets were prepared by direct compression technique and evaluated for their physical properties, *in vitro* dissolution rate and kinetics of drug release. The best formulae were selected for *in vivo* studies in rabbits in comparison with marketed oral tablets; Motinorm®.

Results: Solid dispersions of DMP with Pluronic F-68 in a weight ratio of 1:7 (w/w) showed the highest dissolution rate and were selected for sublingual tablets formulation. Sublingual tablets formulae S16 (containing Fructose and 10% w/w Ac-Di-Sol) and S20 (containing Fructose and 10% w/w Explotab) showed the best results and were selected for *in vivo* studies in rabbits. The selected formulae showed marked enhancement of DMP bioavailability compared with the commercial oral tablets; Motinorm®, with relative bioavailability values of 432.49±10.13% and 409.32±11.59 % for S16 and S20, respectively.

Conclusion: The results confirmed that sublingual tablets were an effective tool for DMP delivery with marked enhancement of bioavailability.

Keywords: Domperidone, Solubility, Solid dispersions, Sublingual tablets, First-pass metabolism, Bioavailability

INTRODUCTION

The first-pass metabolism is a critical challenge that faces effective oral delivery of many drugs. It means extensive metabolism of the drug in the gut wall and liver before reaching systemic circulation resulting in poor bioavailability and low efficacy of drug [1]. Researchers have developed several approaches to overcome the first-pass metabolism including rectal [2], buccal [3] and transdermal drug delivery systems [4]. Sublingual tablets have become one of the top promising approaches for this purpose due to their ease of administration, rapid disintegration in the mouth and instant drug delivery which is very useful for emergency management of many health disorders [1]. Poor water solubility of many drugs limits the ability for their delivery via sublingual route [1]. Solid dispersion technology has provided the solution for solubility problems of an enormous number of drugs [5]. Domperidone (DMP) is 5-chloro-1-[1-[3-(2, 3-dihydro-2-oxo-1H-benzimidazol-1-yl)-propyl] 4-piperidinyl]-1, 3-dihydro-2H-benz-imidazol-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 [6]. According to Biopharmaceutical Classification System (BCS), DMP is classified under class-II drugs which are poorly soluble and highly permeable [6].

It is practically insoluble in water (1 part in 50 000 part of water) [7] with poor oral bioavailability (13-17%) due to extensive first-pass metabolism in the gut wall and liver [8]. The aim of this study was to improve DMP bioavailability via formulation of sublingual tablets. DMP was solubilized through the formulation of solid dispersions with Pluronic F-68 in different weight ratios by fusion method and the prepared systems were evaluated for their *in vitro* dissolution rate to select the best ratio for final formulation. Then, solid dispersions were incorporated into sublingual tablets in combination with various soluble excipients including Sorbitol, Mannitol, Anhydrous lactose and Fructose. Sublingual tablets were prepared by direct compression technique and evaluated for their weight uniformity, drug content, friability, hardness, thickness, diameter, disintegration time and *in vitro* dissolution rate. The best formulae were selected for *in vivo* studies in rabbits in comparison with marketed oral tablets; Motinorm®.

MATERIALS AND METHODS

Materials

-Domperidone was supplied as a gift sample by "Pharco, for pharmaceutical and chemical industry", Egypt.

-Pluronic F-68 and Polyethylene glycol 6000 (PEG 6000) were purchased from "Sigma-Aldrich Co.", USA.

-Sorbitol, Mannitol, Fructose, and Ac-Di-Sol were purchased from "Cooperation Pharmaceutique Francaise", France.

-Anhydrous lactose was purchased from "Prolabo", France.

-Explotab was purchased from "BDH Co.", UK.

-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.

-Thiopental sodium was supplied by "Pharco, for pharmaceutical and chemical industry", Egypt.

-All other used chemicals and reagents were of analytical grade and were used as received.

Methods

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 the drug-excipient

compatibility using FT-IR spectrometer (Shimadzu IR-470, Japan). 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} 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 check the drug-excipient compatibility. DSC thermo grams were obtained by using a shimadzu DSC-50 (Japan) equipped with a computer software program. Samples of about 5 mg were placed in an aluminum pan of 50 µl capacity and 0.1 mm thickness, press-sealed with an 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 a 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 DMP solid dispersions

Solid dispersions of DMP with Pluronic F-68 were prepared in weight ratios of 1:1, 1:3, 1:5 and 1:7 w/w by fusion method. The calculated amount of Pluronic F-68 was placed in a porcelain dish and heated till melting over a steam bath. The accurately weighed amount of DMP was dispersed into molten Pluronic F-68 gradually using a glass rod. After complete dispersion of drug within carrier, the dish was removed from the steam bath and left aside to cool at room temperature till solidification of its contents. Then, the solid dispersion formed was pulverized, sieved to obtain a particle size range of 125-250 µm and stored in a dessicator over calcium chloride till used [9].

