PREPARATION AND EVALUATION OF LAFUTIDINE NANOEMULSION AS ORAL DELIVERY SYSTEM

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Abstract

Objective: Lafutidine is a histamine (H2) receptor antagonist utilized for the treatment of gastric ulcer. Its oral bioavailability is low due to poor water solubility and an extensive first-pass hepatic. So, the present work aims to formulate and characterize of an oil in water (o/w) nanoemulsion of lafutidine as oral liquid dosage form and this could enhance drug solubility and improve its bioavailability.

Methods: The pseudo-ternary phase diagrams were constructed via titration method. The diagram plots derived from oil, various ratios of surfactant and co-surfactant (S mix), and double distilled water. The selected optimized lafutidine nanoemulsions formula was determined via a variety of investigative studies like particle size, polydispersity index (PDI), zeta potential, pH, drug content, and an in vitro drug release.

Results: Characterization studies revealed that the optimum formula of nanoemulsions was (NE5), which consist of 0.2% of lafutidine, 30% of surfactant and co-surfactant (S mix) (3:1), which mean (22.5%) of tween 20-7.5% of polyethylene glycol 200 (PEG 200), 10% of peppermint oil and 59.4% of double distilled water. The optimized formula exhibited droplets size (62.56 ± 96.2 nm), PDI (0.11), good pH value (7.1), zeta potential (-32.2 mV), high drug content (99.2%), in vitro release of lafutidine was significantly higher (P<0.05) for NE5. Scanning probe microscopy (SPM) revealed that the droplets size of NE5 was in nano-scale.

Conclusion: It is possible to conclude that the optimized formula (NES) was promised formula of nanoemulsion for increasing the orally delivered lafutidine bioavailability.

Keywords: Nano emulsion, Solubility, Pseudo-ternary phase diagram, Lafutidine

Introduction

The bioavailability of oral dosage forms regarded as an important and critical parameter in order to achieve the required therapeutic action of a drug. The oral bioavailability affected by many factors such as water-solubility of a drug, dissolution rate, permeability of drug and first pass metabolism. The most important factors that determine the oral bioavailability of drugs are solubility and permeability [1]. According to the Biopharmaceutical Classification System (BCS), the drugs can be classified into four classes depending on their water solubility and membrane permeability, class II includes the drugs that have low water solubility and high membrane permeability. Several techniques were used for improving the solubility of poorly–water soluble drugs such as salt formation, co–solvent, self–emulsification, particle size reduction and nanotechnology approach [2]. Lafutidine is a histamine (H2) blocker that used for the treatment of gastric ulcer through inhibition of gastric secretion. Lafutidine is one member of class II drugs (low solubility–high permeability) corresponding to BCS. It has a poor solubility in intestinal aqueous medium and excessive hepatic metabolism [3]. Nanoemulsion regarded as a more advanced drug delivery system and defined as transparent colloidal dispersions of oil and water that stabilized by presence of surface active agent (surfactant) and co-surfactant. Its characterized by clarity and thermodynamic stability with particle size range 5-200 nm. There are about three kinds of nanoemulsions which are oil in water (o/w) nanoemulsion in which the continuous or external phase is oil, water in oil (w/o) nanoemulsion in which the external phase is oil and the last type was the bi-continuous nanoemulsions where oil and water are inter dispersed as micro domains inside the system, all these kinds were stabilized by presence sufficient amount of surfactant and co-surfactant [4]. Nanoemulsion has advantages over other drug delivery system which are increasing the rate of absorption, solubilizing of lipophilic drug, enhancing the drugs bioavailability. Nanoemulsion can be used to deliver the product via various routes of administration like topical, oral and intravenous and improve patient compliance because of its liquid dosage form. S. Khani et al. 2016 developed oral nanoemulsion of mebudipine in order to increase the oral bioavailability of mebudipine, they found that the relative bioavailability of mebudipine nanoemulsion was improved by about 2.6, 1.9 and 2.0, respectively compared with suspension, micellar solution and ethyl oleate solution [5]. So, this study was aimed to formulate and characterize oral (o/w) nanoemulsion of lafutidine as an attempt to increase drug solubility thereby enhancing its oral bioavailability.

