University of Basrah
College of Pharmacy

Preparation and Evaluation of Paracetamol Emulsion Dosage Form

A project submitted to the department of pharmaceutics as a partial fulfillment for graduation in College of Pharmacy

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Abstract

Paracetamol is OTC drug, commonly prescribed and dispensed as an analgesic and antipyretic agent, it is safe drug (with high margin of safety) in compare with other pain killers. It is widely used in pediatric ages which requires use of palatable dosage form.

Paracetamol has bitter taste and low solubility in water, so to be administered in form of oral liquid formulation, there are several approaches have been used to solve these problems like preparation of syrups in presence of co solvent and as suspension form specially for higher doses.

In this study, we try to prepare simple formula of oral O/W paracetamol emulsion (250mg/5ml) using different types of oils (clove, olive, almond, mint and peppermint oil) at different proportions (20, 30 and 40%) and specified type of hydrophilic surfactant (tween 20) at different proportions (0.25-1%).

These formula were evaluated regarding the physical stability, drug loading, droplet size and dissolution testing which compared with that of commercially available paracetamol suspension (Adol®).

The results showed successful formulation of one formula using peppermint oil at 20% with relatively good physical properties (size and homogeneity) and enhanced drug release which imparts higher absorption rate.

Acknowledgement

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1. Introduction

An emulsion may be defined as a biphasic system consisting of two immiscible liquids, one of which (the dispersed phase) is finely and uniformly dispersed as globules throughout the second phase (the continuous phase). Since emulsions are a thermodynamically unstable system, a third agent, the emulsifier is added to stabilize the system. Emulsifier stabilizes the system by forming a thin film around the globules of dispersed phase. The dispersed phase or the continuous phase may vary in consistency from that of a mobile liquid to semisolid. Thus, the pharmaceutical emulsions range from lotions (low viscosity) to creams (high viscosity). The particle size of the dispersed phase commonly ranges from 0.1 to 100 μm. **(1)**

1.1 Advantages and disadvantages of emulsions as dosage forms: (2)

● Advantages:

- Increase the palatability of oils and oil-soluble drugs.
- The aqueous phase is easily flavoured.
- The rate of absorption is increased.
- It is possible to include two incompatible ingredients, one in each phase of the emulsion.

● Disadvantages:

- Preparation needs to be shaken well before use.
- A degree of technical accuracy is needed to measure a dose.
- Storage conditions may affect stability.
- Bulky, difficult to transport and prone to container breakages.