***In vitro* dissolution rate study of DMP from the prepared solid dispersions**

USP dissolution apparatus II (Erweka, Germany) was used at a rotation speed of 50 r. p. m. Powdered samples of solid dispersions equivalent to 10 mg of domperidone were added to the dissolution medium (250 ml phosphate buffer solution with pH 6.8, kept at 37±0.5 °C). The 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 min, samples (5 ml) of the solution were withdrawn with a volumetric pipette using the cotton plug as a filter and replaced with an equal volume of fresh dissolution medium equilibrated at 37±0.5 °C. The samples were analyzed for the released amount of DMP spectrophotometrically at λ_{max} of 284 nm. Each experiment was performed in triplicate and the mean recordings were used for calculations. The solid dispersions of DMP with Pluronic F-68 in a weight ratio of 1:7 (w/w) showed the highest dissolution rate and thus; this ratio was selected for being used in the formulation of sublingual tablets.

Formulation of DMP sublingual tablets

Sublingual tablets of DMP were prepared by the direct compression technique using the formulae shown in tables (1-3). A fixed amount (80 mg) of DMP-Pluronic F-68 solid dispersion in a weight ratio of 1:7 (w/w) was used in the formulations which was equivalent to 10 mg of DMP. Different water-soluble diluents were used including Sorbitol, Anhydrous lactose, Mannitol and Fructose, which also imparted a sweet taste to tablets which would be useful in enhancing patient acceptability. Ac-Di-Sol and Explotab were used as super disintegrants to promote fast disintegration of tablets and they were incorporated in different concentrations of the final tablet weight (200 mg). Polyethylene glycol 6000 (PEG 6000) was used as a water-soluble lubricant in a concentration of 4% (w/w). All powders were mixed by trituration in a glass mortar with a pestle to obtain a uniform mixture. The blended powders were compressed into tablets weighing 200 mg using a single punch tablet machine (Erweka, Germany) having a die set of 8 mm diameter.

Physical evaluation of the prepared sublingual tablets

Uniformity of tablets weight

According to European Pharmacopoeia 2014 [7], twenty randomly selected tablets from each formula were individually weighed. The average weight was determined and the standard deviation was calculated. For tablets weighing 80-250 mg, tablet weight should not deviate from claimed value by more than 7.5%.

Uniformity of drug content

The European Pharmacopoeia 2014 method was adopted [7]. 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 the flask were stirred continuously and filtered. After suitable dilution with phosphate buffer solution (pH 6.8), the solution was assayed spectrophotometrically at 284 nm. Drug content was expressed as a percentage of label claim and should be 100±15%.

Table 1: Composition of formulated sublingual tablets of DMP containing different water-soluble diluents

Ingredients	Formula composition (mg)[a]			
	S1	S2	S3	S4
Solid dispersion	80	80	80	80
Sorbitol	112	-	-	-
Anhydrous lactose	-	112	-	-
Mannitol	-	-	112	-
Fructose	-	-	-	112
PEG 6000	8	8	8	8
Ac-Di-Sol	-	-	-	-
Explotab	-	-	-	-

[a] Total tablet weight= 200 mg.

Table 2: Composition of formulated sublingual tablets of DMP containing different water-soluble diluents and 5% (w/w) super-disintegrants

Ingredients	Formula composition (mg) [a]							
	S5	S6	S7	S8	S9	S10	S11	S12
Solid dispersion	80	80	80	80	80	80	80	80
Sorbitol	102	-	-	-	102	-	-	-
Anhydrous lactose	-	102	-	-	-	102	-	-
Mannitol	-	-	102	-	-	-	102	-
Fructose	-	-	-	102	-	-	-	102
PEG 6000	8	8	8	8	8	8	8	8
Ac-Di-Sol[b]	10	10	10	10	-	-	-	-
Explotab[b]	-	-	-	-	10	10	10	10

[a]Total tablet weight= 200 mg., [b]The used amounts of Ac-Di-Sol or Explotab represent 5% (w/w) of the total tablet weight.

