Solubility Enhancement of Domperidone by Solvent Change In situ Micronization Technique

Abstract

Background: Domperidone (DOM), a dopamine receptor antagonist, is used as antiemetic for the treatment of gastroparesis, vomiting, and nausea. The low water solubility of DOM leads to a low dissolution rate and variable bioavailability. The aim of this study was to enhance the solubility of DOM by the preparation of micron-sized particles. Materials and Methods: The in situ micronization process was carried out using solvent change method in the presence of Soluplus® or PEG6000 as stabilizing agents. DOM was dissolved in appropriate solvent (acetone and methanol 1:1 v/v), and the stabilizing agent was dissolved in water (as nonsovent). The nonsolvent was poured rapidly into the drug solution under stirring by a homogenizer, and the resultant was freeze dried. The crystalline shape and particle size of DOM and interaction of DOM with stabilizers were investigated by scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and differential scanning calorimetry (DSC), and then, dissolution test was carried out. Results: Optimum formulation was composed of DOM (0.5%) and PEG6000 (0.1%) with the lowest particle size (3 μm) and the highest DE95% (95.95%) as compared to pure DOM (particle size of 13.4 μm and DE95%, 52.18%). Conclusion: SEM micrographs showed uniform and spherical shape of microcrystals. FTIR, XRD, and DSC studies indicated the micron size of the microcrystals and no interference between the drug and the stabilizer.

Keywords: Differential scanning calorimetry, domperidone, Fourier transform infrared spectroscopy, in situ micronization, microcrystals, scanning electron microscopy, solvent change method, water solubility, dissolution rate, X-ray diffraction

Introduction

The solubility of low water-soluble drugs has always been a challenge to the discovery and design of new drugs.[1] More than 40% of the recent developed drugs are practically insoluble in water, and their poor solubility in water (<0.1 mg/ml) results in their slow and incomplete absorption, low and variable bioavailability, as well as gastrointestinal toxicity.[2-4] In addition, to achieve an effective dose and appropriate treatment response, these drugs should be used at a dose above the usual dose of other drugs.[4] The solubility of a drug depends on several factors including the composition of the dissolution medium, the physical form of the solid as well as the temperature and pressure of the environment, particle size, molecular size, polarity, and polymorphism.[5] Solubility enhancement techniques are divided into physical and chemical modification and other methods. Physical methods include particle size reduction (micronization and nanosuspension), changing in the crystal habit, solid solutions, solid dispersions, and cryogenic methods. Chemical modifications consist of pH adjustment, complexation, use of buffer, derivatization, and salt formation.[6] Choosing the appropriate method depends on the characteristics of the drug, excipients, and the desired pharmaceutical formulation.[7] A common method to reduce the size of large particles is comminution using milling techniques such as ball mill, colloid mill, jet mill, or high pressure homogenizer. However, these techniques are inefficient and have disadvantages including the creation of electrostatic effects and unstable thermodynamic surfaces as well as large particle size distribution. Furthermore, in some cases, the newly created surfaces by this method have weak wetting properties and particles become agglomerated.[8] New in situ micronization methods have been

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developed to reduce the physical and chemical instabilities in milling techniques. In this process the particle size falls below 10 µ. As the micron size particles are formed directly during the process without any reduction in size, this method is named in situ micronization technique.[6] Compared to the milling technique, the particles have a uniform size and the powder is less cohesive. The molecularly dissolved drug is converted into the desired particle size by solvent change or pH change method, and a stabilizer is used to stabilize and cover the particles. Stabilizer is a lyophilic molecule or a polymer which has a strong tendency to be adsorbed on the newly created hydrophobic surfaces of particles and prevent the growth of micron-sized crystals by steric hindrance, in addition to increase their water solubility.[7] In situ micronization technique is used to increase the solubility of some poorly water-soluble drugs including piroxicam,[8] rifabutin,[9] azithromycin,[10] disodium cromoglycate,[11] and zaltoprofen.[12]

