Formulation and Evaluation of Domperidone Nanoemulsions for Oral Route

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Abstract

The aim of the present study is to formulate, evaluate and characterize the nanoemulsion of Domperidone a poorly water-soluble anti-emetic drug.

Domperidone powder is white or almost white powder, photostable, practically insoluble in water, slightly soluble in ethanol and in methanol; soluble in dimethylformamide. It is used as an
antiemetic for the short-term treatment of nausea and vomiting of various etiologies.

Solubility studies were conducted to select the oil, surfactant and cosurfactant. Phase diagrams were constructed by aqueous phase titration method. Formulations were selected from the phase diagrams. The formulations were characterized for particle size, Polydispersity index (PDI), zeta potential and in vitro drug release.

All the formulations were in nanoscale and Formula 1 (which contain anise oil as oil phase, mixture of Surfactant Tween 80 and cosurfactant (ethanol) at ratio 1:1 in addition to double distilled water as aqueous phase in ratio 1:6:3 respectively ) was the selected formula depending on particle size, PDI, zeta potential and in vitro drug release.

The Formula 1 has the best ratio because it gives the smallest nanoemulsion globule size (Formula 1 (w/o) emulsions with mean droplet diameters (w/o) emulsions with mean droplet diameters 77nm, 78nm and 81nm..)

The selected formula gives accepted physical and chemical properties.

Keywords :Nanoemulsion, Domperidone.

Introduction

Domperidone have been the most widely prescribed prokinetic agent in the UK. Cardiac risks was observed in patients older than 60 years, adults taking daily oral doses of more than 30mg Domperidone, and those taking QT- prolonging medicines, CYP3A4 inhibitors or diuretics concomitantly. In April 2014 the European CHMP and the UK MHRA published their final recommendations which state that the benefit-risk balance of Domperidone remains positive in the relief of the symptoms of nausea and vomiting (1).

Nanoemulsion are oil-in-water (o/w) or (w/o) emulsions with mean droplet diameters ranging from 50 to 1000 nm. Usually, the average droplet size is between 100 and 500 nm.. Nanoemulsion are made from surfactants approved for human consumption and common food substances that are “Generally Recognized as Safe” (GRAS) by the FDA (2).
Reducing droplet sizes to the nanoscale leads to some very interesting physical properties, such as optical transparency and unusual elastic behavior (3).

Additionally, the lack of flocculation, sedimentation and creaming, combined with a large surface area and free energy, offer obvious advantages over emulsions of larger particle size, for this route of administration. Their very large interfacial area positively influences the drug transport and their delivery, along with targeting them to specific sites (4).

Depending on the composition there are three types of nanoemulsion:

- O/W Nanoemulsion : Wherein oil droplets are dispersed in the continuous aqueous phase
- W/O Nanoemulsions : Wherein water droplets are dispersed in the continuous oil phase
- Bi-continuous Nanoemulsions: Wherein microdomains of oil and water are interdispersed within the system.

In all three types of nanoemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants (5).

Domperidone is an anti-emetic drug. Its chemical formula C22H24CIN5O2 is a white or almost white powder, practically insoluble in water; slightly soluble in ethanol (96 per cent) and in methanol; soluble in dimethylformamide. The systemic bioavailability of Domperidone is only about 15% in fasting subjects given an oral dose (6).

The objective of this study was to prepare nanoemulsion of a poorly water-soluble anti-emetic drug domperidone in order to enhance the solubility, dissolution rate and to studying the effect of different formulation variables in order to obtain the best formula with appropriate physical properties and higher dissolution rate.

Materials and Methods

Materials

The following materials were used: Domperidone Powder (Vasudha Pharma Chem. Co. India), Oleic acid (BDH, UK), Peppermint oil (BAR-SUR-LOUP, France), Anise oil (BDH, UK), Orange oil, Lemon oil, Nut Meg oil (Al-Emad company, Iraq), Sweet almond (WELL’S, Spain), Carawax oil, Tween 80, Tween 40, Tween 20, Propylene glycol (PG) (J.T Baker, China), PEG 400 , Glycerin (Fluka Chemi AG, Switzerland), Methanol, propanol, butanol (Loba Chemie Pvt. Ltd, India), Ethanol 95% (GCC Analytical reagents, UK), Di-sodium hydrogen orthophosphate Na₂HPO₄ (Thomas Baker, India), Potassium dihydrogen Orthophosphate KH₂PO₄ (Sd fine-chem. Limited, Mumbai, India).