1.2 Types of emulsions: (3)

- **Oil in water emulsion (O/W):**

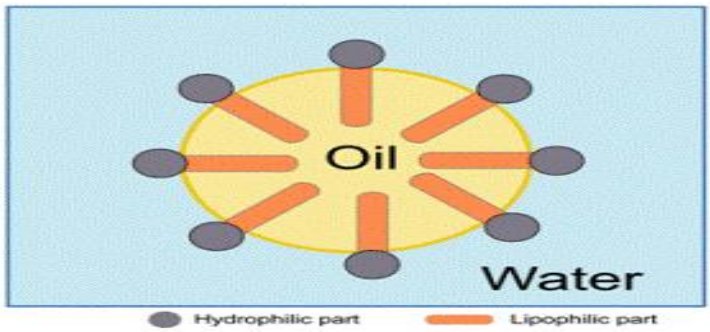

Figure (1): O/W emulsion

- **Water in oil emulsion (W/O):**

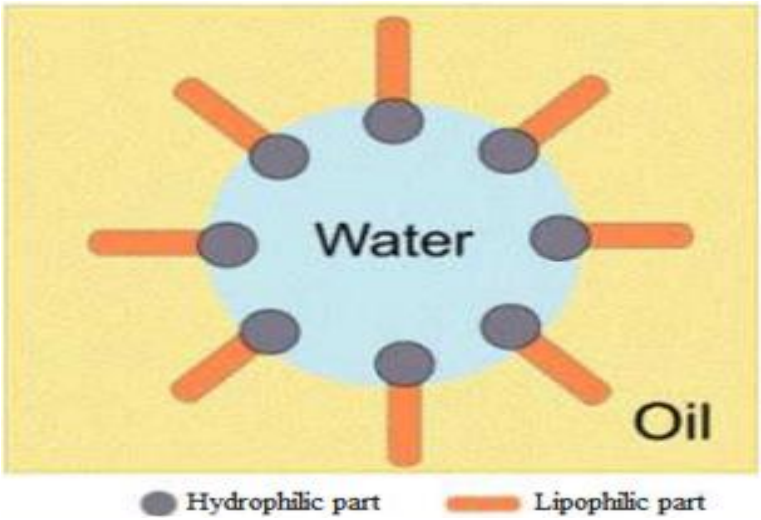

Figure (2): W/O emulsion

- **Multiple emulsion (W/O/W)&(O/W/O)**

- **Micro and Nano-emulsions**

1.3 Emulsification process

● *General method:*

Generally, an O/W emulsion is prepared by dividing the oily phase completely into minute globules surrounding each globule with an envelope of emulsifying agent and finally suspends the globules in the aqueous phase. Conversely, the W/O emulsion is prepared by dividing aqueous phase completely into minute globules surrounding each globule with an envelope of emulsifying agent and finally suspending the globules in the oily phase.**(4)**

● *Phase inversion method:*

In this method, the aqueous phase is first added to the oil phase so as to form a W/O emulsion. At the inversion point, the addition of more water results in the inversion of emulsion which gives rise to an O/W emulsion.**(5)**

● Continental and dry gum method:

Extemporaneously emulsions are usually made by continental or dry gum method. In this method, the emulsion is prepared by mixing the emulsifying agent (usually acacia) with the oil which is then mixed with the aqueous phase. Continental and dry gum methods differ in the proportion of constituents.**(4)**

● Wet gum method:

In this method, the proportion of the constituents is same as those used in the dry gum method; the only difference is the method of preparation. Here, the mucilage of the emulsifying agent (usually acacia) is formed. The oil is then added to the mucilage drop by drop with continuous trituration.**(4)**

● *Membrane emulsification method:*

It is a method, which is based on a novel concept of generating droplets “drop by drop” to produce emulsion. Here, a pressure is directly applied to the dispersed phase which seeps through a porous membrane into the continuous phase and in this way the droplets formed are

then detached from the membrane surface due to the relative shear motion between the continuous phase and membrane surface.**(6)**

1.4 Stability of emulsions

A very important parameter for emulsion products is their stability; however, the evaluation of emulsion stability is not easy **(7)**. Pharmaceutical emulsion stability is characterized by the absence of coalescence of dispersed phase, absence of creaming and retaining its physical characters like elegance, odor, color and appearance. The instability of emulsion may be classified into four phenomena : Flocculation, creaming, coalescence and breaking (Figure.3) **(8)**.