Domperidone (DOM) (5-chloro-1-[1-3(2, 3-dihydro-2- oxo-1H-enzimidazole-1-yl)propyl]-4-piperidinyl]-1,3- dihydro-2H-benzimidazole-2-one) is a benzimidazole derivative with a molar mass of 426, a weak base with poor water solubility and high permeability and is classified as Class II of biopharmaceutical classification system. It is an antagonist for dopamine (D2) receptors in the brain and the gastrointestinal system. It has an antinausea effect and is a prokinetic agent. Its plasma protein binding and bioavailability are 91%–93% and 13%–17%, respectively. Its low water solubility is the reason of the low bioavailability.[13,14] To increase the dissolution rate of this drug, some techniques have been used such as melt granulation technique,[15] orodispersible tablet,[16] solid lipid nanoparticles,[17] self-microemulsifying systems,[18] inclusion complex with cyclodextrins,[19] and solid dispersion[44] technique.

The aim of this study is to enhance the water solubility and dissolution rate of DOM by in situ micronization. Micron-sized DOM was prepared by a solvent change process that precipitates and stabilizes the drug in a small particle size by the use of Soluplus® and polyethylene glycol 6000 (PEG_{6000}) as stabilizers.

Materials and Methods

DOM maleate was provided as a gift sample by Farabi Company (Iran). Polyethylene glycol–polyvinyl caprolactam–polyvinyl acetate-grafted copolymer (Soluplus®, MW = ∼118,000 Da) was bought from BASF (Germany). PEG_{6000}, acetone, methanol, HCl (37.5%), Tween 20, and distilled water were purchased from Merck Chemical Company.

In situ micronization technique (solvent change method)

In the first step, the appropriate amount of DOM was dissolved in 30 ml of solvent (acetone and methanol (1:1 v/v)); then, a proper amount of stabilizer was dissolved in 100 ml of water (as antisalvation). Nonsolvent was rapidly poured into the drug solution under homogenizer in the ice bath (4°C). The mixture was homogenized for 15 min, and then, the organic solvent was evaporated using a vacuum oven under stirring, the remaining suspension was frozen and then freeze dried. The lyophilized powder was used for future studies. By changing the three variables, each at two levels, eight different formulations were prepared with full factorial design [Table 1].

The physical mixture of the drug and each of the polymers (PEG_{6000} and Soluplus®) was provided by the simple mixing as negative control in the same ratio as listed in Table 2.

Determination of the particle size for each of the formulations and its physical mixture as well as the pure powder of DOM was done by dynamic light scattering method (Malvern-2101 Shimadzu, Japan). For this purpose, an appropriate amount of each formulation powder was dispersed in carbon tetrachloride, and its particle size was analyzed.

DOM was determined by spectrophotometric method. A standard calibration curve of the drug solution in HCl (0.1 N, pH 1.2) in the range of 2–40 µg/ml was plotted using ultraviolet (UV)-visible spectrophotometer (Shimadzu, Japan) at 283.5 nm as λ_{max} of DOM. In this wavelength, the stabilizers do not have any absorbance and interfere with the drug.

Saturated solubility of DOM was determined by taking an excess amount of drug in water. Each solution was sonicated for 10 min, then shaken mechanically for

| Table 1: Different variables and their levels studied in full factorial design |
|---|
| Different variables | Level I | Level II |
| DOM concentration | 0.5% | 1% |
| Type of stabilizer | PEG_{6000} | Soluplus® |
| Stabilizer concentration | 0.05% | 0.1% |
| DOM: Domperidone |

| Table 2: Different formulations studied for the production of microcrystals of domperidone |
|---|
| Formulations | Drug concentration (%) | Type of stabilizer | Percentage of stabilizer |
| D_P_{0.05} | 1 | PEG_{6000} | 0.1 |
| D_P_{0.1} | 1 | PEG_{6000} | 0.05 |
| D_S_{0.05} | 1 | Soluplus® | 0.1 |
| D_S_{0.1} | 1 | Soluplus® | 0.05 |
| D_P_{0.05} | 0.5 | PEG_{6000} | 0.1 |
| D_P_{0.1} | 0.5 | PEG_{6000} | 0.05 |
| D_S_{0.05} | 0.5 | Soluplus® | 0.1 |
| D_S_{0.1} | 0.5 | Soluplus® | 0.05 |

D: Domperidone, P: PEG_{6000}, S: Soluplus
24 h at room temperature and centrifuged for 10 min at 2000 rpm. The supernatant of each sample was filtered and an appropriate amount of each filtrate was diluted suitably with distilled water and analyzed spectrophotometrically at 283.5 nm.