Methods

Solubility study

The solubility of Domperidone in different oils, surfactants and co-surfactants was determined. Briefly, an excess amount of Domperidone was added to 5 ml of the vehicle in stoppered vials separately and shaken continuously at 25°C for 72 hrs to get equilibrium. The equilibrated samples were removed and centrifuged at 5000 rpm for 30 min. The supernatant was separated, filtered through a membrane filter (0.45 μm) and after appropriate dilution with methanol; solubility was determined spectrophotometrically by UV Spectrophotometer at λmax 284 nm.

using calibration curve in methanol. The oils preparations which were highly solubilized Domperidone were selected for further study (7).

Preparation of nanoemulsion

Construction of pseudo-ternary phase diagram (8)

Pseudoternary phase diagrams were constructed to examine the formation of oil in water nanoemulsion using four components: oil, surfactant, cosurfactant, and aqueous phase.

The four component system consisted of:

1. One of these oils (Anise oil, Peppermint oil and Oleic acid) as oil phase.
2. One of these surfactants (Tween 80, Tween40, Tween20) as surfactant.
3. Ethanol or propanol was utilized as cosurfactant.
4. Double distilled water as an aqueous phase.

The pseudoternary phase diagrams were constructed by instillation of homogeneous liquid mixtures of oil, surfactant, and cosurfactant, with double distilled water at room temperature. At desired surfactant-cosurfactant mixture (1:1, 1:2, 2:1), oily mixtures of oil, surfactant and cosurfactant were prepared. Double distilled water was added drop by drop under gentle stirring to each liquid mixture at a ratio listed in Table (1).

If turbidity appeared followed by a phase separation, the samples were considered to be biphasic. If clear and transparent mixtures were visualized after stirring, the samples were considered monophasic. The samples were marked as points in the phase diagram. The area covered by these points was considered to be the nanoemulsion region of existence. All the ratios in this study are reported as weight-to-weight ratios (W/W).
Preparation of domperidone nanoemulsion

Nanoemulsion were prepared by aqueous phase titration method. The composition of the nanoemulsion was chosen according to the pseudo ternary phase diagram. 10 mg of Domperidone powder was dissolved in the selected oil, surfactant and cosurfactant mixture was added in the chosen concentration, and water was added drop wise with continuous stirring until clear nanoemulsion was formed. The final concentration of Domperidone in the nanoemulsion was 10mg/10g as shown in table 1 (9-11).

**Table (1): Composition of the domperidone nanoemulsion**

<table>
<thead>
<tr>
<th>Nanoemulsion</th>
<th>Oil</th>
<th>Surfactant</th>
<th>Cosurfactant</th>
<th>S./Cos.</th>
<th>Oil %w/w</th>
<th>Smix. %w/w</th>
<th>DDW %w/w</th>
<th>Drug (DMP) %w/w</th>
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<tbody>
<tr>
<td>F1</td>
<td>A</td>
<td>Tween80</td>
<td>Ethanol</td>
<td>1:1</td>
<td>10</td>
<td>60</td>
<td>30</td>
<td>0.1</td>
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<tr>
<td>F2</td>
<td>P</td>
<td>Tween80</td>
<td>Ethanol</td>
<td>1:1</td>
<td>10</td>
<td>60</td>
<td>30</td>
<td>0.1</td>
</tr>
<tr>
<td>F3</td>
<td>O</td>
<td>Tween80</td>
<td>Ethanol</td>
<td>1:1</td>
<td>10</td>
<td>60</td>
<td>30</td>
<td>0.1</td>
</tr>
<tr>
<td>F4</td>
<td>A</td>
<td>Tween80</td>
<td>Propanol</td>
<td>1:1</td>
<td>10</td>
<td>60</td>
<td>30</td>
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</tr>
<tr>
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<td>P</td>
<td>Tween80</td>
<td>Propanol</td>
<td>1:1</td>
<td>10</td>
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<td>0.1</td>
</tr>
<tr>
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<td>O</td>
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<td>Propanol</td>
<td>1:1</td>
<td>10</td>
<td>60</td>
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<td>Tween40</td>
<td>Ethanol</td>
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<td>10</td>
<td>60</td>
<td>30</td>
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<tr>
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<td>A</td>
<td>Tween20</td>
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<td>10</td>
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<td>A</td>
<td>Tween80</td>
<td>Ethanol</td>
<td>1:2</td>
<td>10</td>
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<td>30</td>
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<td>A</td>
<td>Tween80</td>
<td>Ethanol</td>
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<td>A</td>
<td>Tween80</td>
<td>Ethanol</td>
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<td>10</td>
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<td>40</td>
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<td>Ethanol</td>
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<td>10</td>
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<td>40</td>
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<td>F14</td>
<td>A:P</td>
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<td>30</td>
<td>0.1</td>
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<td>F15</td>
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<td>Tween80</td>
<td>Ethanol</td>
<td>1:1</td>
<td>10</td>
<td>60</td>
<td>30</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Where: A: Anise oil, P: Peppermint oil, O: oleic acid

Evaluation of domperidone nanoemulsion

The optimal formulations were evaluated for the following characteristics.