Materials and Methods

Materials

Lafutidine (as a pure powder) was purchased from China by Hyperchem company. Oleic acid, tween 20 and tween 60 were purchased from Thomas baker (chemicals) Pvt Ltd, India. Castor oil, peppermint and garlic oils were obtained from Al-Amee company for plants oil. Baghdad, Iraq. The Soybean oil was obtained from Genuine chemicals, India. Propylene glycol and Poly ethylene glycol 200 were supplied by M/s provider pharma, India. Methanol purchased by Avantor performance materials, Norway.

Methods

Determination of melting point

A small amount of powdered lafutidine was introduced into a capillary glass tube that was sealed from one side in order to determine the drug melting point. A compact column of lafutidine powder was prepared, then the tube fitted into digital melting point instrument and watched until complete melting of the powder occurs and the temperature of melting was recorded.

Screening of components by solubility study

Solubility study is considered as an important factor for determining the components utilized in formulation of stable nanoemulsion. The solubility of lafutidine was studied in different oils (peppermint oil, castor oil, oleic acid, garlic oil and soya bean oil). Also the solubility was estimated in a variety of surfactants (tween 60 and tween 20)
and co-surfactants (PEG200 and propylene glycol). The study was performed by placing an excess amount of drug in 5 ml of plain tubes that contains different oils, surfactants and co-surfactants. Then the tubes were fixed into an isothermal shaker water bath for about 72 h with a temperature maintain at 25±0.5 °C along the duration of study. Then the samples were centrifuged at 3000 rpm for 15 min and the separated supernatant layer for samples filtered by using filtration membrane of size 0.45 μm. After filtration, all samples of each component that utilized in the study were diluted by using methanol and the extent of lafutidine solubility was determined at maximum λ max of lafutidine by using UV-visible spectrophotometer [6].

**Pseudo-ternary phase diagrams construction**

Pseudo-ternary phase diagram was made up of oil, S mix (mixture of surfactant and co-surfactant) and water. Ternary phase diagram was made by using low energy method of emulsification which is aqueous titration method. Surfactant and co-surfactant were mixed in different weight ratios (1:1, 2:1, 3:1 and 4:1). Twelve different combinations of oil and S mix were made and titrated slowly with aqueous phase (deionized water) and the titration was continued until the transparent, clear and oil in water (o/w) nanoemulsion was obtained, the pseudo-ternary phase diagram was plotted by using Pro Sim ternary phase diagram software. There is no need for using heat during formulation. The formulated nanoemulsions that obtained from pseudo-ternary phase diagram doesn’t contain drug (lafutidine). Such nanoemulsions were prone to thermodynamic stability tests which are centrifugation test, freezing–thawing test and heating-cooling test in the direction to obtain more stable formulations that employed in preparation of lafutidine nanoemulsions [7].

**Preparation of lafutidine nanoemulsion**

The quantity of drug was dissolved in specialized oil. Then the amount of S mix was added for oil entrapped or loaded drug. Then the entire mixture was mixed by using vortex mixer. The aqueous phase (deionized water) titrated drop by drop until a transparent clear (o/w) nanoemulsion was obtained. These nanoemulsions must be stored in tightly closed glass containers at 25 °C for characterization study.

**Characterizations of nanoemulsions**

**Droplet size measurement**

The samples of nanoemulsions were placed in the sonicator for 30 min at 35 °C. By utilizing the particle size analyzer ABT-9000 nano laser, the measurement of droplet size and distribution plot of droplets were recorded.

**Measurement of polydispersity index (PDI)**

Polydispersity index provides an indication regarding the droplet distribution uniformity within the entire prepared nanoemulsion. The higher the value of (PDI) indicates the lowest of droplet distribution uniformity within the formulation. The measurement was made by utilizing the ABT-9000 nanolaser instrument for particle size analyzer [8].

**Percent of light transmittance (%T) measurement**

By using UV, visible spectrophotometer at 650 nm, the measurement of (%T) for nanoemulsions of lafutidine was made by using deionized water as blank [9].