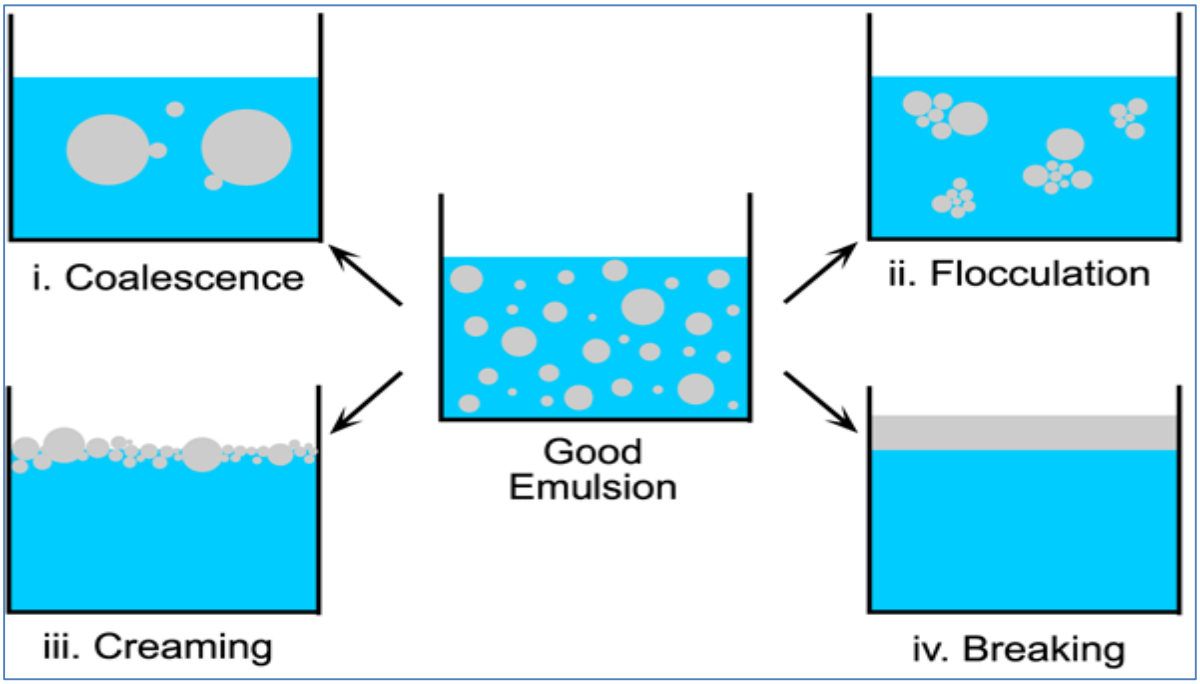

Figure (3): Instability types of emulsion

1.5 Emulsifying agent

Emulsifying agent or surfactant may be defined as" a compound that lowers the surface tension and forms a film at the interface of two immiscible liquids making them miscible". Some commonly used emulsifying agents are shown in (Table 1). The efficiency of an emulsifying agent is related to its chemical structure, solubility, pH and physical properties. There are two types of emulsifying agents on the basis of their effects:

1. Primary agents (true emulsifying agents) can form and stabilize emulsions by themselves.
2. Auxiliary agents (stabilizers) alone do not form fine emulsions but assist the primary emulsifying agents.**(9)**

Table 1. Some commonly used emulsifying agents, their HLB values, characteristics and functions.

Chemical name	HLB	Miscible with H_2O	Function
Oleic acid	1.6	Immiscible	Antifoam
Sorbitan tristearate	2.1	Immiscible	Antifoam
Ethylene glycol monostearate	2.9	Immiscible	Antifoam
Glyceryl monostearate	3.8	Disperses with difficulty	W/O emulsifier
Sorbitan monostearate	4.7	Disperses with difficulty	W/O emulsifier
Sorbitan monopalmitate	6.7	Forms milky dispersion	W/O emulsifier
PEG-4 dilaurate	6	Forms milky dispersion	W/O emulsifier
Sucrose dipalmitate	7.4	Forms milky dispersion	W/O emulsifier
PEG-4 monooleate	8	Forms milky dispersion	W/O emulsifier
PEG-4 monolaurate	9.8	Form milky stable dispersion	O/W emulsifier
Polysorbate 85	11	Form clear dispersion	O/W emulsifier
PEG-8 monooleate	11.4	Form clear dispersion	O/W emulsifier

1.6 Paracetamol **(10)**

Paracetamol or acetaminophen is a widely used over-the-counter analgesic (pain reliever) and antipyretic (fever reducer). It is commonly used for the relief of headaches and other minor aches and pains and is a major ingredient in numerous cold and flu remedies. In combination with opioid analgesics, Paracetamol can also be used in the management of more severe pain such as post-surgical pain and providing palliative care in advanced cancer patients **(11)**. The

onset of analgesia is approximately 11 minutes after oral administration of Paracetamol **(12)**, and its half-life is 1-4 hours. Though acetaminophen is used to treat inflammatory pain, it is not generally classified as an NSAID because it exhibits only weak anti-inflammatory activity.

● ***Organoleptic properties:***

- Odorless and colorless crystals or white crystalline powder, with slightly bitter taste.

● ***Assay:***

- **Ultraviolet spectrum:** Aqueous acid—245 ; aqueous alkali—257 nm.

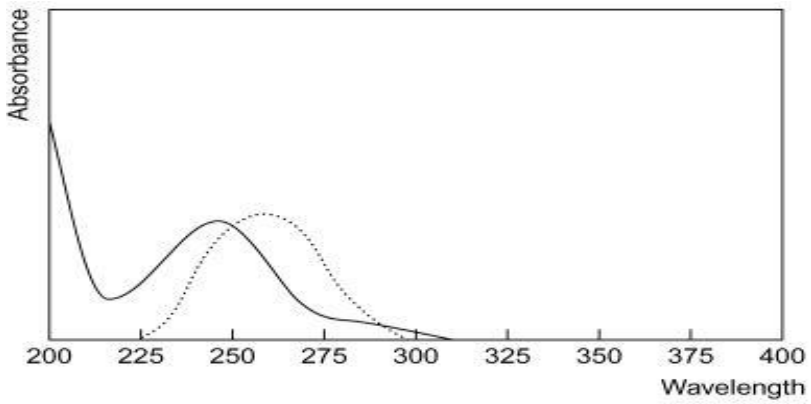

Figure (4): Ultraviolet spectrum of Paracetamol

● ***Solubility:***

- In water : 14000 mg/L (at 25 °C).**(13)**

- Very slightly soluble in cold water, soluble in boiling water.**(14)**

- Freely soluble in alcohol; soluble in methanol, ethanol, dimethylformamide, ethylene dichloride, acetone, ethyl acetate; slightly soluble in ether; practically insoluble in petroleum ether, pentane, benzene.**(14)**

● ***Melting point:***

- M.P= 169-170.5 °C.