Table 3: Composition of formulated sublingual tablets of DMP containing different water-soluble diluents and 10% (w/w) super-disintegrants

Ingredients	Formula composition (mg) [a]							
	S13	S14	S15	S16	S17	S18	S19	S20
Solid dispersion	80	80	80	80	80	80	80	80
Sorbitol	92	-	-	-	92	-	-	-
Anhydrous lactose	-	92	-	-	-	92	-	-
Mannitol	-	-	92	-	-	-	92	-
Fructose	-	-	-	92	-	-	-	92
PEG 6000	8	8	8	8	8	8	8	8
Ac-Di-Sol [b]	20	20	20	20	-	-	-	-
Explotab [b]	-	-	-	-	20	20	20	20

[a]Total tablet weight= 200 mg., [b]The used amounts of Ac-Di-Sol or Explotab represent 10% (w/w) of the total tablet weight.

Tablet friability

According to European Pharmacopoeia 2014 [7], 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 min. 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%.

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 randomly-selected tablets was determined and the average was considered [10].

Thickness and diameter of the prepared tablets

The thickness and the diameter of 20 randomly-selected tablets from each formula were measured by means of a micrometer (Mitutoyo Co., Japan). The average thickness and diameter were determined [11].

Disintegration time of the prepared tablets

According to European Pharmacopoeia 2014 [7], the test was carried out on randomly selected 6 tablets using the apparatus specified in the pharmacopoeia (Erweka, Germany). 250 ml phosphate buffer solution (pH 6.8) at 37±0.5 °C was used as a disintegration medium and the time taken for complete disintegration of the tablet with no solid mass remaining in the apparatus was measured. For sublingual tablets, disintegration time should be less than 3 min.

***In vitro* dissolution rate of DMP from the prepared sublingual tablets**

USP dissolution apparatus II (Erweka, Germany) was used at a rotation speed of 50 r. p. m. Each of the tested tablets was added to the dissolution medium (250 ml phosphate buffer solution with pH 6.8, kept at 37±0.5 °C). At time intervals of 5, 10, 15, 20, 25 and 30 min, samples (5 ml) of the solution were withdrawn with a volumetric pipette using the cotton plug as a filter and replaced with an equal volume of fresh dissolution medium equilibrated at 37±0.5 °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 releases 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 [12]:

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 [12]: $M_t/M_\infty = Kt^n$.

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 the case of tablets (cylindrical sample), n= 0.45 for Fickian diffusion while in the 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 super case II transport, n>0.89.

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

Treatment of animals

On basis of the previously mentioned tests, formulae S16 (containing Fructose and 10% w/w Ac-Di-Sol) and S20 (containing Fructose and 10% w/w Explotab) showed the best results and thus; they were selected for *in vivo* studies in rabbits in comparison with the commercial oral tablets; Motinorm®. The protocol of the 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. The food was withheld for 24 h 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 [13]. 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 group rabbits were given an oral dose of 0.514 mg/kg of DMP (equivalent to 10 mg per human tablet dose) from Motinorm® tablets using a stomach tube. The 3rdand 4th groups were anesthetized using IP Thiopental sodium (15 mg/kg) before administration of 0.514 mg/kg DMP sublingually from formulae S16 and S20, respectively to prevent the rabbits from swallowing the tablets. 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 h following drug administration. The samples were centrifuged at 5000 r. p. m for 15 min. 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.* was adopted [14]. 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 min followed by centrifugation at 5000 r. p. m for another 10 min. 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 the mobile phase. Then, 20 µl samples were 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 [15, 16]:

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 the 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 the 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 sublingual formulations and the commercial Motinorm® tablets using a statistical computer package (SPSS version 13.0)

RESULTS AND DISCUSSION

Fourier-transform infrared (FT-IR) studies

Table (4) shows the FT-IR frequencies of DMP with the different excipients used in the formulation of sublingual tablets. Pure DMP showed characteristic peaks at 3390 cm^{-1} (N-H stretching vibration), 3080 cm^{-1}(aromatic =C-H stretching vibration), 2915 cm^{-1} (sp^3–C-H vibration), 1697 cm^{-1} (C=O stretching vibration) and several bands at 1400-1600 cm^1 (aromatic C=C stretching vibration). The same characteristic peaks of DMP appeared in the physical mixtures with excipients (1:1 w/w) without significant changes. These results confirmed the absence of chemical incompatibilities between drug and the used excipients. FT-IR spectra of DMP with Anhydrous lactose are shown in fig. (1) as a representative example.