**Zeta potential measurement**

Zeta potential regarded as good indicator for the colloidal dispersions stability, so, it gives an indication about the charge described on the surface of droplet. Zeta size instrument (nano brook zeta plus) was used for assaying the zeta potential of lafutidine nanoemulsion [10].

**Electrical conductivity measurement**

Electrical conductivity responsible for determining the type of produced nanoemulsion. When the external phase is water which has an electrical conductivity, the produced nanoemulsion was oil in water (o/w). While in (w/o) nanoemulsion, the external phase is oil which don’t poses an electrical conductivity. The conductivity meter was utilized for measurement of conductivity [11].

**Drug content estimation**

A given quantity of lafutidine nanoemulsion was obtained and diluted by methanol. After that the UV-visible spectrophotometer was used for measurement of absorbance at maximum λ max of drug. The drug content was estimated by using the following equation:

\[
\text{Drug content} = \frac{\text{Measured content}}{\text{Theoretical content}} \times 100 \quad \text{Eq. 1}
\]

**Measurement of viscosity**

The NDI digital viscometer (spindle no. 1) was used for measurement the viscosity of lafutidine nanoemulsions at 25 °C. The measurement was done without dilution for the sample of formulations [12].

**In vitro release study**

Lafutidine nanoemulsion and pure lafutidine powder were subjected to release study (in vitro study) which made utilized the dissolution apparatus USP-II (Copley dissolution tester DIS 8000, UK) and by using the dialysis bag technique. Equal quantity of lafutidine both as pure drug powder solution and in drug nanoemulsion was used (10 mg). This quantity was placed within the dialysis bag and then involved within dissolution medium. For the first two hours the 900 ml of HCl buffer pH (1.2)+0.5% tween 20 was used as dissolution medium. Then after replaced by 900 ml of phosphate buffer pH (6.8)+0.5% tween 20 and continue for only one hour [13]. The dissolution apparatus was adjusted at 37±0.5 °C and revolution rate of 50 rpm for entire of 3 hours. Regular sampling of dissolution mediums was continued during the duration of study which include a 5 ml samples were withdrawn at every 15 min time interval and each withdrawn samples were replenished by 5 ml of fresh corresponding medium in order to maintain the sink condition state. All samples that have been withdrawn should be filtered utilizing the filter membrane of size 0.45 μm. The UV-visible spectrophotometer was used for samples analysis for lafutidine content at 286 nm.

**Kinetic and mechanism of lafutidine release**

The dissolution data were fitted in various kinetics models that are including zero order, first order, korsmeyer and peppa’s model, and higuchi model. The preferred mode for selecting the kinetic of release was regression coefficient (R²). The higher value of (R²) indicates the kinetic of drug release. To determine the mechanism of drug release, the dissolution data were fitted for korsmeyer and peppa’s model in which the value of diffusion exponent (n) will determine the best mechanism that is fitting with the release of formulations [14].

**Scanning Probe Microscopy (SPM) study**

The study by SPM (triple probe microscope) was made in order to indicate the morphology and distribution of droplets within the prepared emulsion system. On a glass slide, one drop of lafutidine nanoemulsion was placed and then detect [15].

**Statistical analysis**

Each evaluation or measurement should be repeated three times and the results should be represented as average of triplicate readings for each measurement. Analysis of Variance Test (ANOVA) was utilized to consider the results of study as significant results (P<0.05) or not significant (P>0.05).

**RESULTS AND DISCUSSION**

**Analysis of melting point**

The measured melting point range of lafutidine was found to be 98-101 °C. The result was the same as described by official literature and this result reflects the purity of the powder used in the study.

**Screening of components by solubility study**

The main components that used in preparation of nanoemulsion are including (oil, surfactant and co-surfactant) were selected on the basis of solubility study. The selection of suitable components aids in production of stable nanoemulsion. The results of solubility study for lafutidine in different oils were showed in the descending rank.
peppermint oil>oleic acid>soybean oil>castor oil>garlic oil while, the lafutidine solubility study in different surfactants resulted in to be more soluble in tween 20 than in tween 60 and that in co-surfactants showed that lafutidine more highly soluble in PEG200 than in propylene glycol. Such results are showed in the table 1. So, the selected components in the preparation of nanoemulsion were based on their higher solubility for lafutidine are peppermint oil as oil phase, tween 20 as surfactant and PEG200 as co-surfactant [16].

