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The mixing process in the production of paracetamol suspension and its stability

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Abstract— *The mixing process is a common and important process in the chemical, food and pharmaceutical industries with the objective of producing suspensions and emulsions and increasing the process rate of mass and heat transfer.*

In this paper, the mixing process was studied during the production of paracetamol syrup in a new formula with a concentration of (10 g / 100 ml). For this purpose, a four-blade mixer was designed and the factors affecting the mixing process and the stability of the final product were studied including the mixing time and speed of rotation.

Keywords— ***Paracetamol, Stability Studies, Mixing Process.***

I. INTRODUCTION

Paracetamol or **acetaminophen** is the common name for the compound N-Acetyle-P-aminophenol or 4-Hydroxy acetanilide with a molecular formula of $C_8H_9NO_2$. This compound is a white crystalline powder with a molecular weight of 151.2 and a melting point of (168-172 ºC). It is soluble in alcohol, but has low solubility in ether or methylene chloride and it dissolves partially in water (1.0 - 5.0 g / 100 ml). Similarly to phenol, it has weak acid properties, as the pH of its solution is in the range (5.5-5.6). In view of the market's need for paracetamol in high concentrations (10 g / 100 ml) and the lack of a suitable method for its production, this study was undertaken for the production and stability of this drug with the required concentrations and the production of paracetamol suspension using new solvents. A spectrophotometer was used to study the mixing process of the paracetamol suspension. As is well known, the UV visible spectrum is one of the most common techniques used in pharmacological analysis which depends on measuring the amount of UV or visible radiation absorbed by the material in the solution.

II. MATERIAL AND METHODS

1. Paracetamol production

A number of solvents (PEG 400 - PEG 6000 - Glycerol) were used in the preparation of the paracetamol syrup. The solvents were used in different proportions as shown in Table 1.The paracetamol sample and all the substances mentioned in Table 1 were obtained from the Aphamia Pharmaceutical Industries Lab.

Initially the first phase was prepared at a temperature of 40ºC consisting of PEG400 with paracetamol and stirred until dissolving (we note that paracetamol does not dissolve until the addition of the second phase), then we prepare the second phase by adding methyl paraben with propyl paraben and PEG 6000 to boiling distilled water and stirring until dissolving. We cool the second phase to the temperature of the first phase and add local materials, antioxidants and acidity control materials, and then we add the second phase to the first phase, at the end we add flavorings and complete the volume with distilled water and then adjust the pH of the solution between (4-6).

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Table 1: Paracetamol Formulation

USE	gr	Formula	Parameters
Active	100 gr	$C_8H_9NO_2$	Paracetamol
Solubilizer	360 ml	$C_{2n}H_{4n+2}O_{n+1}$ n = 8.2 to 9.1	400Polyethylene glycols
Solubilizer	100 gr	$H(OCH_2CH_2)_nOH$	Polyethylene glycol 6000
Solubilizer	120 ml	$C_3H_8O_3$	Glycerol
Preservative	1.8 gr	$C_8H_8O_5$	Methyl parabenSodium
Preservative	0.2 gr	$C_{10}H_{12}O_3$	Propyl parabenSodium
-	420 ml	H_2O	Water
sweetening Agent	2 gr	$C_{12}H_{19}Cl_3O_8$	Sucralose
Sweetening Agent	12 gr	$C_4H_4KNO_4S$	Acesulfame
Flavouring Agent	2 ml	-	Strawberry
Flavouring Agent	2 ml	-	Grape flavor
Flavouring Agent	0.2 ml	-	Orange flavor
Colouring Agent	0.08 gr	-	E120Red colored
Antioxidant	1.3 gr	$C_4H_6O_5$	Malic acid
Acidifier	1.5 gr	$Na_3C_6H_5O_7$	Trisodium citrate

Evaluation of Syrup:

1. Determination of pH

The pH value conventionally represents the acidity or alkalinity of an aqueous solution. The pH value of a solution was determined potentiometrically by means of glass electrode. A digital pH meter could stabilize. Then the pH meter was standardized using buffer tablets. The suspension formulation was placed in the pH meter. The reading was noted when there is no fluctuation in the pH meter.

2. Determination of density

A pre weighed 50 ml volumetric flask was taken and the oral syrup was added up to the mark. The net volume was noted. Then the volumetric flask was weighed and the density calculated.