Table 4: FT-IR frequencies of DMP with the different excipients used in the formulation of sublingual tablets

DMP characteristic groups	FT-IR frequencies (cm^{-1})							
	Pure DMP	DMP-excipients physical mixtures (1:1 w/w)						
		Anhydrous lactose	Sorbitol	Mannitol	Fructose	PEG 6000	Ac-Di-Sol	Explotab
N-H	3390	3400	3405	3402	3395	3412	3385	3395
aromatic =C-H	3080	3050	3070	3090	3085	3075	3097	3090
sp^3–C-H	2915	2890	2901	2950	2970	2962	2971	2950
C=O	1697	1694	1700	1695	1705	1707	1700	1695
aromatic C=C (several peaks)	1400-1600	1400-1600	1400-1600	1400-1600	1400-1600	1400-1600	1400-1600	1400-1600

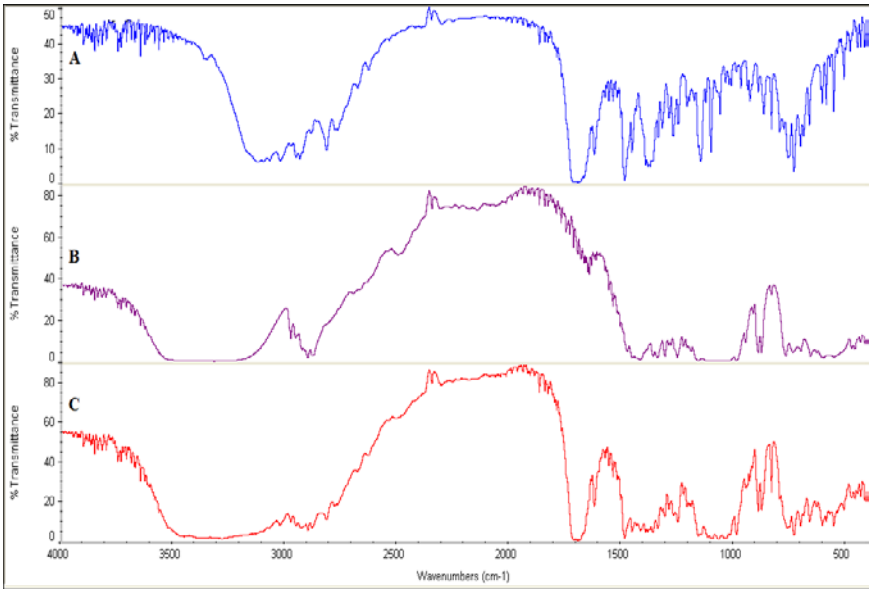

Fig. 1: FT-IR spectra of DMP (A), Anhydrous lactose (B) and 1:1 (w/w) physical mixture of them (C)

Differential scanning calorimetry (DSC) studies

Table (5) shows the temperature and heat of fusion (ΔH) obtained from DSC spectra of DMP with the different excipients used in the formulation of sublingual tablets. Pure DMP 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. Each of individual excipients showed a melting endothermic peak corresponding to its melting point. DMP-excipients physical mixtures (1:1 w/w) showed no significant shift in the position of melting endothermic peak of DMP, but with a reduction in the intensity and fusion enthalpy due to dilution effect [17]. These results confirmed the absence of chemical incompatibilities between drug and the investigated excipients and indicated the suitability of their use in the formulations. DSC thermograms of DMP with Anhydrous lactose are shown in fig. (2) as a representative example.

***In vitro* dissolution rate study of DMP from the prepared solid dispersions**

Fig. 3 shows the release profiles of DMP from its different solid dispersions with Pluronic F-68 in comparison with the pure drug. It was obvious that DMP had a very poor dissolution rate at pH 6.8 (only 16 % of the drug released after 2 h) which could be attributed to its weakly-basic nature (pka=7.9) making it insoluble at relatively high pH values [17]. All prepared solid dispersions showed higher dissolution rates than the pure drug. This can be explained as when solid dispersions are exposed to aqueous media, the carrier dissolves, and the drug is released as very fine colloidal particles. This greatly reduces particle size and increases surface area, which results in marked improvement of dissolution rates [5]. Increasing the amount of carrier in solid dispersion system increased the dissolution rate (the percent of dissolution improvement was 371.88 %, 487.46 %, 714.28 % and 937.2 % for 1:1, 1:3, 1:5 and 1:7 w/w solid dispersions, respectively in comparison with the pure drug). Solid dispersions of DMP with Pluronic F-68 in a weight ratio of 1:7 showed the highest dissolution rate and thus; this ratio was selected for being used in the formulation of sublingual tablets.