The dissolution rate of DOM crystals was determined in a USP no. 2 dissolution test apparatus at 37°C and 100 rpm. The dissolution medium was 900 ml of HCl (0.1 N, pH 1.2) with 0.1% Tween 20. Triplicate samples (5 ml) were withdrawn from the dissolution vessels at selected time intervals and analyzed for DOM by UV spectrophotometer at 283.5 nm. Each sample was replaced with fresh dissolution medium, and dissolution efficiency up to 60 min (DE_{60}) was calculated according to equation:

\[ \int_0^{60} \frac{y}{100} dt \times 100 \]

Crystal’s morphology was studied by a scanning electron microscope (LEO 440i, UK). Before the specimens were observed, they were placed on a metal stub and coated with gold under vacuum in an argon atmosphere.

X-ray diffraction (XRD) analysis is a special technique for determining the crystallinity of a substance. XRD patterns of DOM formulations were obtained using the X-ray diffractometer (Seimens, ModelD5000, and Germany).

Crystals were analyzed by Fourier transform infrared spectroscopy (FTIR) spectrophotometer (Bomem, Canada, at 4 cm\(^{-1}\) resolution for scan, at 4000–400 cm\(^{-1}\)). For these tests, appropriate amount of freeze-dried sample was mixed with dry KBr and turned to a compressed disc by the hydraulic press at a pressure of 10 tons force for 30 s.

Differential scanning calorimetry (DSC) is a thermal analysis technique used to investigate the response of polymers to heating. The amount of energy absorbed or distributed during warming and cooling is measured and shown as an endothermic or exothermic peak. The machine (Shimadzu, DSC-60, Japan) consists of two aluminum pans, one contains 3–6 mg test sample and the other is an empty pan as a reference; these were heated at a rate of 10°C/min over temperature range of 30°C–250°C under nitrogen atmosphere.

All data were expressed as the average ± standard deviations of three determinations, and one-way analysis of variance was used for statistical analysis of the results.

**Results**

**Particle size of microcrystals**

The particle size of the pure untreated powder of DOM and the microcrystal formulations are shown in Table 3. The particle size of the physical mixture (M) of the drug with each polymer in each specific ratio is also shown in Table 4. As shown in Table 3, the pure powder of DOM has the largest mean particle size of 13.4 ± 1.02 μm and the smallest particle size related to D0.5P0.1 formulation with the size of 3 ± 0.81 μm.

**Drug content and saturated solubility tests**

The drug content and saturated solubility of the pure untreated powder of DOM and the microcrystal formulations are shown in Table 3. The drug content was high and uniform in all microcrystalline formulations and was in the range of 94.1 ± 0.52%–99.3 ± 0.97%. In all formulations, the drug content was increased with increasing the polymer percent (P < 0.05). Saturation solubility test was carried out in distilled water.

**Dissolution test**

Release profile of DOM and microcrystalline powder formulations in the HCl 0.1 N medium are shown in Figure 1. Based on Figure 1, the drug dissolution rate from the microcrystalline samples was much higher than the untreated drug and the physical mixture of the drug [Figure 2] and the stabilizer. In most formulations, 80%–100% of the drug was released within the first 5–10 min, while the drug was dissolved slowly from the untreated DOM and in 60 min. The DE60% for different microcrystalline formulations and physical mixture of DOM and stabilizers compared to the intact powder of DOM are shown in Tables 3 and 4, respectively; the drug dissolution rate from microcrystals was 1.84 times higher than the untreated drug. The lack of crystallinity, reduction of drug particle size, and increased wettability were considered to be predominant factors in increasing the dissolution rate of DOM from the microcrystals.[20] The D0.5P0.1 formulation had the smallest particle size with the value of 3 ± 0.81 μm and the highest DE60% (95.95 ± 3.6%). The lowest DE60% was related to the pure untreated DOM with the largest particle size of 13.4 ± 1.02 μm.