3. Study the mixing process

The blade of a four-blade electric blender was manufactured with a diameter (3.36 cm) as shown in Figure 1. That was used in the design of the mixing unit. (Cheremisinoff, 2000)

Fig.1: A four-blade electric mixer blade

An experimental mixing unit consisting of:

- Electric mixer type Heidolph RZR 2020.
- A four-blade electric mixer blade fig 1.
- Double jacket reactor.

As the blade is designed in Figure (1) according to the following dimensions of the mixing vessel:

- Internal diameter (7 cm).
- External diameter (9.5 cm).
- Internal length (9 cm).
- External length (12.5).
- Nozzle diameter (4 cm).
- Internal nozzle height (6.5 cm).

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- Diameter of the input and output nozzles (2.5 cm).

- Water bath.

Spectral measurements were performed by a device type A simtronics UV/ Visible recording spectrophotometer (single beam)Model: SE 807.with matched quartz cells (1 cm).

And the use of a sensitive balance type Sartorius.

(Robert H. Perry, 2008)

Standard preparation (100 mg/ml):

0.025 g active substance (Paracetamol) was dissolved in a quantity of distilled water and was shaken well. Then the volume was increased to (250 ml) capacity with distilled water. (Siladitya Behera*, 2012)

Preparation of the calibration curve:

To prepare standard chain solutions, we carefully measured (100.0 mg) of standard paracetamol and dissolved with an appropriate amount of distilled water, then transferred to a 100 ml volumetric flask and complete the volume with distilled water.

Then it is taken from the standard paracetamol solution with a standard pipette volume (0.5 ml) of the solution and placed in a volumetric flask with a capacity of (100 ml) and extended with distilled water until the full volume and thus we will have prepared the standard solution -1- with a concentration of (5 ppm), then to prepare the standard solution - 2- It was taken from a standard paracetamol solution (0.7 ml) with a standard pipette and the solution is placed in a volumetric flask (100 ml) and we dilute the distilled water until the volume is complete and the solution concentration is (7 ppm), and to prepare the standard solution -3- take (1 ml) as well From a standard paracetamol solution with a standard pipette and placed in a volumetric flask (100 ml) capacity and extended with distilled water until the volume is complete and the concentration of the solution is (10 ppm), then for Preparation of standard solution No. -4- A volume of (1.5 ml) is taken from the standard paracetamol solution by a standard volumetric pipette. The volume is placed in a volumetric flask (100 ml) and extended with distilled water until the volume is complete. The concentration of the solution is here (15 ppm). To prepare the standard solution -5- The volume (2 ml) of the standard paracetamol solution is taken by a standard volumetric pipette and the volume is placed in a volumetric flask (100 ml) and the solution is extended with distilled water until the volume is complete and the solution concentration here (20 ppm), as shown in table (3).

Table 2: Data stability studies for Final Formulation.

S.NO	PARAMETERS	INITIALS	TIME PERIODS		
			1 MONTH	2 MONTHS	3 MONTHS
1.	**Color**	Red color	Red color	Red color	Red color
2.	**Appearance**	Clear Solution	Clear Solution	Clear Solution	Clear Solution
3.	**Odor**	Stable	Stable	Stable	Stable
4.	**Taste**	Sweet	Sweet	Sweet	Sweet
5.	**pH**	5.1	5.1	5	4.9
6.	**Assay**	100.00	99.87	99.79	99.58

In this method, a series of standard solutions with known concentrations of the substance whose concentration is to be prepared are prepared. After reading the absorption of each solution at a fixed wavelength, we draw the absorption readings in terms of concentration to obtain the calibration curve, and from this curve we can determine the concentration of the unknown solution after knowing its absorption that Give her the device. The concentration is found by the coordinate projection process, where the absorbance of the unknown solution is fixed on the coordinate axis Y, then a straight line is taken parallel to the coordinate axis X until it cuts the straight calibration curve, then a straight line is dropped parallel to the coordinate axis Y on the coordinate axis X and the intersection point with the coordinate axis X The concentration of the unknown substance.

Or by the following equation:

$C_{test} = (A_{test} \times C_{std}) A_{std}$

(Siladitya Behera*, 2012)

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Table 3: Concentrations of Paracetamol Standard chain Solutions

Standard solution	Concentration	Absorbance
-1-	5 ppm	0.349
-2-	7 ppm	0.486
-3-	10 ppm	0.701
-4-	15 ppm	1.023
-5-	20 ppm	1.317

We determine the absorbances of the standard chain solutions by means of a UV spectrophotometer at a wavelength (243 nm), and then draw the straight line passing through the largest number of points that express the absorbances of the standard chain solutions against their concentrations, so we get the standard curve Figure 2.