**Droplet size, Zeta potential and size distribution**

Droplet size Zeta potential and Size Distribution were determined by Zetasizer (1000 HS, Malvern Instruments, U.K). Small amount (0.1 ml) of the formula to be tested was dispersed in 50 ml of water in a volumetric flask, mixed thoroughly with vigorous shaking and light scattering was monitored at 25°C at a 90° angle (12).

Droplet size was determined by photon correlation spectroscopy that analyzed the fluctuations in light scattering due to Brownian motion of the particles. It accurately measures size in the range of 0.3 nm to 10 μm.

Zeta potential measures the surface charge of nanoemulsion. Specialized cuvettes were used to measure zeta potential.

Polydispersity index (PDI) (which determines size range of particles in the system), for the formulations was determined as ratio of standard deviation to the mean droplet size of the formulation. The polydispersity index indicates the quality or homogeneity of the dispersion (13).

**In-vitro drug release studies**

The release of domperidone nanoemulsion carry out by using Dialysis Tube MW (8000 -14000) domperidone nanoemulsion containing 10 mg of drug was placed into dialysis bag. USP24 rotating paddle apparatus was used to measure the In vitro drug release of all formulas. The dissolution medium, 900 ml 0.1 N HCl was placed into the release jar maintaining the speed of 100 rpm and temperature at 37±0.5°C. Release studies were carried out for 2 hours. 5 ml of aliquot is withdrawn at an interval of 5,10,20,30,45,60,90,120 min. After collecting the sample, the dissolution medium was replenished with the same volume of fresh medium, and the sample was filtered. The samples were analyzed at 284nm by UV-visible Spectrophotometer (14).
Depending on the release profile, the best formula will be selected and comparison of the selected formula of the prepared domperidone nanoemulsion with Marketed Domperidone suspension (Motillium suspension) will done for the Drug Release Profile.

**Morphology by atomic force microscopy (AFM)** (15, 16)

AFM is capable of scanning the surfaces in controlled environmental conditions and is complementary to SEM imaging and also can measure the particle size of the nanoemulsion accurately. The size and surface morphology of Domperidone nanoemulsion in F1 (the selected formula), F2 and F3 were confirmed by atomic force microscopy. Particle size, 3D-dimension graph and histogram of particle size distribution were obtained.

**Measured of pH of the formula**

The apparent pH of the formulation is measured by putting the probe of pH meter inside the prepared nanoemulsion and read the result of the instrument (12, 17).

**Dilutability test**

O/w Nanoemulsion are dilutable with water whereas w/o are not and undergo phase inversion into o/w nanoemulsion. The dilution done by dding different volumes of double distilled water to the prepared nanoemulsions (15).

**Phase separation**

Nanoemulsion system were subjected to centrifugation at 3500 rpm for a period of 30 minute and examined for any separating into two phases (8).

**Entrapment efficiency**

The amount of domperidone in the emulsions was assayed by UV Spectroscopic method. Drug content was expressed as a percentage of domperidone entrapped in the system to the theoretical quantity of the drug added. For estimation, 1.0 ml of nanoemulsion was diluted in methanol and the resulting solution was analyzed at 284 nm in UV-Visible Spectrophotometer (18).

**Phase analysis (conductance measurement)**

O/w Nanoemulsion where the external phase is water, are highly conducting whereas w/o are not, since water is the internal or dispersal phase. To determine the nature of the continuous phase and to detect phase inversion phenomena, the electrical conductivity measurements are highly useful. Dielectric measurements are a powerful means of probing both structural and dynamic features of nanoemulsion systems (15, 19).

Measuring the electrical conductivity using a conductometer (Cond7110, WTW, Germany) by putting the conductometer probe current in the selected formula (20).

**Transparency measurement by refractive index**

Refractive Index (RI) of Nanoemulsion was determined using an Abbes type refractometer at 25± 0.5°C. RI of nanoemulsion prove the transparency of the systems (12).