- Boiling point = >500°C.

- ***Stability:***

Stable under recommended storage conditions.**(15)**

- ***Biopharmaceutical classification:***

Initially, paracetamol had been classified as a BCS class III compound (highly soluble and poorly permeable), however, following a technical report from the WHO expert committee on specifications for pharmaceutical preparations, it is classified as a BCS class I compound (highly soluble and highly permeable). When an API is absorbed to an extent of 85% or more, it is considered to be "highly permeable".

- ***General information:***

2D structure:

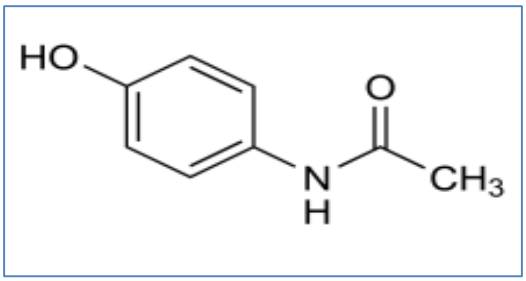

Figure (5): Chemical structure of Paracetamol

Molecular Formula: $C_8H_9NO_2$

Molecular Weight: 151.165 g/mol

Density: 1.293 g/cu cm at 21 deg C. **(16)**

Partition coefficient (Log P): 0.5

pH: Saturated aqueous solution (5.5-6.5).**(17)**

pKa: 9.5 (25 C °)

2. Experimental work

2.1 Materials:

The materials used in this study with their suppliers are listed below.

Table (2): The materials that were used in this study with their suppliers

Materials	Suppliers
Paracetamol pure powder	China
Peppermint oil	France
Clove oil	Lab
Almond oil	Turkey
Olive oil	England
Mint oil	Lab
Tween 80	India
Tween 20	India
Ethanol	SDI
Distilled water	Lab
Potassium dihydrogen phosphate	India
Disodium phosphate	India
Paracetamol suspension (ADOL®) (250 mg/5ml)	Julphar comp. U.A.E

2.2 Instruments:

The instruments used in this study are listed below.

Table (3): Instruments and the manufacturing company

Instrument	Company
Electrical melting apparatus	Stuart; UK
UV spectrophotometer	Aquarius
Electronic balance	Denver instrument
Hot plate	DAIHAN LABTECH
0.45 micrometer filter	EMD Millipore
Sonicator	Bandelin electronic ;Berlin / Germany
pH meter	HANNA instrument
Dissolution USP apparatus	CALEVA England
Zeta sizer NANO ZS	UK

2.3 Characterization of Paracetamol raw powder:

2.3.1 Melting point:

The melting point of Paracetamol was measured by the capillary tube method that complies with requirements of the BP and USP. A sufficient quantity of Paracetamol powder was introduced into a one side sealed capillary glass tube to give a compact column of (4 – 6 mm) in height. The tube was placed inside electrical melting point apparatus and the temperature was increased gradually, the melting point was recorded, which is the temperature at which the last solid particle of drug in tube passed into liquid phase. **(18)**

2.3.2 Determination of Paracetamol λmax.

Most of drugs absorb UV light in range (200 – 400 nm) because they are generally aromatic or contain double bonds in their structures.

The stock solution of (0.1 mg/ml) of Paracetamol in ethanol was prepared and suitably diluted then scanned by UV-visible spectrophotometer and the λmax of the drug was determined.

2.3.3 Calibration curves of Paracetamol

The calibration curve of Paracetamol in ethanol was constructed by preparing serial dilutions at different concentrations (1,2,3,10, 20, 30, 40, 50 µg/ml) from the stock solution.

The prepared samples were analyzed spectrophotometrically at the estimated λmax, then the measured absorbance of each sample was plotted versus concentration. **(19)**

Additionally, The calibration curves of Paracetamol in 0.1N HCl was constructed by preparing serial dilutions at different concentrations (1,2,3,4,5,6,7,8,9 and10 µg/ml) from the stock solution (0.01 mg/ml) at the same λmax which is mentioned in references.**(10)**

2.4 Preparation of Paracetamol emulsion formulas:

Several formulas of paracetamol O/W emulsion coded (B1-B7) were prepared using different types and proportions of oils and constant drug concentration (250mg/5ml) and surfactant as shown in Table (4).