Table 1: Solubility of lafutidine in oils, surfactants, and co-surfactants

<table>
<thead>
<tr>
<th>No.</th>
<th>Components</th>
<th>Solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peppermint oil</td>
<td>63.2±11.3</td>
</tr>
<tr>
<td>2</td>
<td>Oleic acid</td>
<td>36.79±4.20</td>
</tr>
<tr>
<td>3</td>
<td>Soya bean oil</td>
<td>28.42±2.11</td>
</tr>
<tr>
<td>4</td>
<td>Castor oil</td>
<td>16.13±2.70</td>
</tr>
<tr>
<td>5</td>
<td>Garlic oil</td>
<td>9.4±1.13</td>
</tr>
<tr>
<td>6</td>
<td>Tween 20</td>
<td>71.63±10.32</td>
</tr>
<tr>
<td>7</td>
<td>Tween 60</td>
<td>42.14±3.66</td>
</tr>
<tr>
<td>8</td>
<td>PEG200</td>
<td>53.72±6.43</td>
</tr>
<tr>
<td>9</td>
<td>Propylene glycol</td>
<td>22.13±2.81</td>
</tr>
</tbody>
</table>

Where the results of solubility as mean±SD, n=3.

Pseudo-ternary phase diagrams construction

The components that were included in plotting of the pseudo-ternary phase diagram are oil, double distilled water and S mix. S mix utilized in different weight ratio including 1:1, 2:1, 3:1 and 4:1 that explained in fig. 1. The colored region in the plot represents the region of nanoemulsion and the larger colored region indicates a good nanoemulsifying activity.

Fig. 1: Pseudo-ternary diagrams; A with S mix (1:1), B with S mix (2:1), C with S mix (3:1) and D with S mix (4:1), the thermodynamic stability studies for constriction the diagram for pseudo-ternary phase were assayed in the table 2

Table 2: Studies of thermodynamic stability for pseudo-ternary phase

<table>
<thead>
<tr>
<th>S mix ratio</th>
<th>Formula NO.</th>
<th>%W/W component for nanoemulsions</th>
<th>Thermodynamic stability studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>F-1</td>
<td>40(20:20)</td>
<td>Centrifuge: Pass</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F-2</td>
<td>45(22.5:22.5)</td>
<td>Freeze-thawing: Pass</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F-3</td>
<td>55(27.5:27.5)</td>
<td>Heating–cooling: Pass</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F-4</td>
<td>55(27.5:27.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:1</td>
<td>F-5</td>
<td>35(23.33:11.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F-6</td>
<td>45(30:15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F-7</td>
<td>55(36.66:18.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F-8</td>
<td>60(40:20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:1</td>
<td>F-9</td>
<td>30(22.5:7.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F-10</td>
<td>40(30:10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F-11</td>
<td>50(37.5:12.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F-12</td>
<td>55(41.25:13.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:1</td>
<td>F-13</td>
<td>30(24:6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F-14</td>
<td>40(32:8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F-15</td>
<td>45(36:9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F-16</td>
<td>50(40:10)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
According to the results of thermodynamic stability studies in table 2 and taking in consideration low percentage of S mix and high percentage of water for different S mix of formulations, eight formulas were selected for preparation of lafutidine nanoemulsions which are F-1(NE1), F-2(NE2), F-5(NE3), F-6(NE4), F-9(NE5), F-10 (NE6), F-13(NE7), F-14(NE8).

Preparation of lafutidine nanoemulsions

Preparation of drug loaded in nanoemulsions was made by dissolving 0.01 gm of drug in pre-determined quantities of oil and S mix to prepare a formula of 5 gms. Such nanoemulsions were stored in a tightly closed amber glass containers for further evaluation tests [17].

Characterizations of nanoemulsions

Drop size measurement

The results of droplet size measurement revealed that all formulations of nanoemulsions were found in nano-size as in table 3. It was found that an increase in the S mix ratio results in decreasing of droplet size. This result due to increasing the quantity of surfactant (Tween 20), which lead for good lowering of interfacial tension and decreasing of droplet size [18]. Analysis of variance explains that there was a significant correlation between S mix ratio and droplet size (P<0.05).