**Percentage transmittance** (21, 22)

Percentage transmittance (%T) of nanoemulsion prove the transparency of the systems.

For measurement of percentage transmittance (%T), NEs were diluted 10 times with distilled water and %T was checked against distilled water using UV–Visible spectrophotometer.

The percent transmittance of the all formulations was measured at 646 nm.

**Optical transparency**

Optical transparency of the formulas was determined by inspecting the sample in clear and transparent container under the presence of good light against reflection into the eyes, and viewed against black and white illuminated background (21, 24).

**Viscosity measurement**

Viscosity of nanoemulsion was measured by using a Brookfield viscometer equipped with the spindle no.64. The measurement was performed at ambient temperature of the selected formula (23).

**Factors affecting the prepared formulas**

**Effect of types of oil**

Formulas F1, F2 and F3 in table (1) were utilized to study the effect of oil type (Anise oil, Peppermint oil and Oleic acid) in concentrations (10%w/w) for all oils on the drug release profile of the prepared Domperidone nanoemulsion.

**Effect of type of surfactant**

Formulas F1, F7 and F8 in table (1) were used to study the effect of different Grades of selected surfactants in the same concentration (30%w/w) on the drug release profile of the prepared Domperidone nanoemulsion.

**Effect of type of co-surfactant**

Formulas (F1 and F4) in table (1) were utilized to investigate the effect of different cosurfactant type (ethanol and propanol) in the same concentration (30%w/w) on the drug release profile of the prepared Domperidone nanoemulsion.
Drug and excipient compatibility study by FTIR

These studies were achieved to detect any sign of complexation and interaction between domperidone and excipients used in the preparation of domperidone nanoemulsion.

The Domperidone pure drug and Domperidone Nanoemulsion were analyzed by Fourier transform infrared system (FTIR -8300 Shimadzu, Japan). The spectrum was obtained between the wave number 4000-400 cm\(^{-1}\) (25).

Results and discussion

Solubility of domperidone in different oils, surfactants and co-surfactants for nanoemulsion

Solubility of Domperidone in different oils, surfactants and co-surfactants was illustrated in figure1. Oleic acid found to has higher solubilizing activity toward domperidone and found to be 65mg/ml followed by peppermint oil 33.75 mg/ml and then anise oil 12.86 mg/ml then the other oils as following:

Construction of phase diagrams

Pseudoternary phase diagrams were constructed to examine the formation of oil in water nanoemulsion using four components: oil, surfactant, cosurfactant, and aqueous phase.

The phase diagram was constructed by using ProSim Ternary Diagram software. The nanoemulsion region results listed in Figures: (2-11).

Figure (1): Solubility of the domperidone in different oils, surfactants and co-surfactants

Figure (2): Phase diagram for anise oil, tween 80 and ethanol mix. (1:1) and double distilled water.

Figure (3): Phase diagram for anise oil, tween 80 and ethanol mix. (1:2) and double distilled water.

Figure (4): Phase diagram for anise oil, Tween 80 and propanol mix. (2:1) and double distilled water.

Figure (5): Phase diagram for anise oil, tween 80 and propanol mix. (1:1) and double distilled water.
Formulation of domperidone nanoemulsion

Depending on the nanoemulsion regions results in the Pseudoternary phase diagrams, fifteen different formulations of Domperidone nanoemulsion were prepared (table 1) and will evaluate them to get the optimized formula with the best properties. F1 is the selected formula because it gives the smaller globule size, small accepted PdI and higher zeta potential (table 2).

Evaluation of domperidone nanoemulsion: droplet size

The nanometric size range of the particle was retained even after 100 times dilution with water which proves the compatibility of the system with excess water. Droplet size of selected formula F1 was 20.81nm. It checked after three months of storage at three different temp. 4°C, 25°C and 40°C the results was 34.26, 44.59 and 50.08nm respectively. (figure 12, 14, 16, 18).

Zeta potential

Zeta potential is used to identify the surface charge properties and further the long term physical stability of nanoemulsion. Its values were determined from the electrophoretic mobility of the oil droplets.
In prepared nanoemulsion formulas, the charge on an oil droplet is negative due to presence of free fatty acids. Zeta potential of selected formula F1 was -33.9mv indicate the stability of it. It checked after three months of storage at three different temp. 4°C, 25°C and 40°C the results was -31.1, -30.3 and -29.9mv respectively. (Figure 13, 15, 17, 19).