| Formulations | Particle size (μm) | Drug content (%) | Saturated solubility (µg/ml) | DE_{60} (%) |
|--------------|-------------------|------------------|-----------------------------|------------|
| Pure untreated | 13.4±1.02 | 95.2±0.31 | 1181.9±7.11 | 85.38±2.2 |
| D_{0.1}P_{0.1} | 6.4±0.41 | 94.1±0.52 | 1113.02±5.02 | 72.1±7.4 |
| D_{0.1}P_{0.1} | 6.9±0.52 | 98.4±0.25 | 1344.7±11.01 | 65.14±6.4 |
| D_{0.1}S_{0.1} | 5.8±0.64 | 96.2±1.2 | 1329±12.00 | 78.6±0.9 |
| D_{0.1}S_{0.1} | 3.4±0.81 | 97.1±0.59 | 1133.65±10.21 | 95.95±3.6 |
| D_{0.1}S_{0.1} | 4.1±0.36 | 96.6±0.48 | 1161.3±6.10 | 93.06±2.1 |
| D_{0.1}S_{0.1} | 5.7±0.95 | 99.3±0.97 | 1619.7±15.01 | 78.74±3.9 |
| D_{0.1}S_{0.1} | 6.3±0.62 | 98.4±0.26 | 1494.6±13.00 | 75.45±0.5 |

*a: Domperidone, P: PEG_6000, S: Soluplus, DOM: Domperidone
Scanning electron microscopy

The morphology of the microcrystals was studied by scanning electron microscopy (SEM). Figure 3a and b show the pure DOM and microcrystals of D0.5P0.1 formulation, respectively. The micrographs show that the particles of the pure DOM are cubic with the size of about 13 µm, but the microcrystalline particles are spherical with the size of about 3 µm.

X-ray powder diffraction

XRD spectrum of DOM powder, PEG6000, physical mixture, and D0.5P0.1 formulation are shown in Figure 4. In the XRD pattern of DOM, there are several sharp and distinct peaks at 2θ-scattered angles at 9.28°, 13.94°, 15.58°, 19.8°, and 24.8° that indicate the crystalline nature of the drug. PEG showed the major XRD peaks at 2θ =19.3° and 23.3°. The XRD pattern of the physical mixture was very similar to the pure drug and the carrier; most of the peaks of DOM and PEG are visible in the XRD diffractogram of physical mixture [Figure 4]. Major DOM and PEG peaks are also present in the optimum microcrystalline formulation pattern, with the exception that the peak intensity is decreased.

Fourier transform infrared spectroscopy

The FTIR spectra are shown in Figure 5. There are four main peaks in the spectra of DOM in the regions of 3026, 1701, 1624, and 1487 cm⁻¹ that are related to the C-H, anhydride CO, C-C, and aromatic ring C-C groups, respectively [Figure 5a]. Furthermore, there are two peaks in the FTIR spectra of PEG6000 at 2891 and 1109 cm⁻¹ that are attributed to C-H and etheric CO. The major peaks of DOM and PEG6000 are also seen in the physical mixture and optimum formulation spectra (D0.5P0.1) [Figure 5b and c, respectively] although were slightly shifted.

Differential scanning calorimetry test

Figure 6 shows the DSC thermograms of DOM, PEG6000, physical mixture, and microcrystalline D0.5P0.1 formulation. There is a characteristic sharp endothermic transition Tm of DOM at 233.8°C. PEG with Mn=6000 showed one transition (Tm) in 70.4°C when crystallized at above 55°C, corresponding to the melting point of the folded chain crystals. The physical mixture of DOM and PEG6000 and optimum microcrystal formulation thermogram exhibited the same two endothermic transitions of DOM and PEG6000, with a slight decrease or a low shift.

