FORMULATION, IN-VITRO RELEASE AND BIOAVAILABILITY STUDY OF DOMPERIDONE RECTAL SUPPOSITORIES

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ABSTRACT

Domperidone is practically insoluble prokinetic drug; the systemic bioavailability of the drug following oral administration is only 13-17\% because of extensive presystemic metabolism in the gut wall and liver. The applicability of the solid dispersion technique as a method for enhancing absorption of the drug through achieving better dissolution characteristics and better bioavailability for domperidone had been utilized. Solid dispersions of domperidone were prepared using Pluronic F-127, Myrj 52, PEG 4000 and PEG 6000 as carriers, at different drug to carrier ratios. The spectroscopic infra-red (IR), differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and powder X-ray diffractometry (PXRD) studies were performed to characterize the role of these carriers in increasing bioavailability through decreasing the crystallinity of domperidone. Selected solid dispersion of the drug with these carriers was used to formulate domperidone suppositories. It was found that, the release of pure domperidone from the hydrophilic bases was remarkably higher than that from the lipophilic ones. Domperidone solid dispersion with Pluronic F-127 formulated into suppository, showed enhanced release reaching about 33.188 $\pm$ 5.655\% in 45 min from PEG suppository base, compared to drug alone 15.834 $\pm$ 1.538\%. Addition of 4 $\%$ w/w cetrimide as a release enhancer increased the release to 82.997 $\pm$ 1.306 \% in 30 min. Bioavailability of domperidone formulated as suppositories containing solid dispersion with Pluronic F-127 (F-18) was studied in rabbits. The results were promising with significant increase in both maximum plasma concentration and the area under the plasma concentration - time curve compared with the marketed domperidone rectal suppository Motinorm$^\text{\textregistered}$. So we can conclude that inclusion of the drug in this form into suppositories enhanced bioavailability and avoids the presystemic metabolism.

Keywords: Domperidone; Solid dispersion; Suppositories; Bioavailability studies.

1. Introduction

Domperidone is 5-Chloro-1-\{3-\{2,3-dihydro-2-oxo-1H-benzimidazol-1-yl\} propyl\}-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one [1]. It is a dopamine (D\textsubscript{2}) receptor antagonist, has been used for the treatment and prevention of acute nausea and vomiting from any cause but specifically; cytotoxic therapy and radiotherapy, l-dopa and bromocriptine treatment for parkinsonian patients, used in case of stimulation of gut mobility as in non-ulcer dyspepsia, esophageal reflux and gastritis, and also used in the treatment of functional dyspepsia [1-2]. Systemic bioavailability following oral administration is 13-17\% because of extensive presystemic metabolism (83-87\%) in the gut wall and liver. Furthermore, domperidone is practically insoluble in water and the solubility characteristics of a drug greatly influence its ability to penetrate the biological membranes [3-4]. Solid dispersion technique is one of the most promising strategies to improve the dissolution properties and hence bioavailability of slightly water-soluble drugs. It provides the possibility to reduce the drug particle size to a molecular level and increased wettability. In addition, a transformation of the drug from the crystalline to the amorphous state can occur [5-7]. Rectal administration is used for systemic distribution when the oral administration of drugs was not suitable. Also, absorption of drug from the rectal mucosa directly into the venous circulation may bring about a faster onset of action than is found after the oral one and avoids enzymatic decomposition of numerous drugs in the gastrointestinal tract. Surfactants are one of the most important classes of adjuvants in pharmaceutical preparations. They could affect the rate and/or extent of absorption of drugs from suppositories [8-10]. There are suppositories of domperidone available in the Egyptian market. However, to date no information concerning domperidone suppository formulations have been found in the current literature. The present work has been undertaken to improve the bioavailability of domperidone after rectal administration by by-pass the presystemic metabolism of the drug. Characterization of solid dispersion systems were studied by infra-red spectrophotometry (IR),...
differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and powder X-ray diffractometry (PXRD). Moreover, the bioavailability study of domperidone in rabbits was investigated from the selected suppository formulation (F18) and compared to the marketed rectal suppository, Motinorm®.

