ORIGINAL ARTICLE

Extemporaneous Compounding and Stability Evaluation of Paracetamol-honey Based Syrup for Pediatric use

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Abstract

Background: Paracetamol is an analgesic and antipyretic agent. Honey is a nutrient that has many medicinal benefits and uses. It is has a demulcent activity and used in alternative medicine as a mild antitussive agent. Moreover, honey demonstrated an antitoxic activity in paracetamol-induced hepatotoxicity. **Objective:** The aim of this study is to formulate and assess the general stability of paracetamol-honey based syrup using four different sources of honey. **Materials and Methods:** Four different formulas of paracetamol-honey based syrup were prepared by changing the source of honey. The formulated syrups were then stored at two different storage conditions (25°C and 40°C). The organoleptic properties, microbial contamination, pH, and assay were assessed according to compendia guidelines. An ultraviolet spectrophotometer was used to quantify paracetamol in the obtained syrups. **Results:** Formula four (F4) honey-based syrup showed the best stability within 4-month period at both room and accelerated conditions. The pH remained constant, no change in organoleptic properties was observed, and the assay of paracetamol was always higher than 93% of the initial value. However, formula three (F3) of honey showed the worst stability. **Conclusion:** Honey would be a beneficial alternative for common syrup due to its numerous benefits in the medicinal field. Pharmacist and industry could benefit from F4 formulation to produce this kind of syrup to achieve an antitussive formulation with antipyretic activity and nutritional value.

Key words: Honey, paracetamol, stability, syrup

INTRODUCTION

Honey is a natural product that is widely used and has valuable importance in nutrition. It contains proteins as well as it is rich in minerals and vitamins.[1] Honey is also rich with natural ingredients such as alkaloid, anthraquinone, flavonoid, and antioxidant.[2] In the medical field, honey proved to have anti-infective proprieties, due to its activity against bacteria, fungi, and virus. It is also used as a remedy for diarrhea, gastric ulcer, immune inducer, hair loss, antitussive, and many other medical conditions.[3] Honey is widely used as antitussive due to its demulcent and indirect peripheral cough suppressant activity. In fact, it forms a protective coating over sensory receptor in the pharynx, preventing the cough reflex from reaching the brain.[4] According to Paul *et al.,* honey maybe a preferable treatment for a cough and sleep difficulty associated with childhood upper respiratory tract infection (URTI) when compared with dextromethorphan and placebo.[5] Moreover, honey plays an important role as a cytoprotective agent against pathological effects of penicillin and streptomycin when it is coadministered with them.[6] Honey has been used in many pharmaceutical formulations due to its many chemical and physical characteristics that made it a very important product in pharmaceutical compounding. Among these uses, honey was used as sweetening and taste masking agent.[7] In addition, the rheological properties and the antiseptic properties of honey were exploited in syrup and suspension making.[8,9]

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Paracetamol (acetaminophen) chemically is N-acetyl-p-aminophenol [Figure 1].[10,11]

Paracetamol is a very common over the counter analgesic and antipyretic agent.[12] It has weak anti-inflammatory activity because it has negligible effect on cyclooxygenase in peripheral tissue.[13] It is well absorbed in the gastrointestinal tract, and its oral bioavailability is about 63-89%.[14] It is classified as category B and is considered the drug of choice in pregnancy as analgesic and antipyretic.[15]

It is produced by many pharmaceutical companies in several dosage forms and strengths.[16] It is also found in many cold and cough formulations, and it is a very important choice in case of URTI and cough, pain, and hyperthermia.

Several studies were conducted to determine the benefits of honey in pharmaceutical formulations. One of these studies was designed to determine the protective effect of sundarban honey against acetaminophen-induced hepatonephrotoxicity. The result indicated that honey protects against paracetamol-induced hepatic and renal damage, which could be attributed to the honey's antioxidant properties.[17] Another study was conducted to compare honey with dextromethorphan, diphenhydramine, and placebo in relief of cough. It was found that honey might be better than placebo when used as a cough suppressant. Furthermore, honey has similar effect compared to dextromethorphan.[18]

To the best of our knowledge, there are no published studies about using honey as vehicle in oral solutions in pharmaceutical dosage forms. Accordingly, this study aims to formulate and evaluate the stability of paracetamol-honey based syrups using different sources of honey.