Discussion

Two water-miscible solvents such as acetone and methanol (1:1 v/v) were selected as DOM solvents for solvent change method. The microcrystal production process creates new surfaces and increases the energy of the system; stabilizers are used to stabilize these systems. These materials are adsorbed on the hydrophobic surfaces of the micronized drug and prevent the growth of drug crystals. Therefore, the more hydrophobic the stabilizer, the higher its surface adsorption and the drug stability. This is due to the greater similarity and interaction between the surfaces of the hydrophilic stabilizer and the drug particles. In this study, we selected PEG6000 and Soluplus® as stabilizer. Soluplus® is an amphiphilic polymer which is used as a stabilizer. Its molecular weight is in the range of 90000–140000 g/mol, and also, it has the ability to dissolve poorly water-soluble drugs in water.

Table 4: Particle size, saturated solubility, and dissolution efficiency (DE₆₀ %) of untreated domperidone and its physical mixture with stabilizers after 60 min of dissolution test

| Physical mixture | Particle size (µm) | Saturated solubility (µg/ml) | DE₆₀ (%) |
|------------------|-------------------|-----------------------------|----------|
| Pure untreated DOM | 13.4±1.0 | 894±11.01 | 52.18±6.7 |
| MD P₀.₁ | 10.5±0.21 | 924.1±0.00 | 67.92±5.1 |
| MD P₀.₀₅ | 11.5±1.35 | 953.1±0.00 | 70.62±0.6 |
| MD S₀.₁ | 9.4±1.62 | 941.0±0.05 | 61.07±9.9 |
| MD S₀.₀₅ | 10.4±0.95 | 960.0±0.04 | 64.8±5.1 |
| MD P₀.₁ S₀.₁ | 9.9±0.52 | 932.7±0.00 | 79.8±2.7 |
| MD P₀.₀₅ S₀.₀₅ | 12.4±0.61 | 925.4±0.01 | 75.39±2.9 |
| MD S₀.₁ S₀.₀₅ | 13.8±0.48 | 970.6±0.01 | 65.06±1.3 |
| MD P₀.₁ S₀.₀₅ | 9.2±1.02 | 980.8±0.06 | 61.98±3.7 |

M: Physical mixture, D: Domperidone, P: PEG₆₀₀₀, S: Soluplus, DOM: Domperidone
The percentage of drug and also the concentration of the stabilizer affected the size of the microcrystals. The lower the percentage of the drug, the smaller the particle size, but conversely, the higher the concentration of the stabilizer, the lesser the particle size of the microcrystals. These results are consistent with the research of Varshosaz et al., where in situ micronization method and HPMC and Brij35 were used as stabilizer to increase the solubility of gliclazide.

Microcrystals had higher solubility than untreated DOM, the solubility in formulations made with Soluplus® was higher than those prepared with PEG6000 possibly due to the branch and porous structure of Soluplus® as compared with the linear structure of the PEG6000, the amount of drug content, and on the other hand, the saturation solubility of the drug was higher with Soluplus® ($P < 0.05$). Saturated solubility for all physical mixture formulations was higher than pure DOM ($P < 0.05$).

The particle size directly affected the dissolution rate of the drug from microcrystal conversely. The smaller the particle size, the faster the drug release rate ($P < 0.05$). Because according to the Fick’s law, the distance that the dissolved drug must pass through the particle in smaller particles is less, so the dissolution rate is higher.

As shown in Table 3, increasing the concentration of the drug in the microcrystals led to a decrease in dissolution rate. Similar results were obtained with solid dispersions of temazepam-PEG 6000 and PVP k30 and solid dispersion of dimenhydrinate-PEG6000, where a direct relationship was found between the polymer percent and the dissolution rate constant. As shown in Table 4, all physical mixture formulations had higher dissolution rate than untreated drug and lower dissolution rate than microcrystalline formulations. The presence of stabilizers because of their lyophilic nature led to a higher wettability, dispersibility, and in conclusion, higher solubility of drug in physical mixture formulations. In addition, during dissolution tests, the physical mixtures were immediately sunk to the bottom of the dissolution vessel as the microcrystals did, whereas the pure drug was floated for a long period on the surface of the dissolution medium.