2. Materials and methods

2.1. Materials
Domperidone (Pharco, for Pharmaceutical and Chemical Industry, Egypt), Propylene glycol (PG) (Evans Chem.Co, Egypt), Pluronic F-127 (PF-127), Myrj 52, Myrj 58, Polyethylene glycol 600, 1000, 1500, 4000, and 6000, (Sigma – Aldrich Co, USA), Cocoa butter (B.P. grade) (Al-Goumhouria Co, for trading Chemicals and Medical Apparitions), Witepsol H-15 (Dynamite Nobel, Germany), Suppocire AM (Gattefosse établissements, France), Gelatin (The General Chemical and pharmaceutical Co., LTD, England), Glycerol (B.P. grade) (Lab chemical trading Co. laboratory reagent, Egypt), Cetrimide (Danochem a subsidiary of Ferrosan, manufacturing chemists, Copenhagen, Denmark), Polysorbate 20, 40, 60 and 80, Sodium lauryl sulphate, and Dimethyl formamide (El-Nasr pharmaceutical and chemicals Co, Egypt), Beta cyclodextrin (β- CD) (Winlab Laboratory chemicals reagents Fine chemicals, UK), Brij 35 (Merck Schuchardt OHG Hohenbrunn, Germany), Motinorm® oral suspension 5mg/5ml, and Motinorm® infants suppositories 10mg (manufactured by Glaxo SmithKline S.A.E. El-Salam City, Cairo, A.R.E.). All other chemicals were of analytical grade and solvents used in the HPLC experiment were of HPLC grade.

2.2. Methods

2.2.1. Preparation of solid dispersions by co-evaporation method
Solid dispersions of domperidone with PEG 6000, PEG 4000, Myrj 52, and Pluronic F-127 at weight ratio of (1:1, 1:2, and 1:3), drug to carrier were prepared by solvent evaporation method. Solutions of the drug and the investigated carriers, in the calculated ratios, were prepared and the solvent was removed by evaporation at room temperature on magnetic stirrer. The co-precipitates were then scrapped and dried in a hot air oven at 40°C for 24 hours, pulverized, then sieved to 212µm and kept in a desiccator. A specified sample of the prepared solid dispersion was assayed for the drug content.

2.2.2. Preparation of Domperidone suppositories
Suppositories were prepared from either fat or water soluble bases by the melting technique to contain 10 mg of domperidone per suppository. Domperidone suppositories in PEG 6000: PG (40:60%w/w) suppository base containing the equivalent of 10 mg of the drug in its solid dispersion with Pluronic F-127 at 1:3 drug to carrier ratio with the addition of different additives were prepared. The composition of each suppository was illustrated in tables (I-IV). After solidification at room temperature the prepared suppositories were packed in tightly closed containers and placed in a refrigerator. Before use, the suppositories were left for 2 hours at room temperature.

2.3. Characterization of solid dispersions

2.3.1. Infra-red spectroscopy studies (IR)
Studies of the IR spectra of the intact drug, polymers used, the physical mixture, and the solid dispersion at the selected ratios were conducted using Shimadzu spectrophotometer (model 470, Japan) and the KBr disk method.

2.3.2. Differential scanning calorimetry (DSC)
The DSC thermograms were obtained using differential scanning calorimeter (DSC model 50, Shimadzu, Japan). Samples (5mg) were weighed in aluminum pans and heated at a scanning rate of 10°C/ min from 30 to 350°C in the presence of nitrogen at flow rate of 40 ml/min.

2.3.3. Powder X-ray diffraction (PXRD)
The Powder XRD patterns were performed on domperidone, Pluronic F-127, physical mixture, and solid dispersion with Pluronic F-127 at (1:3) drug to carrier ratio. Each powder sample was carried out with Philips (PW-1050, Bragg-Brentano) diffractometer; Cu Kα radiation (35 Kv, 40 mA, slit 1.5418 Å).

2.3.4. Scanning electron microscopy (SEM)
SEM was performed on domperidone, Pluronic F-127, physical mixture, and solid dispersion with Pluronic F-127 at (1:3) drug to carrier ratio using a JSM-6400 (Joel, Japan) by coating the samples with gold using ion sputtering at 15 Kv. Digital images of the samples were obtained.

2.3.5. In-vitro release studies
The in-vitro release of domperidone from the different suppository formulae was performed. The release system was composed of a glass beaker containing 100 ml of the release media in which a suppository was placed. The beaker was placed into a constant temperature shaker water bath, agitated at 100 rpm at 37±0.5°C. At specified intervals, samples (2 ml) were withdrawn from the release media and were replaced with equal volumes of the fresh buffer, and then the drug was assayed spectrophotometrically at 284 nm. Each release experiment was performed in triplicate, and the mean readings were used for calculation.