**Size distribution**\(^{12, 13}\)

The selected formula F1 has accepted size distribution because it has low poly dispersible index which indicate the high quality and homogeneity (PDI 0.266). It checked after three months of storage at three different temp. 4°C, 25°C and 40°C the results was 0.280, 0.225 and 0.176 nm respectively.
In-vitro drug release studies

The release of the prepared formulas at pH 1.2 is faster than that in pH 6.8 due to higher solubility of domperidone at acidic media because it is weak base (pKa 7.9) (28).

Effect of type of oil

Formulas F1, F2 and F3 in table (1) were utilized to study the effect of oil type (Anise oil, Peppermint oil and Oleic acid) in concentrations (10%w/w) for all oils on the drug release profile of the prepared Domperidone nanoemulsion.

Figure (16): Droplet size for F1 after three months at 25°C.

Figure (17): Zeta potential for F1 after three months at 25°C.

Figure (18): Droplet size for F1 after three months at 40°C.

Figure (19): Zeta potential for F1 after three months at 40°C.

Figure (20): Dissolution of (F1-F3) at pH 1.2 and temp. 37°C.

The release of domperidone nanoemulsion from F1 which contain anise oil as dispersed phase is rapid and faster than F2 which contain peppermint oil and F2 faster than F3 which contain oleic acid as shown in figure (20) this may be due to different in globule size. The anise oil considered the best oil because it gives the smallest nanoemulsion globule size (Particle size Average 20.81nm) and the best homogeneity (lowest PDI 0.266) and highest stability (higher zeta potential -33.9) as shown in figure (12, 13).

Smaller droplet size increases the total surface area for transfer, release, and absorption of the drug and improve the bioavailability (29).

Effect of type of surfactant

Formulas F1, F7 and F8 in table (1) were used to study the effect of different grades of selected surfactants in the same concentration (30%w/w) on the drug release profile of the prepared domperidone nanoemulsion.
The release of domperidone nanoemulsion from F1 which contain Tween 80 as surfactant was rapid and faster than F7 which contain Tween 40 and F7 faster than F8 which contain Tween 20 with fixing the other component of nanoemulsion as shown in figure (21) this may be due to different in globule size. The Tween 80 considered the best surfactant because it gives the smallest nanoemulsion globule size (Particle size Average 20.81nm) and the best homogeneity (lowest PDI 0.266) and highest stability (higher zeta potential -33.9) as shown in figure (12, 13). Smaller droplet size increases the total surface area for transfer, release, and absorption of the drug and improve the bioavailability (29).

In addition, Tween 80 has higher drug solubility (7.55mg/ml) than tween 40 (7.018mg/ml) and Tween 20 the smallest solubility (6.29 mg/ml) (figure 1).

**Effect of type of co-surfactant**

Formulas (F1 and F4) in table (1) were utilized to investigate the effect of different cosurfactant type (ethanol and propanol) in the same concentration (30%w/w) on the drug release profile of the prepared domperidone nanoemulsion.

The release of domperidone nanoemulsion from F1 which contain ethanol as cosurfactant is rapid and faster than F4 which contain propanol as cosurfactant with fixing the other component of nanoemulsion (Figure 22). This may be due to difference in globule size. The ethanol considered the best cosurfactant because it gives the smallest nanoemulsion globule size (Particle size Average 20.81nm) and the best homogeneity (lowest PDI 0.266) and highest stability (higher zeta potential -33.9) in the selected formula (F1) as shown in figure (12, 13).

**Comparison of the selected formula of the prepared domperidone nanoemulsion with Marketed domperidone suspension (Motillium suspension produced by Sanofi drug company) for the drug dissolution profile at pH 1.2 and temp. 37°C**

F1 is considered as the selected formula depending on its dissolution profile (give faster release) and its best results in evaluation of droplet size, zeta potential, PDI and morphology.

There is significant differences between the F1 and marketed suspension where P value equal to 0.000151 (P<0.05).
Figure (23): Dissolution profile of F1 and marketed suspension at pH 1.2 and temp. 37°C.

Morphology by atomic force microscopy (AFM)

The atomic force microscope (AFM) is one kind of scanning probe microscopes (SPM) which is an approach to measure the properties of particles surfaces. AFM is capable of scanning the surfaces in controlled environmental conditions and is complementary to SEM imaging with the high precision of the AFM, in principle it is possible to determine the dimensions of Nano globules with high accuracy. AFM allows the visualization of samples with resolution in three dimensions x-, y- and z-directions in atmospheric or submerged conditions. (30), (31)

Results show spherical shaped nanoemulsion globules and a size within the Nano size as it approved by the histogram of particle size distribution (figure 24- 25).