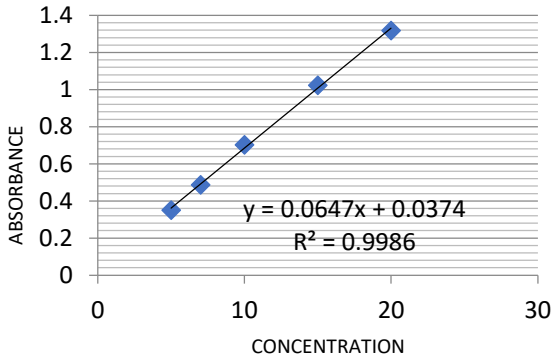

Fig.2: Standard curve of paracetamol

Whereas, the absorbance calculations that were performed on the entire research within the field mentioned in the standard curve.

1- Study the factors affecting the mixing process of paracetamol suspension:

The mixing process was studied using the A four-blade electric mixer blade on the experimental unit, where the factors affecting the speed of the mixing process were studied:

1. Rounds number: The process was studied at the round number (2000, 1650, 1300, 1060, 800) rpm.
2. Mixing time: The experiments were conducted at times (15, 30, 45, 60, 75, 90) min.

During the work, absorptivity curves with wavelength were drawn at the rounds number and times mentioned previously.

In order to increase the picture clarity, the relationship between the concentration and the number of mixing cycles was drawn at different times.

The following curves were obtained as a result of the study:

Absorbance curve with wavelength and at different rounds number:

Figure 3 expresses the relationship of the absorbance with the wavelength at the maximum wavelength of (λ = 243 nm) and at the number of rounds.

(n1 = 2000 rpm, n2 = 1650 rpm, n3 = 1300 rpm, n4 = 1060 rpm, n5 = 800 rpm)

Table 4: Shows the relationship between the five curves of wavelength with absorbance at the all rounds number.

Rounds number	Absorbance
2000 rpm	0.770
1650 rpm	0.751
1300 rpm	0.745
1060 rpm	0.725
800 rpm	0.710

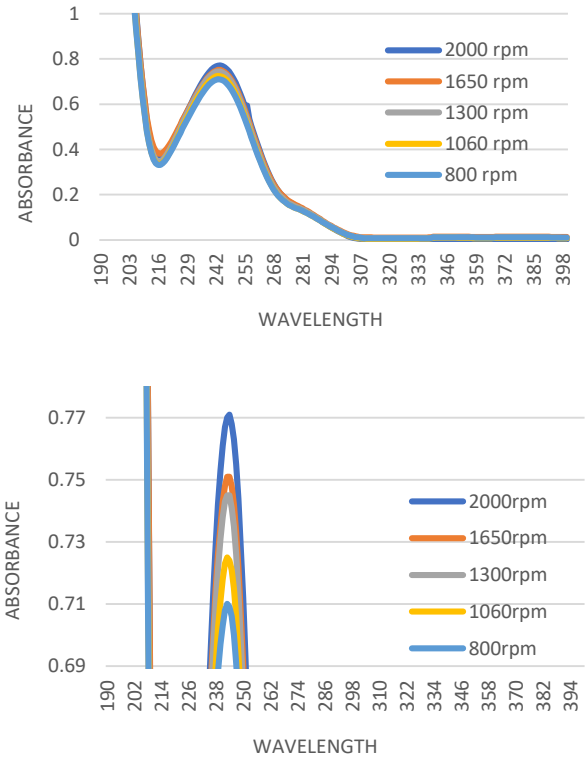

Fig.3: The relationship between absorbance and wavelength

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Curved concentration with rounds number:

The mixing process was studied by determining the concentration and absorption of the resulting solution at different times (30, 60, 90) min.

In order to show the image in its graphic form, the relationship between concentration and rounds number (2000, 1650, 1300, 1060, 800) rpm, was drawn at different times (90, 60, 30) min, As shown in the figure4.

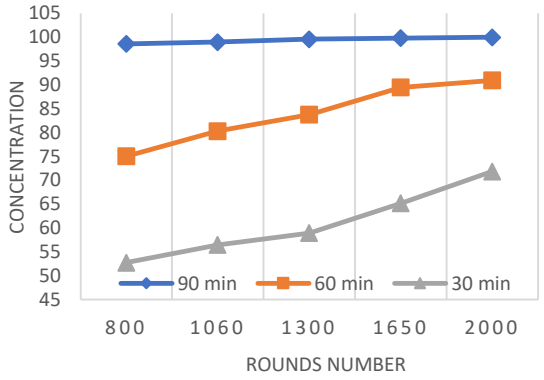

Fig.4: The relationship between concentration and rounds number

Curves of concentrations with times and at a different rounds number:

Mixing time is one of the important parameters affecting the mixing process.