2.4. Bioavailability studies
The water soluble suppository base (F18) (Table IV) was selected to evaluate the bioavailability of the rectal formulation of domperidone in comparison with that of the marketed rectal formulation. The commercial oral suspension of domperidone, Motinorm® (5mg/5ml), was used as the oral formulation in this study. For both oral and rectal administrations, the dose level of 0.7 mg/kg of the drug corresponding to 10 mg human dose was used [11]. Nine healthy rabbits, weighing 1.5-2.25kg, were divided into three groups, each group of three animals. In the morning, control blood samples were taken from each rabbit immediately before drug administration. The 1st group received (Motinorm® 5mg/5ml) oral suspension by using stomach tube, the 2nd group received the selected medicated rectal suppository formula (F18), and The third group received marketed rectal suppository, Motinorm® (10 mg). Blood samples of about 1-2 ml were withdrawn via an indwelling catheter in the orbital venous plexus in the eye into a 5 ml screw-capped centrifuge tubes at the following time intervals: predose, 0.25, 0.5, 1, 2, 4, 8, and 12 hrs following drug administration. Samples were centrifuged at 5000 rpm 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 [12]. For extraction, 0.1 ml of plasma sample, 0.1 ml of 0.1 M sodium hydroxide and 3 ml of dichloromethane were mixed [13]. The mixture was shaken for 10 min and centrifuged for 15 min at 1200 x g. Then organic phase was transferred to another glass tube and evaporated till dryness under gentle nitrogen stream. The dried residue was dissolved in 200µl of mobile phase. Then 20 µl aliquot was injected into the HPLC column for analysis. HPLC apparatus with fluorescence detector was used. The column used was C18 reversed phase, the mobile phase consisted of Acetate buffer [10mM,
pH 6.50: Methanol: Acetonitrile (30:40:30) [14], and the flow rate was set at 1 ml/min and the eluent was monitored at 282 nm.

3. Results and discussion

3.1. Characterization of solid dispersions

Characterization of solid dispersion systems was studied by infra-red spectrophotometry (IR), differential scanning calorimetry (DSC) powder X-ray diffractometry (PXRD) and scanning electron microscopy (SEM). The results of IR spectrophotometry indicated the absence of well defined interaction between domperidone and other polymers. Furthermore, the DSC data showed a reduction in the crystallinity of domperidone in the solid dispersion systems, confirmed by broadening and shifting of the melting endotherm of domperidone in solid dispersions and in physical mixtures to temperature range lower than the melting point of drug. Also PXRD and SEM support the transformation of drug from the crystalline to the amorphous state, Fig.1-4, [15].

### Table I: Composition of polyethylene glycol suppository bases.

<table>
<thead>
<tr>
<th>Formula no.</th>
<th>Composition</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>PEG 6000 : PEG 600</td>
<td>50:50</td>
</tr>
<tr>
<td>F2</td>
<td>PEG 1000 : PEG 4000</td>
<td>96:4</td>
</tr>
<tr>
<td>F3</td>
<td>PEG 4000 : PEG 600</td>
<td>50:50</td>
</tr>
<tr>
<td>F4</td>
<td>PEG 1500 : PEG 6000</td>
<td>75:25</td>
</tr>
<tr>
<td>F5</td>
<td>PEG 6000 : PG</td>
<td>50:50</td>
</tr>
<tr>
<td>F6</td>
<td>PEG 6000 : PG</td>
<td>60:40</td>
</tr>
<tr>
<td>F7</td>
<td>PEG 6000 : PG</td>
<td>40:60</td>
</tr>
</tbody>
</table>

### Table II: Composition of gelatin suppository base.

<table>
<thead>
<tr>
<th>Formula no.</th>
<th>Composition</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>F8</td>
<td>Gelatin</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Glycerin</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Propylene glycol</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Water</td>
<td>40</td>
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</tbody>
</table>

### Table III: Composition of fatty suppository bases.

<table>
<thead>
<tr>
<th>Formula no.</th>
<th>Base type</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>F9</td>
<td>Witpesol H15</td>
<td>100</td>
</tr>
<tr>
<td>F10</td>
<td>Cocoa butter</td>
<td>100</td>
</tr>
<tr>
<td>F11</td>
<td>Suppocire AM</td>
<td>100</td>
</tr>
</tbody>
</table>

3.2. In-vitro release studies

The release of domperidone from water soluble PEG suppository bases (F1-F7), gelatin suppository base (F8), and from fatty bases (F9-F11) is illustrated in Fig.5, and 7 respectively. The results indicated that drug release from PEG suppository bases was superior to that from the fatty and gelatin bases. This release pattern was expected due to the higher affinity of the hydrophobic domperidone to the lipophilic bases which leads to decrease amounts of drug available for absorption. These results are in good agreement with Miyake et al. [16].