Measurement of Polydispersity Index (PDI)

The results of PDI were in range [0.11-0.35] as in table 3. All nanoemulsion (NE1-NE8) have PDI value less than one; this indicates that all nanoemulsions have good uniformity in droplet size distribution within the formulations. The lower value of PDI indicates the higher uniformity of droplet distribution and the lower value of PDI was 0.11 for NE5.

Percent of light transmittance (%T) measurement

The results of (%T) were in range (95.1-98.4%), as in table 3. The results revealed that all nanoemulsion have good transparency and clarity. The higher (%T) value indicates that the system was clear and transparent and the higher value of (%T) was 98.4% for NE5[19].

Zeta potential measurement

Zeta potential value explains the degree of electrostatic repulsion between the same charged particles in a dispersion medium. Zeta potential regarded as good indicator for the colloidal dispersions stability and particles that are small enough have high zeta potential that will accord stability. The results of zeta potential for NE1-NE8 were in range (-25.3 mV to -32.2mV) as in table 3 and according to rule of thumb, the nanoemulsions stability range from short-term stability to good stability [20]. The higher value of zeta potential was -32.2 mV was for NE5. This indicates that the system of NE5 has good stability.

Electrical conductivity measurement

The electrical conductivity results were in the range of (0.13-0.24 mS/cm). Such result indicate that the type of system produced was oil in water (o/w) nanoemulsion, that mean the continuous phase is double distilled water.

Drug content estimation

The percent of drug content for lafutidine nanoemulsions were found to be in range (94.3%-99.2%). As in table 3. NE5 with S mix (3:1) has higher percent of drug content (99.2%). NE8 with S mix (4:1) has lower percent of drug content.

Viscosity measurement

The viscosity of nanoemulsions that measured without dilution by NDJ-8 digital viscometer (spindle no. 1) were in range (38.77-114.677 mPa. sec). Such results explain that all eight formulas of nanoemulsions have low viscosity and this essential for nanoemulsions need to be administrated via oral route [21].

In vitro release study

The in vitro release study of lafutidine nanoemulsions (NE1-NE8) and of pure drug was made by dialysis bag technique in dissolution medium of HCl buffer (pH=2)+0.05% twenos 20 for two hours and phosphate buffer (pH=6.8)+0.05% twenos 20 for one hour. The result of drug release from nanoemulsions (NE1-NE8) and pure powder drug revealed the order; NE5>NE6>NE4>NE1>NE3>NE2>NE7>NE8=pure drug. The profile for drug release of NE1and NE2 with S mix (1:1), NE3 and NE4 with S mix (2:1), NE5and NE6 with S mix (3:1) and NE7and NE8 with S mix (4:1) ensures the order; NE1>NE2, NE4>NE3, NE5>NE6 and NE7>NE8. As shown in the figure 2. Analysis of variance indicates that there was a significant difference (P<0.05) between release of drug and time. The release of drug in the dissolution medium reflects the effect of concentration of surfactant which mean as the tween 20 concentration increase, the rate of drug release of will be high but up to certain concentration. This explained that in high concentration of surfactant, diffusion of drug from dialysis bag to the dissolution medium will occur leading for lower release of drug [22]. So, this noted that in Smix (1:1) the release was low but in Smix (2:1) the release was increased and in Smix (3:1) the higher release of drug was obtained. In Smix (4:1), the higher amount of surfactant causes diffusion of drug from dialysis bag to the dissolution medium, resulting in lower release of drug.