Physical evaluation of the prepared sublingual tablets

The results revealed that all prepared tablets had uniform weight (195-205.5 mg), thickness (2.36-2.56 mm) and diameter (7.92-8.11 mm) and showed acceptable results regarding their drug content and friability according to the previously-mentioned specifications. The tablet hardness values ranged from 2.4-5.5 kg/cm2which were suitable values for sublingual tablets. So, the tablets were accepted to be used for further studies.

Formulae S1-S4 containing no super disintegrants showed unacceptable disintegration times longer than 3 min. The addition of 5% (w/w) super disintegrant decreased tablet disintegration time due to wicking and capillary action exerted by super disintegrant which resulted in the faster disintegration of tablet upon contact with water [18]. Increasing super disintegrant concentration in tablets from 5% to 10% (w/w) resulted in shorter disintegration time (less than 1.5 min). Tablets containing Ac-Di-Sol showed shorter disintegration time than those containing Explotab. This can be attributed to slow water uptake and the gelling tendency of Explotab that delay its effect [18].

Table 5: Peak temperatures and enthalpy changes (ΔH) for DSC thermograms of DMP alone and its physical mixtures with the investigated excipients (1:1 w/w)

Samples	Peak temperature of the drug (°C)	ΔH (J/g)
DMP alone	252.49	-94.37
DMP: Anhydrous lactose	248.00	-23.00
DMP: Sorbitol	248.50	-27.47
DMP: Mannitol	245.74	-42.55
DMP: Fructose	249.8	-39.17
DMP: PEG 6000	248.36	-32.26
DMP: Ac-Di-Sol	250.80	-32.51
DMP: Explotab	249.11	-44.49

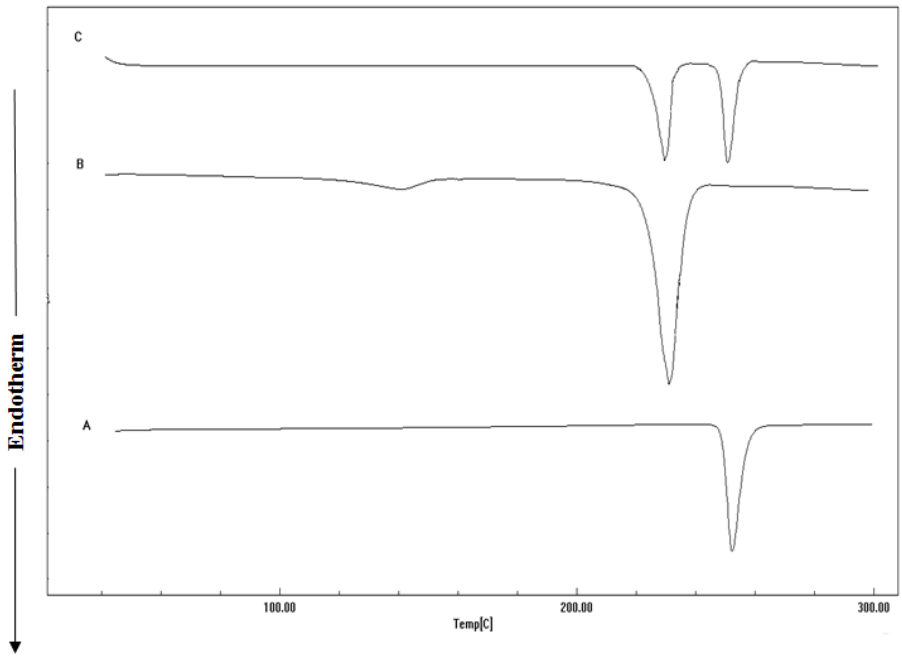

Fig. 2: DSC thermograms of DMP (A), Anhydrous lactose (B) and 1:1 (w/w) physical mixture of them (C)