The general procedure for preparation can be summarized as follows:

1. Dissolve 1 gm of Paracetamol in the specified volume of oil in the mortar (with trituration).
2. Add 0.2 mL of the tween 20 (emulsifier).
3. Add water gradually (as portions).
4. Transfer the mix into a graduated cylinder (with stopper) , shake then complete the volume into 20 mL with D.W.

Additionally, the proportions of surfactant were varied (0.25-1%) to reach the suitable ratio.

Table (4): O/W emulsion formulas of Paracetamol (1% tween 20)

Formula Code	Type and (%) of the oil	(%) of water
B1	40% Clove oil	60%
B2	30% Cove oil	70%
B3	20% Clove oil	80%
B4	20% Olive oil	80%
B5	20% Peppermint oil	80%
B6	20% Mint oil	80%
B7	20% Almond oil	80%

2.5 Characterization of Paracetamol emulsion formulas:

2.5.1 Visual inspection

Visual inspection of emulsions may include appearance, particles and color requirements: not conspicuous, no oil separation, no phase separation, practically free from visible particles ,no turbidity or precipitation, change of color not more than one degree.

2.5.2 Assay of drug loading

Addition of specified volume (5ml) of the selected formula of paracetamol emulsion in a suitable organic solvent like ethanol followed by sonication, then filtered sample is determined spectrophotometrically at the determined λmax.

2.5.3 Determination of droplet size

The droplet size of selected formula was examined using zeta sizer instrument to get idea about the micromeritic properties of the prepared formula.

2.5.4 Dissolution test

Accurately measured volumes of Paracetamol emulsion and commercially available paracetamol suspension (250mg/5ml) were carefully added into the dissolution media (500ml of 0.1N HCl) using type II USP apparatus (Paddle method) at temperature (37 °C) and stirring speed (25 rpm). Five milliliters of samples were periodically withdrawn (not exceed 30 minutes) from a fixed position of the vessel and replaced with equivalent volume of fresh 0.1N HCl solution. The withdrawn samples were filtered, suitably diluted and analyzed spectrophotometrically at λmax of 243nm.**(20)**

3. Results and discussion

3.1 Characterization of Paracetamol raw material

3.1.1 Melting point determination

The measured melting point of pure Paracetamol powder was ranged (169-171 °C). The reported value of the sample was within the reference value **(10)**, this indicates the purity of paracetamol powder.

3.1.2 Determination of Paracetamol λmax.

Scanning the stock solution of (Paracetamol in ethanol) in the UV range 200 – 400 nm gave the spectrums shown in figure (6).

The maximum UV wave length of Paracetamol in ethanol was 243nm which approximates the reference value. **(10)**