The in-vitro release of domperidone from polyethylene glycol bases (F1 to F7) is presented in Fig.5, was ranked as follows: F7 > F5 > F6 > F3 > F4 > F1 > F2. It is obvious that increasing the concentrations of the high molecular weight polyethylene glycols and decreasing the concentration of the low molecular weight polyethylene glycols or propylene glycol in the base resulted in raising the melting point and increasing the hardness of the base, consequently retarding the in-vitro release of drug and vice versa [17]. Relatively, suppository base formula (F7) gave the highest drug release as it contained low concentration of PEG 6000 and high concentration (60%) of propylene glycol.

Statistical analysis of the release data was done by ANOVA using (Graph pad prism programme, version 5). It was found that there was a highly significant difference in percent of domperidone released between F7 and that of F1, F2, F3, and F4, (P<0.001). Also, there was a highly significant difference in percent of domperidone released between F7 and that of F6 till the first 45 minutes (P<0.001), then a non significant difference exists between them till the end of 120 minutes (P>0.05). However, there was a non significant difference in percent of domperidone released between F7 and that of F5, (P>0.05). So PEG 6000: PG (40:60%w/w) suppository base was chosen to investigate the effect of different additives on the release rate of the solid dispersion of drug with pluronic F-127 at (1:3) drug to carrier ratio.

Different surface active agents were incorporated into PEG suppository base (F7) with the aim of enhancing the release of the drug by increasing wetting and facilitating better fluid penetration into base as a result of interfacial tension lowering effect. The surfactant effect of increasing the wettability of the active medicament brings closer contact between the external diffusion medium and the medicament itself offering good release characteristics. The effect of surfactants in 4% w/w concentration on the release of domperidone solid dispersion from (F7) suppository base are represented in Figs. 8-10. The rationale for using the surfactants at a general concentration of 4% (w/w) was to ensure that the amounts of the adjuvants incorporated reflect the intermediate range of concentrations that have been shown to be safe following rectal administration to the humans [18-20]. Higher concentrations of nonionic surfactants have been demonstrated to be associated with adverse histological changes in the rectal tissue of rats [21].

Fig.6, reveals that there was a highly significant difference between the release from suppository formulation containing solid dispersion (F12) and that containing drug alone (F7) (P<0.001). Domperidone solid dispersion release from formula (F12) was about 33.188±0.655% in 45 min, while the release of domperidone from formula (F7) containing intact drug was 15.834±1.538% in 15 min. These results are also in agreement with Gamal [22], who found that the release rate of azapropazone from the hydrophilic bases was significantly increased by solid dispersion and solvent deposition techniques compared to untreated drug. Fig.8 shows the role of addition of different grades of Tweens, it was found that the grades of Tweens had little effect on the release rate. There was a non significant difference between Tween 80 and tween 60, or 40. However, there is a moderate to highly significant difference between Cetrimide and that of Brij 35, Myrj 58, and Beta- cyclodextrin till 45 min. then the difference was non significant (P>0.05). Also addition of SLS or Tweens, (P<0.001). However, There is a highly significant difference between Cetrimide and that of Brij 35, Myrj 58, and Beta- cyclodextrin till 45 min. then the difference was non significant (P>0.05). Also addition of Cetrimide on the base containing solid dispersion of the drug (F18) resulted in a highly significant increase in the percent of the drug released than that without Cetrimide (F12) till 45 min. (P<0.001). Then at 60 min the difference was moderately significant (P<0.01) and the difference was non significant at 90, and 120 minutes (P>0.05). Fig.9. The release behavior of suppository after addition of cetrimide additive is accompanied by extended supersaturation; this may explains the decline in the release curve after 30 minutes of the release time [23]. However, the results showed that the release rate decreased upon using SLS, since the tendency to form micelles increases with increasing surfactant concentration, the
decrease in drug release rate at higher surfactant concentration is most likely due to micellar entrapment of the drug, resulting in retardation of the drug release. There was a non significant difference between the suppository formulation containing solid dispersion without the drug, resulting in retardation of the drug release. The difference was not significant after 120 min of the release.  