The optimum formulation between microcrystals prepared by PEG6000 and Soluplus® and by solvent change method with acetone and methanol solvents was D0.5P0.1 with particle size of 3 ± 0.81 μm, saturated solubility of 1133.65 ± 10.21 μg/ml, and DE60% of 95.95 ± 3.6%. This formulation was used for the next solid state characterizations including morphology, X‑ray diffractometry, fingerprint FTIR, and thermal analysis.

XRD is a common technique for the study and characterization of crystalline materials. It is one of the most frequent spectroscopic methods for the physicochemical investigations with the view of detecting the possible interactions and compatibility between the excipients and the active drug substance. Reducing the size of crystals and their micronization decreases the peak intensity, and also, reducing the crystallinity of the particles will make them more stable. Reduction of the particle size also increases the dissolution rate or bioavailability of microcrystals, and thus, the therapeutic action is obtained in shorter times. The amorphous, semicrystalline, and semistable form, as compared to pure crystalline form, is dissolved faster because it has more internal energy and more molecular motion than crystalline state.

Similar findings were reported in preparing the inclusion complex of DOM-hydroxypropyl-β-cyclodextrin and DOM hydrogels. Due to the fact that all of the major drug and polymer peaks in the XRD pattern of microcrystals formulation are seen, moreover, no other peaks than those which could be assigned to pure DOM and PEG 6000 were detected in the microcrystals; it may be concluded that there was no chemical interaction between the drug and the stabilizer during the production of microcrystal. Similar results were obtained by Mandal et al. and Van den Mooter et al. in the preparation of calcium alginate beads containing
difflunisal and solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30, respectively.

FTIR is another spectrophotometric powerful tool for investigation of the chemical interactions between drug and polymer. It identifies different types of chemical bonds (functional groups) in a molecule by producing an infrared absorption spectrum and is like a molecular “fingerprint.” There is not any change in the functional peaks in none of the spectra, thus revealing that there is no significant chemical interaction and incompatibility between drug and stabilizer (PEG6000) at the molecular level. In addition, no new bonds were observed in the drug/polymer mixture spectra; this proves that no new chemical bonds between drug and polymer has been formed. Similar findings were reported by Mohamed et al. in preparing clindamycin-chitosan films. Reduction of the size of the crystals in optimum formulation compared to the physical mixture and pure drug is another reason in decreasing the peak intensity of the drug. Adsorption of PEG as a stabilizer on the surfaces of micronized particles of the drug reduces the free energy and stabilizes the system; as a result, the system enthalpy comes down (for example: 315.3–215 µVs/mg for DOM peak) [Figure 6]. The enthalpy is area under the diagram of the DSC-melting thermogram and an indicator for the crystallinity of system.

**Conclusion**

The simple in situ micronization technique produces microcrystals with uniform size and dissolution rates higher than conventional drugs. This method requires a proper stabilizer. In the present work, Soluplus and PEG6000 were used as stabilizer. The size of the microcrystals obtained in this study was between 3 and 6.9 µm compared to the initial size of pure DOM that was 13.4 µm. Optimum formulation was chosen according to its smaller size and higher dissolution rate. Formulation of D0.5P0.1 composed of DOM (0.5%) and PEG6000 (0.1%) as stabilizer was chosen as optimum microcrystal. SEM morphological study showed the uniform and spherical form with average size of 3 micron for microcrystals. DE60% for the optimum formulation was 95.95%, which was 1.84 times higher than the DE60% of pure drug (52.18%). Saturation solubility was significantly increased...
for optimum formulation than the initial drug (1133.65 µg/ml compared to 894 µg/ml). FTIR, XRD, and DSC tests indicated that there was no chemical interaction between the drug and the stabilizer in the molecular level. The results of this study indicate that the solvent change method can be used to produce DOM microcrystals avoiding a lot of energy input in the system happened by the milling procedure.

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Conflicts of interest
There are no conflicts of interest.

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