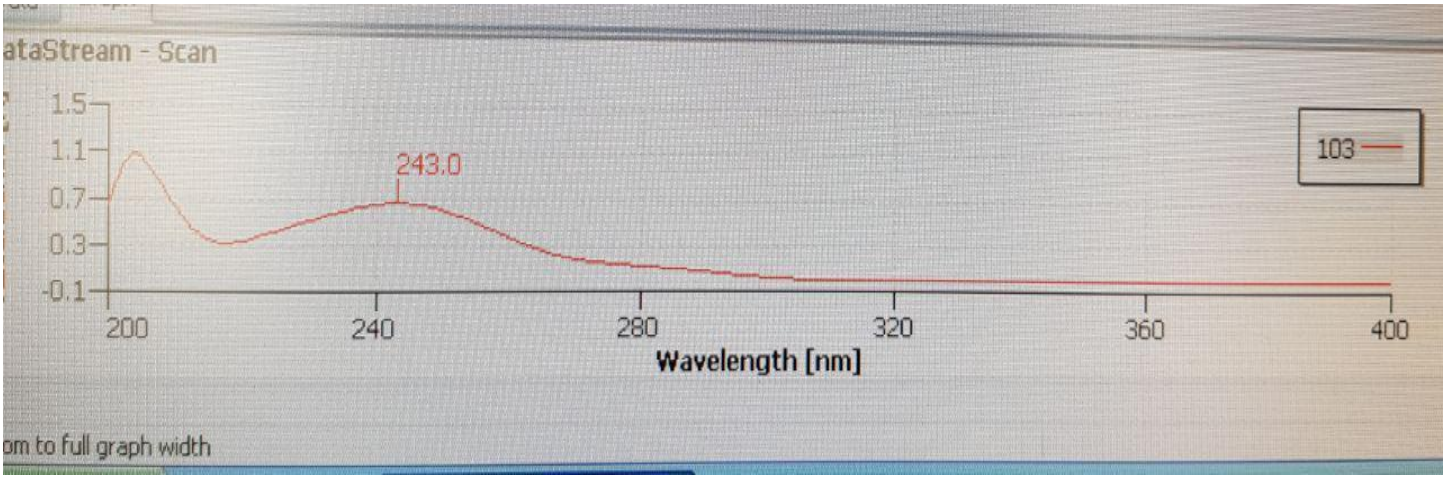

Figure (6): λmax of Paracetamol in ethanol

3.1.3 Calibration curves of Paracetamol

The figures (7 and 8) illustrate the calibration curves of Paracetamol in ethanol and 0.1N HCl respectively.

The best fitted equations of calibration curves when straight lines were obtained by plotting absorbance versus concentrations with higher correlation coefficient (R^2) of 0.9926 and 0.9931 for ethanol and 0.1N HCl respectively which indicates that line curve obey Beer–Lambert's law within the range of experimental concentrations used. **(21)**

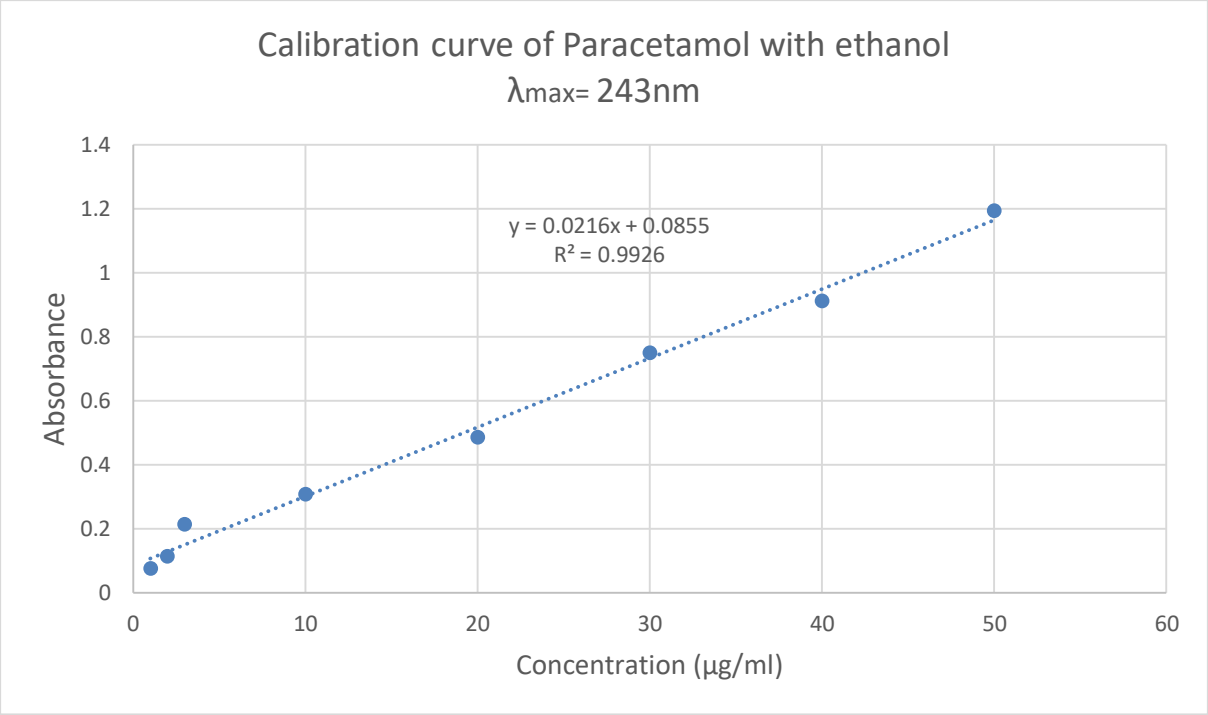

Figure (7): Calibration curve of Paracetamol in ethanol.