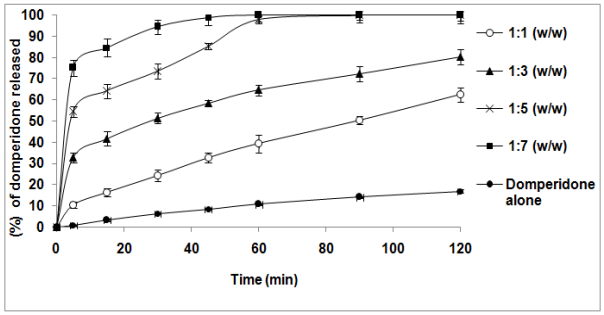

Fig. 3: Release profiles of DMP from its different solid dispersions with Pluronic F-68 at pH 6.8 in comparison with the pure drug (Number of experiments; n=3, results are expressed as mean±SD)

In vitro dissolution rate of DMP from the prepared sublingual tablets

Fig. (4) Shows the *in vitro* release profiles of DMP from sublingual tablets containing water-soluble different diluents and 10% (w/w) Ac-Di-Sol. It was obvious that all tablets showed fast drug release with more than 80% of drug released within the first 5 min. The order of drug release from the different tablets was: Fructose-containing tablets > Sorbitol-containing tablets > Anhydrous lactose-containing tablets stelbat gniniatnoc-lotinnaM >. This can be explained on the basis of the difference in aqueous solubility of these sugars [10]. It was observed that the prepared tablets exhibited surface erosion upon contact with water. The speed of surface erosion depends mainly on the solubility of the matrix [10]. Fructose has the highest aqueous solubility among the investigated sugars followed by Sorbitol, Anhydrous lactose and finally, Mannitol [19].

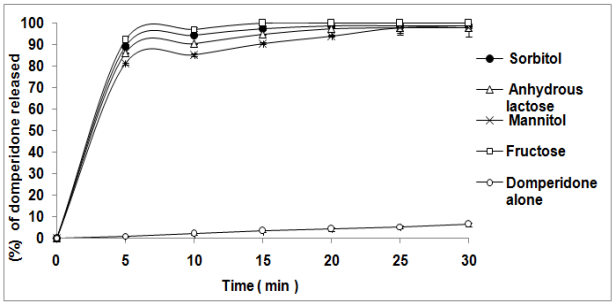

Fig. 4: *In vitro* release profiles of DMP from sublingual tablets containing different water-soluble diluents and 10% (w/w) Ac-Di-Sol (Number of experiments; n=3, results are expressed as mean±SD)

Kinetic analysis of the drug release data from the sublingual tablets

Kinetic analysis of DMP release data from sublingual 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 which was controlled by a combination of diffusion and chain relaxation mechanisms [11].

In vivo studies on the selected formulae of DMP sublingual tablets

According to the previous results, it was obvious that formulae S16 (containing Fructose and 10% w/w Ac-Di-Sol) and S20 (containing Fructose and 10% w/w Explotab) showed the best physical properties and release profiles and thus; they were selected for *in vivo* studies in rabbits in comparison with the commercial oral tablets; Motinorm®. The mean plasma levels profiles versus time obtained after administration of S16, S20 and Motinorm® are shown in fig. (5). Higher peak plasma concentrations (C_{max}) were achieved after administration of S16 and S20 tablets compared with Motinorm® tablets (2.32±0.12, 2.14±0.08 and1.11±0.13 µg/ml, respectively). Also, higher AUC values were obtained with the sublingual tablets S16 and S20 compared with Motinorm® tablets (relative bioavailability values were 432.49±10.13% and 409.32±11.59% for S16 and S20, respectively). These results confirmed that sublingual tablets resulted in enhancement of DMP bioavailability through overcoming the first-pass metabolism following oral administration of drug [20]. Sublingual tablets showed shorter T_{max} values than oral tablets indicating faster absorption of them. The elimination half-lives of DMP were 7.12±0.52, 7.73±0.48 and 7.69±0.35 h and the apparent volume of distribution values were 0.11±0.03, 0.13±0.05 and 0.12±0.06 l/kg for S16, S20 and Motinorm®, respectively. Pharmacokinetic parameters of the investigated tablets and their statistical significance are listed in tables (6 and 7).