Figure (24): Average size range of globule nanoemulsion of F1

Figure (25): Atomic force microscopy images of F1 nanoemulsion (contain anise oil).

Measured of pH of the formula

The pH of the selected nanoemulsion formula (F1) was 6.51 and still stable during three months after periodic checking every two weeks.

Dilutability test

All prepared nanoemulsion (the fifteen formulas) are dilutable with water. That indicate that all of them are o/w nanoemulsion. And still stable during three months after periodic checking every two weeks (15).

Phase separation

All prepared nanoemulsion were subjected to centrifugation at 3500 rpm for a period of 30 minute and examined for any change in phase separation. The result indicate there is no phase separation for all prepared nanoemulsion and still stable during three months after periodic checking every tow week.
Drug content

The drug content of selected nanoemulsion formula (F1) were high (99.98±0.54). This high drug content could be due to incorporating the drug in the lipid phase.

Phase analysis (conductance measurement)

Measuring the electrical conductivity using a conductometer for the selected formula (F1). The result was high conductivity (59.2mcs/cm) prof the formula was o/w because of high conductivity of water and still stable during three months after periodic checking every tow week.

Refractive index (RI)

Refractive Index of Nanoemulsion was determined using a refractometer at 25±0.5°C. RI of F1 (selected nanoemulsion) was 1.38 which prove the transparency of the systems. And still stable during three months after periodic checking every tow week.

Percentage transmittance (%T)

Percentage transmittance of nanoemulsion prove the transparency of the systems. The percentage transmittance of the optimized formulation F1 was found to be 94.23±1.5. The results of percent transmittance indicate that the prepared F1 was nearly transparent. And still stable during three months after periodic checking every tow week.

Optical transparency

The selected Formula F1 was transparent. And still stable during three months after periodic checking every tow week.

Viscosity measurement

The viscosity of selected nanoemulsion formula (F1). The measurement was performed at ambient temperature the result indicate it has a very low viscosity (30 cP). The viscosity of nanoemulsion is a function of the surfactant, water and oil components and their concentrations. Increasing the water content lowers the viscosity, while decreasing the amount of surfactant and cosurfactant increases interfacial tension between water and oil resulting in increased viscosity.

Drug and excipient compatibility study

The FTIR absorption spectrum of Domperidone and its nanoemulsion is shown in figure (26, 27).

Domperidone showed a strong characteristic absorbance band at 1712 cm⁻¹ due to C=O stretching vibrations of amide functional group CONHR. N-H stretching characteristic band of secondary amine appears at 3321 cm⁻¹ as a single weak band and N-H bending characteristic band at 1693 cm⁻¹, symmetric and asymmetric C-H stretching bands appeared at 2820 and 2937 cm⁻¹ respectively as well as aromatic symmetric and asymmetric C-H stretching bands appeared at 3024 and 3098 cm⁻¹ respectively, and the aromatic C=C stretching band appeared at 1624 cm⁻¹. The band associated with C=N stretching of secondary and tertiary amine at 1319 and 1359 cm⁻¹ respectively. C-Cl characteristic absorption band with strong stretching intensities appeared at 756 cm⁻¹.

Figure (26): FTIR spectrum of domperidone
Conclusion

Based on the data obtained from the present study, one can conclude the following:

1. Aqueous phase titration method is an efficient method to prepare drug nanoemulsions and it is easy to operate.
2. Domperidone nanoemulsions were successfully prepared using different types of Oils and Surfactants-Cosurfactant mixtures in different ratio using Pseudoternary phase diagram.
3. In the selection of oil, not always the higher drug solubilizes oil is the best oil.
4. The selected formula F1, containing Anise oil as oil phase, Tween 80 as surfactant, ethanol as cosurfactant and double distilled water as aqueous phase at ratio 1:3:3:3 respectively showed faster dissolution rate than other formulas and marketed suspension.
5. Selected formula F1 has the best ratio because it gives the smallest nanoemulsion globule size (Particle size Average 20.81nm) and the best homogeneity (lowest PDI 0.266) and highest stability (higher zeta potential -33.9) and produced higher dissolution rate in comparison with the marketed suspension (Motilium).  
6. Surface morphology of drug nanoparticles, visualized by AFM, illustrated uniform particle size distribution and there is no particles agglomeration, and accurate particle size was obtained by AFM.
7. Drug–excipients compatibility studies revealed that there is no chemical interaction between Domperidone and other components in the preparation of nanoemulsion.

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