The mathematical evaluation of the in vitro release of the drug has been done by using zero, first, second order, Higuchi diffusion models, Hixon, Baker, and Korsemayer Peppas models. The highest values of the correlation coefficients were obtained with the Korsemayer Peppas kinetic.

Table IV: Composition of the prepared suppositories containing co-evaporates with Pluronic F-127 (1:3 drug to carrier ratio).  

<table>
<thead>
<tr>
<th>Formula no.</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>F12</td>
<td>PEG 6000: PG (40:60 %w/w) + (domperidone: Pluronic F-127 1:3w/w co-evaporate mix.)</td>
</tr>
<tr>
<td>F13</td>
<td>PEG 6000: PG (40:60 %w/w) + (domperidone: Pluronic F-127 1:3w/w co-evaporate mix.) + 4% polysorbate 80</td>
</tr>
<tr>
<td>F14</td>
<td>PEG 6000: PG (40:60 %w/w) + (domperidone: Pluronic F-127 1:3w/w co-evaporate mix.) + 4% polysorbate 60</td>
</tr>
<tr>
<td>F15</td>
<td>PEG 6000: PG (40:60 %w/w) + (domperidone: Pluronic F-127 1:3w/w co-evaporate mix.) + 4% polysorbate 40.</td>
</tr>
<tr>
<td>F16</td>
<td>PEG 6000: PG (40:60 %w/w) + (domperidone: Pluronic F-127 1:3w/w co-evaporate mix.) + 4% polysorbate 20.</td>
</tr>
<tr>
<td>F17</td>
<td>PEG 6000: PG (40:60 %w/w) + (domperidone: Pluronic F-127 1:3w/w co-evaporate mix.) + 4% sodium lauryl sulphate.</td>
</tr>
<tr>
<td>F18</td>
<td>PEG 6000: PG (40:60 %w/w) + (domperidone: Pluronic F-127 1:3w/w co-evaporate mix.) + 4% cetrimide.</td>
</tr>
<tr>
<td>F19</td>
<td>PEG 6000: PG (40:60 %w/w) + (domperidone: Pluronic F-127 1:3w/w co-evaporate mix.) + 4% β-cyclodextrin.</td>
</tr>
<tr>
<td>F20</td>
<td>PEG 6000: PG (40:60 %w/w) + (domperidone: Pluronic F-127 1:3w/w co-evaporate mix.) + 4% Myrj 58.</td>
</tr>
<tr>
<td>F21</td>
<td>PEG 6000: PG (40:60 %w/w) + (domperidone: Pluronic F-127 1:3w/w co-evaporate mix.) + 4% Brij 35.</td>
</tr>
</tbody>
</table>

Fig. 1. IR spectra of pure materials, solid dispersions, and corresponding physical mixtures. (a) domperidone, (b) Pluronic F-127, (c) physical mixture of domperidone / Pluronic F-127, (d) solid dispersion of domperidone / Pluronic F-127, (e) Myrj 52, (f) physical mixture of domperidone / Myrj 52, (g) solid dispersion of domperidone / Myrj 52, (h) PEG 4000, (i) physical mixture of domperidone / PEG 4000, (j) solid dispersion of domperidone / PEG 4000, (k) PEG 6000, (l) physical mixture of domperidone / PEG 6000, (m) solid dispersion of domperidone / PEG 6000.

Fig. 2. DSC curves of single components and binary systems of domperidone with Pluronic F-127, Myrj 52, PEG 4000 and PEG 6000. (a) domperidone, (b) Pluronic F-127, (c) physical mixture of domperidone / Pluronic F-127, (d) solid dispersion of domperidone / Pluronic F-127, (e) Myrj 52, (f) physical mixture of domperidone / Myrj 52, (g) solid dispersion of domperidone / Myrj 52, (h) PEG 4000, (i) physical mixture of domperidone / PEG 4000, (j) solid dispersion of domperidone / PEG 4000, (k) PEG 6000, (l) physical mixture of domperidone / PEG 6000, (m) solid dispersion of domperidone / PEG 6000.
Fig. 3. Powder X-ray diffraction patterns of domperidone/Pluronic F-127 systems. (a) domperidone alone; (b), PF-127; (c), domperidone/Pluronic F-127 physical mixtures (1:3); (d), domperidone/Pluronic F-127 solid dispersion (1:3).