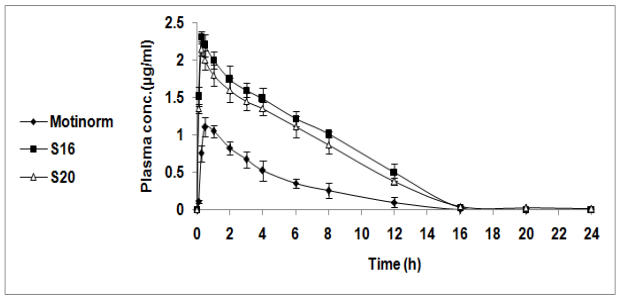

Fig. 5: Plasma concentrations of DMP after oral administration of Motinorm® and sublingual administration of formula S16 and formula S20 tablets at a dose level of 0.514 mg/kg (Number of experiments; n=6, results are expressed as mean±SD)

Table 6: Pharmacokinetic parameters of formula S16 sublingual tablets compared with Motinorm® oral tablets and statistical significance of the difference between them

Pharmacokinetic parameters[a]	S16 tablets	Motinorm® tablets	Significance of the difference [b]
C_{max} (µg/ml)	2.32±0.12	1.11±0.13	Significant
T_{max} (h)	0.25±0.06	0.50±0.16	Significant
K_{abs} (h^{-1})	5.18±1.26	3.06±1.70	Significant
$t_{½\ (abs)}$ (h)	0.13±0.03	0.23±0.08	Significant
$AUC_{(0\text{-}24\ hr)}$ (µg. h/ml)	30.36±3.38	7.02±1.47	Significant
$AUC_{(0\text{-}\infty)}$ (µg. h/ml)	30.36±3.38	7.02±1.47	Significant
$AUMC_{(0\text{-}24\ hr)}$ (µg. h^2/ml)	477.82±26.24	98.55±4.27	Significant
$AUMC_{(0\text{-}\infty)}$ (µg. h^2/ml)	477.82±26.24	98.55±4.27	Significant
MRT (h)	15.74±0.48	14.04±0.44	Significant
Cl_T (ml/min)	0.60±0.07	2.61±0.09	Significant

[a]Number of experiments; n=6, results are expressed as mean±SD., [b]Statistically-significant when ($^*p<0.05$), statistically non-significant when ($^*p>0.05$).

Table 7: Pharmacokinetic parameters of formula S20 sublingual tablets compared with Motinorm® oral tablets and statistical significance of the difference between them

Pharmacokinetic parameters [a]	S20 tablets	Motinorm® tablets	Significance of the difference [b]
C_{max} (µg/ml)	2.14±0.08	1.11±0.13	Significant
T_{max} (h)	0.25±0.05	0.50±0.16	Significant
K_{abs} (h^{-1})	4.88±1.37	3.06±1.70	Significant
$t_{½\ (abs)}$ (h)	0.14±0.02	0.23±0.08	Significant
$AUC_{(0\text{-}24\ hr)}$ (µg. h/ml)	28.73±2.99	7.02±1.47	Significant
$AUC_{(0\text{-}\infty)}$ (µg. h/ml)	28.73±2.99	7.02±1.47	Significant
$AUMC_{(0\text{-}24\ hr)}$ (µg. h^2/ml)	447.95±18.29	98.55±4.27	Significant
$AUMC_{(0\text{-}\infty)}$ (µg. h^2/ml)	447.95±18.29	98.55±4.27	Significant
MRT (h)	15.59±0.29	14.04±0.44	Significant
Cl_T (ml/min)	0.64±0.09	2.61±0.09	Significant

[a]Number of experiments; n=6, results are expressed as mean±SD., [b]Statistically-significant when ($^*p<0.05$), statistically non-significant when ($^*p>0.05$).

CONCLUSION

The dissolution rate of DMP was markedly improved through the formulation of solid dispersions with Pluronic F-68. The incorporation of these solid dispersions with various excipients into sublingual tablets resulted in physically-acceptable tablets. Tablet disintegration study revealed that incorporation of super disintegrants into tablets resulted in faster tablet disintegration and indicated the superiority of Ac-Di-Sol over Explotab. Increasing the super disintegrant concentration in tablets decreased the disintegration time. All the prepared sublingual tablets showed improved patterns of drug release and Fructose-containing tablets were the best among them. Formulae S16 (containing Fructose and 10% w/w Ac-Di-Sol) and S20 (containing Fructose and 10% w/w Explotab) showed the best physical properties and release profiles and were selected for *in vivo* studies in rabbits which revealed a marked enhancement of DMP bioavailability in comparison with the marketed Motinorm® oral tablets.

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CONFLICT OF INTERESTS

The authors report no conflict of interests in this work

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