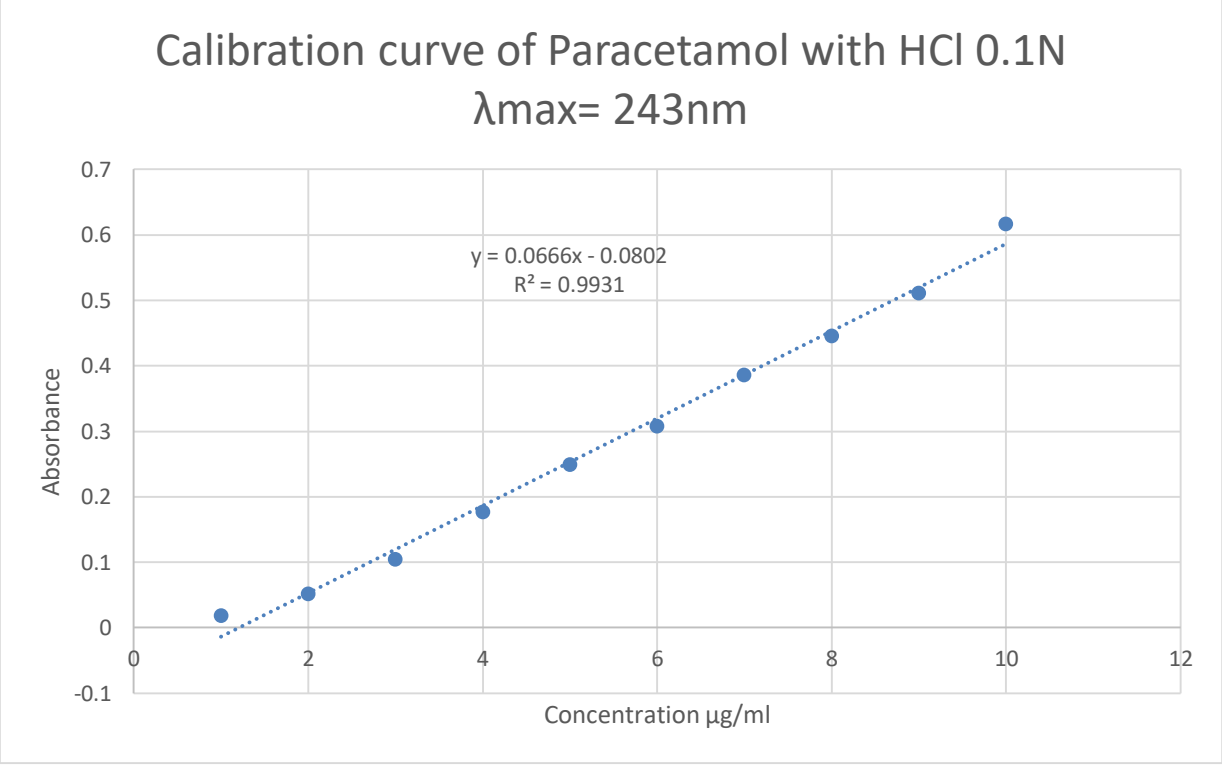

Figure (8): Calibration curve of Paracetamol in 0.1N HCl.

3.2 Preparation of Paracetamol emulsion

Seven formulas of Paracetamol emulsion (B1-B7) were prepared using different types and proportion of oils as internal phase to reach the best formula regarding the physical stability with exceeding 40% of oil to avoid the phase inversion or non-palatable taste of the produced formulas.

The best ratio for tween 20 to act as stabilizer was 1% which is fixed for the selected formulas.

3.3 Characterization of Paracetamol emulsion formulas

3.3.1 Visual inspection

Regarding the physical stability and tendency of the prepared formulas of emulsion toward sedimentation and separation, we can summarize the results of this test as follows:

- **B1, B2 , B3** & **B4** have failed during the formulation in spite of changing the type & (%) of oil and ratio of surfactant. This indicate the failure of clove oil and olive to give acceptable emulsion formula. This may attributed to HLB values of these oils and the single use of surfactant (tween 20) which hydrophilic one. We may alleviate this problem by use less ratio of oil, or use of combination of surfactant (hydrophilic and lipophilic such combination of tween 20 or 80 with span 20 or 80).
- **B5** (using peppermint oil) was succeeded (remained stable for longer time) and the separation was reversible (dispersed by simple shaking) . So, we can consider it as better formula.
- **B6** & **B7** were succeeded during preparation and remained stable for 10 min then separated. The emulsification did not easily return by simple shaking .

Table (5): The physical stability of the prepared formulas

Formula Code	Result
B1	Separated
B2	Separated
B3	Separated
B4	Separated
B5	Succeeded
B6	Separated
B7	Separated

3.3.2 Assay of drug loading

Paracetamol concentration in the selected formula was (49.28 mg/ml) which is very close to the initial concentration (50 mg/ml) indication high drug loading and uniform distribution for drug after shaking (good physical stability).