In this field, depending on the experimental results, the relationship between mixing time and concentration time was determined at the number of different rounds: (2000, 1650, 1300, 1060, 800) rpm, As shown in the figure5.

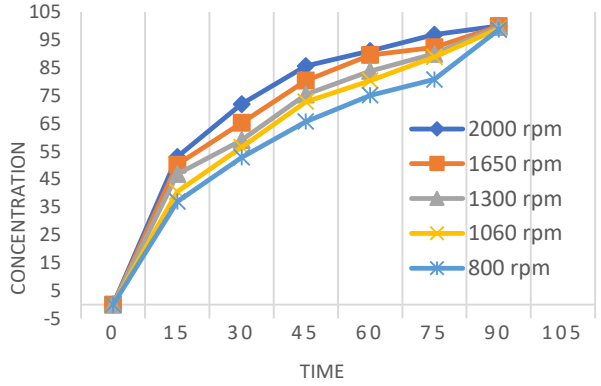

Fig.5: The relationship between concentration and time

Accelerated stability study

syrup was packed in 100 ml Pet bottle. The packed bottles were placed in stability chamber maintained at 40 + 2 °C and 75 + 5% RH for 3 months. Samples were collected at days 0, 30, 60 and 90. The analyses comprised chemical testing of quantifiable parameters, which could possibly change during storage, such as pH, drug contents, color, taste, odor and drug release.

III. RESULTS

Evaluation of Syrup was carried out for various parameters like confirmation of formation of precipitation, pH, odor, and taste.

Accelerated Stability Studies:

Conclusion:

The experimental results that started with preparing a new formula for paracetamol syrup with a concentration of (10 g / 100 ml) and studying the mixing process and the factors affecting it from the moment of adding the raw materials and ending with obtaining the final product according to the fixed mixing conditions of 40 ºC temperature and the type of fixed mixer, by designing a four-blade mixing fan As in Figure (1) in proportion to the dimensions of the mixing vessel used in conducting experiments and the conditions for mixing changing from time and rounds number, and using solvents available at the local market - PEG400, PEG6000, Glycerin - and the alternative to the common solvents, the process of their stability has been studied where results showed Operation It is proven that the new formula of paracetamol suspension is stable and suitable for drug use.

The results of the study of the factors affecting the mixing process, first relying on drawing the standard curve of paracetamol, through which the concentrations of the experimental samples subsequently were determined, that by increasing the number of cycles the concentration of the resulting solution of paracetamol syrup increases until reaching the complete dissolution of the paracetamol granules, which is necessary in producing this. The type of syrup that has high concentrations as it forms transparent crystals after a short period of time, and this indicates that it does not dissolve completely, and therefore the syrup is unstable in this case and is not accepted.

This was illustrated by Figure 4, which shows the relationship of the rounds number to the concentration according to three times. The figure shows three curves, representing the time curve (30) min partial dissolution of paracetamol with the highest dissolution rate of the material by up to (52.7) % at the rounds number (800) rpm

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And (71.9)% at the rounds number (2000) rpm and at the time curve (60) min the mixing ratio increases to (75)% at the rounds number (800) rpm and (90.9)% at the rounds number (2000)rpmand finally the ideal time is The mixing process is (90) min, which achieves degradation when the rounds number (800) rpm reaches (98.6) % and achieves a percentage (100) % at the number of cycles (2000) rpm, as Figure 5 emphasized this by a concentration curve with Time is in a wider field of time (15, 30, 45, 60, 75, 90) min and at all rounds number (2000, 1650, 1300, 1060, 800) rpm, and thus each of the following four rounds is: (2000 rpm, 1650 rpm, 1300 rpm, 1060 rpm) check the mixing process in the mentioned blade pattern.

Thus, we have produced paracetamol suspension, studied the stability of the sample, designed a mixing blade with the appropriate dimensions of the available mixing vessel and achieved an appropriate mixing time and complete dissolution of the studied paracetamol suspension as an active substance.

The following will be studied later:

• Use mixers with other different models and compare the experimental results obtained with the results of experiments with new mixers that can be studied in the future (three-blender mixer number two right-direction - and traditional mixer three-blade number two left direction - mixer blade number two).

• Determination of the energy consumed by the mixing process for the selected models for experimental study, the purpose of carrying out the necessary economic study.

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