MATERIALS, INSTRUMENTS, AND METHODS

Materials

Paracetamol was purchased from Sun Pharma Ltd. (Nablus, Palestine) as pure powder; four types of honey were used in this study. Four identical honey-based syrups were prepared based on the source of honey. These syrups were coded as: F1, F2, F3, and F4. The honey used in F1 was bought from a farm in, Ramallah district, whereas the other two types were bought from farms in Nablus district, Palestine, whereas F4 was purchased from Salamanca, Spain. Propylene glycol was purchased from MP (Milan Panic) Biomedicals (Santa Ana, California). Alcohol USP was purchased from Sun Pharma Ltd. (Nablus, Palestine). Deionized water was obtained from the lab using local column deionizer. NaOH pellets were purchased from GADOT (Israel), which used in preparing NaOH 0.01M solution by mixing 0.4 g of NaOH pellets with 1 L purified water (USP Pharmacopeia, 2007). Nutrient agar was bought from Mast Group Ltd. (UK).

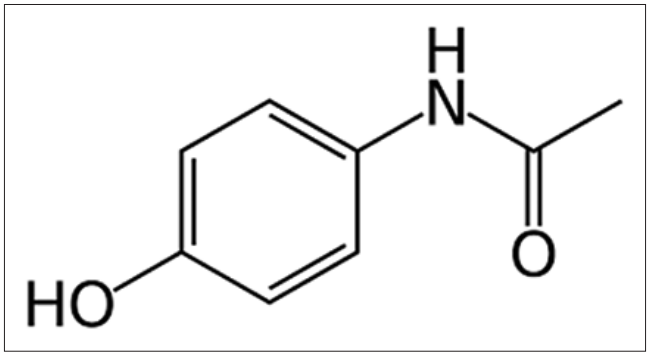

Figure 1: Chemical structure of paracetamol

Instruments

The spectrophotometer (Bibby Scientific Ltd., UK) was used to assess the amount of paracetamol in the compounded syrups. pH meter (Bibby Scientific Ltd., UK) was also used to determine the pH value of the syrups. Oven (Arilevy, Israel) was used to store the formulated syrups at 40°C. Hotplate (Daihan Labtech Co., Ltd., India) was used in this experiment during the formulation of syrups.

Methods

Compounding of paracetamol-honey based syrups

A suitable formula was chosen to produce paracetamol syrup using honey as a vehicle, sweetening, and flavoring agent.

Four syrups were prepared using the same components except for the source of honey [Table 1].

The formulations were prepared according to the following procedure:

1. Paracetamol powder (2.5 g) F was suspended using 15 ml propylene glycol and 7 ml alcohol
2. The mixture was heated at moderate temperature until complete dissolution of paracetamol
3. Water (7 ml) was added to the paracetamol mixture and mixed gently until a clear mixture was obtained
4. Honey was added up to 100 ml volume
5. Syrups were filled in amber glass bottles.

After preparing the syrups, the formulations were coded according to the sources of honey as F1, F2, F3, and F4, and bottles of each syrup were stored at two different temperatures 25°C and 40°C to assess their stability.

Analytical method

The percentage assay of paracetamol in each bottle was assessed periodically using the ultraviolet spectrophotometer

validated analytical method.[19] An exact amount (3 ml) of each syrup, equivalent to 75 mg of paracetamol, was transferred into 100 ml volumetric flask. Then, diluents of 0.01M NaOH (70 ml) were added to the transferred paracetamol and were mixed for 15 min. The solution was completed to exactly 100 ml by the diluents and was mixed well. This solution was then diluted to 100 times using the same solvent. The absorbance of the final solution was measured by the spectrophotometer at 257 nm. The amount of paracetamol was calculated. The pH of each syrup was measured using pH meter at zero time until the end of the study.