3.3.3 Determination of droplet size

From figure (9), we can see that the droplet size range was (5-8 μm) indicating microscopic level of the prepared paracetamol emulsion B5, this gives more physical stability, homogeneity and rapid release of drug.

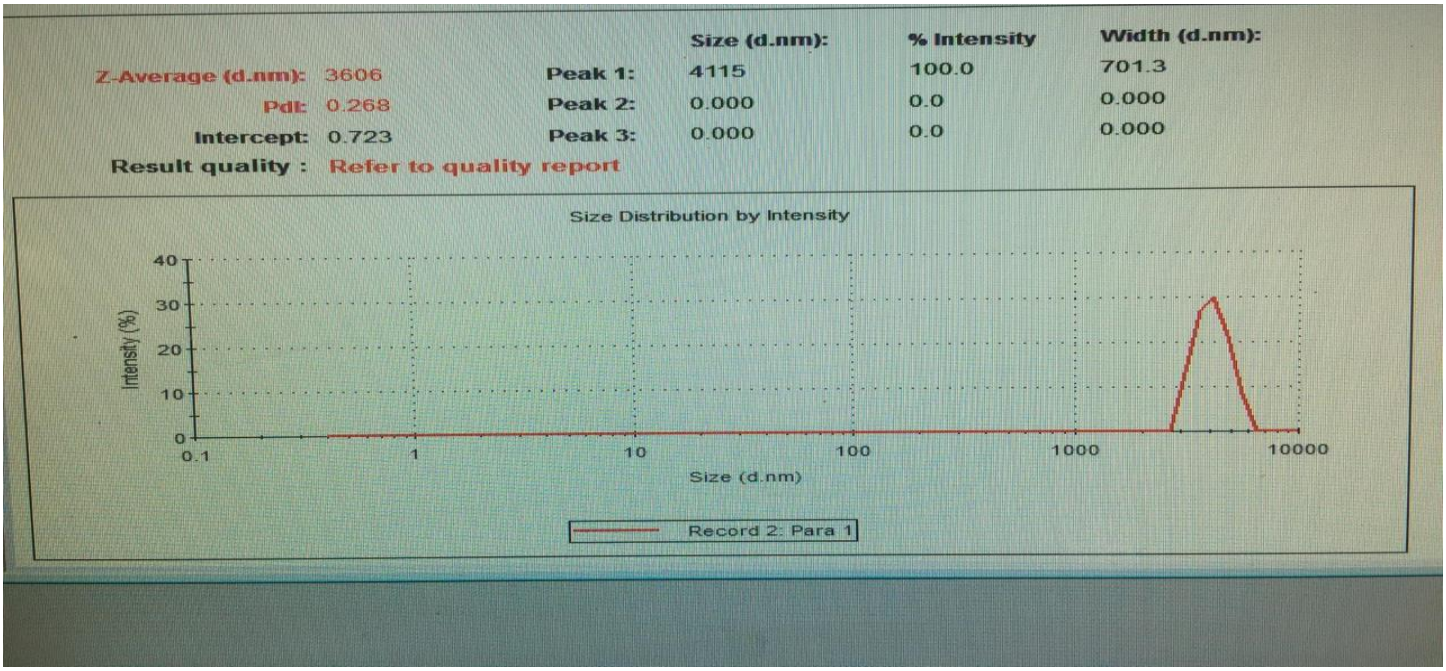

Figure (9): Droplet size distribution of B5

3.3.4 Dissolution test

This test indicates the rapid release of paracetamol if prepared as an emulsion form compared with the commercially available paracetamol suspension which is selected due to absence of official emulsion dosage form.

This result may be due to the difference in the physical properties (particle size and viscosity) between emulsion and suspension.

The release of paracetamol was complete within the first five minutes of test. Unlike, the suspension form, take more time (about 20 minutes)

Table (6): The dissolution data of B5

Time (min.)	% of release
5	100

Table (7): The dissolution data of Adol® suspension

Time (min.)	% of release
5	11
10	22
15	48
20 min	100

4. Conclusion

The basics of emulsions are definitely succeeding and the proficient development and production of excellence pharmaceutical emulsions depends on their basic knowledge of physicochemical properties and stability. From the results of our research we concluded that Paracetamol emulsion dosage form has the same concentration and amount of active ingredient of the suspension dosage form , as well as the emulsion has a higher dissolution rate than suspension , which makes the emulsion dosage form a successful idea for production. However it may has more stability problems and lower shelf life than suspension which could be avoided by addition of proper excipients to the formula.

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