Kinetic and drug release mechanism

The results of the dissolution study revealed that the kinetic of drug release from nanoemulsions (NE1-NE8) was higuchi model, while the kinetic release of pure drug was first-order kinetic, and this depend on the values of regression coefficient (R²) as shown in table 4. The diffusion exponent (n) values for both nanoemulsions (NE1-NE8) and for pure drug was more significantly lower than 0.43 (P<0.05), which give an indication about the mechanism of release of nanoemulsions and pure drug was fickian release (diffusion) [23].
Fig. 2: *In vitro* release of nanoemulsions and pure drug, where (A) release of NE1 and NE2, (B) release of NE3 and NE4, (C) release of NE5 and NE6, (D) release of NE7 and NE8, where the results are given as mean±SD, n=3. Error bars indicate SD values.
### Table 4: The regression coefficient ($R^2$) and diffusion exponent (n) values

<table>
<thead>
<tr>
<th>NE-code</th>
<th>Zero order model</th>
<th>First order model</th>
<th>Higuchi-model</th>
<th>Korsmeyer-peppas model</th>
<th>Diffusion exponent</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE-1</td>
<td>0.893</td>
<td>0.974</td>
<td>0.981</td>
<td>0.948</td>
<td>0.23</td>
</tr>
<tr>
<td>NE-2</td>
<td>0.761</td>
<td>0.928</td>
<td>0.963</td>
<td>0.938</td>
<td>0.25</td>
</tr>
<tr>
<td>NE-3</td>
<td>0.835</td>
<td>0.937</td>
<td>0.949</td>
<td>0.946</td>
<td>0.37</td>
</tr>
<tr>
<td>NE-4</td>
<td>0.908</td>
<td>0.951</td>
<td>0.952</td>
<td>0.927</td>
<td>0.4</td>
</tr>
<tr>
<td>NE-5</td>
<td>0.912</td>
<td>0.844</td>
<td>0.977</td>
<td>0.964</td>
<td>0.37</td>
</tr>
<tr>
<td>NE-6</td>
<td>0.914</td>
<td>0.921</td>
<td>0.929</td>
<td>0.891</td>
<td>0.4</td>
</tr>
<tr>
<td>NE-7</td>
<td>0.894</td>
<td>0.943</td>
<td>0.967</td>
<td>0.961</td>
<td>0.3</td>
</tr>
<tr>
<td>NE-8</td>
<td>0.868</td>
<td>0.951</td>
<td>0.982</td>
<td>0.975</td>
<td>0.4</td>
</tr>
<tr>
<td>Pure drug</td>
<td>0.892</td>
<td>0.992</td>
<td>0.988</td>
<td>0.965</td>
<td>0.28</td>
</tr>
</tbody>
</table>

**Selection of optimized formula of lafutidine nanoemulsions**

The results of characterization studies of lafutidine nanoemulsions exhibited that the optimized formula was nanoemulsion (NE5), the formula NE5 exhibited droplet size range (62.56-96.2 nm) as explained in the fig. 3. Low PDI (0.110), good pH value (7.1), higher percent transmittance (98.4%), drug content percent was high (99.2%), higher zeta-potential (-32.2 mV) as shown by the fig. 4. Effective electrical conductivity (0.24mS/cm), acceptable range of viscosity for oral use (55.322-61.634 m Pa.s) and the drug release was high from the formula.

**Scanning probe microscopy study**

SPM study of lafutidine nanoemulsion (LFNE5) explains that the droplets were spherical in shape as in fig. 5. The size of droplet was in nano-scale and similar to the range of size that previously determined by particle size analyzer ABT-9000 nano laser and the system doesn’t present in aggregation state.
CONCLUSION

Nanoemulsion drug delivery system is considered as a modern approach for enhancing the solubility of poorly-water soluble drugs, especially the drugs that belong to class II in (BCS). The method of preparation of nanoemulsion in this study associated with low energy of emulsification (aqueous titration method), and this result in increasing the stability of prepared nanoemulsion and decreasing the cost of manufactured nanoemulsion. The formula of 5gram (NE5), which contains 10 mg of fluticasone and can be administrated orally.

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Nil

AUTHORS CONTRIBUTIONS

Experiment design was performed by Karrar T. Khudhair and Inas F. Abdul Razzaq, materials and data collection was performed by Abulfadhel J. Neamah, processing of experiment was performed by all authors, interpretation and analysis of results was performed by Abulfadhel J. Neamah and Inas F. Abdul Razzaq, writing of manuscript was performed by Karrar T. Khudhair, checking and review of final version was performed by all authors.

CONFLICTS OF INTERESTS

Declared none

REFERENCES