Fig. 4. Scanning electron micrographic image of domperidone/Pluronic F-127 systems. (a) domperidone alone; (b), PF-127; (c), domperidone/Pluronic F-127 physical mixtures (1:3); (d), domperidone/Pluronic F-127 coevaporates (1:3).

Fig. 5. Release profile of domperidone from water soluble bases (PEG) (F1-F7) (pH 7.4).

Fig. 6. Release profile of domperidone (F7), and its solid dispersion with pluronic F-127 (F12) from the selected PEG 6000: PG 40:60% w/w suppository base (pH 7.4).

Fig. 7. Release profile of domperidone from fatty suppository bases Witepsol H-15 (F9), Cocoa butter (F10), Suppocire AM (F11), compared to Gelatin base (F8).

Fig. 8. Release profile of solid dispersion of domperidone with pluronic F-127 (F12) from the selected PEG 6000: PG 40:60% w/w suppository base with the addition of tween 80 (F13), tween 60 (F14), tween 40 (F15), tween 20 (F16).
pharmacokinetics in plasma was assessed by fitting the plasma concentration-time data to the suitable model using WinNonlin™ standard version 1.5 (Science Consulting, Apex, NC, USA) software. Differences between the means of each pharmacokinetic parameter of the three formulations were analyzed using (Graph pad prism programme, version 5, San Diego, USA).

The plasma drug concentrations of domperidone were represented in Fig. 11. It could be seen that; the rectal formula (F18) of domperidone showed a plasma detectable concentration of \( (1.479 \pm 1.443) \mu g/ml \) after 1/4 hr post treatment and the concentration still detectable for 12 hrs. The plasma drug concentration increased progressively to reach maximum concentration \( C_{max} \) of \( (3.609 \pm 0.858) \mu g/ml \) at \( T_{max} \) of \( (1.492 \pm 0.615) \) hr, then decreasing to \( (0.338 \pm 0.183) \mu g/ml \) at 12 hrs after rectal administration. The marketed rectal suppository (Motinorm®, 10mg) showed a plasma detectable concentration of \( (0.363 \pm 0.254) \mu g/ml \) after 1/4 hr post treatment. The plasma drug concentration increased progressively to reach maximum concentration \( C_{max} \) of \( (1.105 \pm 0.647) \mu g/ml \) at \( T_{max} \) of \( (1.261 \pm 0.162) \) hr, then decreasing to \( (0.0529 \pm 0.024) \mu g/ml \) at 12 hrs after rectal administration. Oral dose of domperidone gave a detectable concentration of \( (0.165 \pm 0.09) \mu g/ml \) after 1/4 hr post treatment. And the maximum plasma concentration \( C_{max} \) was observed to be \( (3.392 \pm 2.228) \mu g/ml \) at \( T_{max} \) of \( (2.907 \pm 0.483) \) hr, then failing to \( (1.001 \pm 0.985) \mu g/ml \) at 12 hrs after oral administration. Statistical analysis of the in-vivo comparative bioavailability study of domperidone from (F18) suppository formulation, and the marketed rectal suppository (Motinorm®, 10 mg) was performed, and it revealed that there was a non significant difference between the \( C_{max} \) and \( AUC \) of domperidone from (F18) suppository formulation, and that of the marketed rectal suppository (\( P > 0.05 \)), a result reflects the higher bioavailability of the drug from (F18) formula. However, the difference in \( T_{max} \) was not significant (\( P > 0.05 \)).

The obtained results showed that there was a non significant difference (\( P > 0.05 \) in \( C_{max}, T_{max} \) and \( AUC \) of (F18) formula and the marketed oral suspension (Motinorm®, 5mg/5ml).

Comparing the results of \( C_{max} \) and \( T_{max} \) between marketed rectal and marketed oral formulae, there was a mild significant difference with (\( P < 0.05 \)), however there was a moderate significant difference in AUC with (\( P < 0.01 \)).

4. Conclusions

Solid dispersion of domperidone with Pluronic F-127 (1:3) drug to carrier ratio exhibited an increase in the percent of the drug released from PEG suppository base compared to that containing drug alone. Addition of cetrimide to suppository base resulted in a highly significant increase in the percent of the drug released from PEG suppository base compared to that containing drug alone. Addition of cetrimide to suppository base resulted in a highly significant increase in the percent of the drug released. A significant increase in bioavailability was attained by using suppositories containing solid dispersion of the drug and cetrimide as additive (F18) reflected by higher \( C_{max} \) and \( AUC \) compared to that of the marketed rectal suppository (Motinorm®, 10mg).

References