Microbial contamination test

The culture media were prepared by dissolving 28 g of nutrient agar dehydrated powder in 1 L of distilled water. The prepared suspension was heated until boiling and keeping vigorous mixing. The solution was placed in the autoclave at 125°C for 15 min. After sterilization, the solution was poured in sterilized Petri dishes. Then, the Petri dishes were placed in the refrigerator for 24 h. After that, 0.1 ml of a sample of each syrup was placed on Petri dish and placed in the incubator at 37°C for 48 h to examine the presence of *Escherichia coli*, aerobic bacteria or yeast, and molds.[20,21]

RESULTS

The visual examination of the prepared syrups revealed no change in the color or smell until the end of the period of stability study for each formula. There were also no signs of precipitation in all the formulated syrups. The initial pH of F1, F2, F3, and F4 were 3.4, 3.5, 3.49, and 4.1 respectively; this pH remained unchanged during the period of the study except for F3, which showed an increase in the pH value. F4 showed the best stability results, in fact, it was stable for 4 months since % of paracetamol in the syrup remained higher than 90% of the initial value. The assay results of the paracetamol for formula F1 and F2 remained stable for 1 month and 2 months, respectively, when stored at 25°C, meanwhile at 40°C both F1 and F2 remained stable only for 1 month. However, F3 was unstable form the first month in both conditions, and thus, no stability study terminated at both storage conditions. The detailed results of percentage assay conducted for the four syrup formulas stored at 25°C and 40°C and are illustrated in Tables 2 and 3, respectively.

The results of the microbial contamination test for formulas (F1, F2, and F4) showed that they were free from contamination and complied with the European Pharmacopeia specification. The results showed that F3 was contaminated and thus failed the microbial test [Table 4].

Table 1: Formulation of the paracetamol-honey based syrups

Ingredient	F1	F2	F3	F4
Paracetamol (g)	2.5	2.5	2.5	2.5
Propylene glycol (g)	15	15	15	15
Alcohol (ml)	7	7	7	7
Water (ml)	7	7	7	7
Honey* (ml)	Up to 100	Up to 100	Up to 100	Up to 100

*F1-Honey was obtained from Ramallah, Palestine. F2 and F3-Honey were bought from Nablus, Palestine. F4-Honey was imported from Salamanca, Spain

Table 2: Percentage of paracetamol concentration at 25°C

Testing time (month)	F1	F2	F3	F4
Zero time	100±0.686	100±0.438	100±0.22	100±0.12
1	91.76±0.467	97.55±0.095	87±032	100±0.23
2	*	97.52±0.680	[a]	100±0.11
3	*	91.2±0.80	*	*
4	*	*	*	95.85±0.23

*The test was stopped, [a]The test was not performed at this time

Table 3: Percentage of paracetamol concentration at 40°C

Testing time (month)	F1	F2	F4
Zero time	100±0.686	100±0.438	100±0.1
1	90±0.912	93.23±2.305	99±0.34
2	*	*	[a]
3	*	*	[a]
4	*	*	93.6±0.12

*The test was stopped, [a]The test was not performed at this time

Table 4: Microbial contamination of paracetamol-honey based syrup

Formula	Results CFU/ml		
	E. coli	Total anaerobic bacteria	Yeast and molds
F1	Absent	30	1
F2	Absent	20	Absent
F3	Present	$<10^2$	<10
F4	Absent	Absent	Absent

E. coli: Escherichia coli

DISCUSION

The use of honey in the pharmaceutical formulation is widely growing due to the great benefits of honey as a flavoring agent, viscosity modifier, and its nutritional value. In fact, there are several pharmaceutical dosage forms in pharmacy containing honey such as lozenges, creams, and syrups. Moreover, honey works as hepatoprotective agent against paracetamol-induced liver damage.[22] In this contest, preparing paracetamol-honey based syrup can help in case of paracetamol overdose. Honey also was evaluated for its antitussive properties. According to Paul *et al.*, honey maybe a preferable treatment for the cough and sleep difficulty associated with childhood URTI when compared with dextromethorphan and placebo.[5] To the best of our knowledge, a pharmaceutical dosage form that contains paracetamol in a syrup vehicle is not available on the pharmaceutical market. Accordingly, we believe that this kind of novel formulation could be beneficial in the pediatric field, especially in case of mild cough associated with fever. Therefore, we decided to prepare this novel paracetamol-honey based syrup. The prepared formulations should be assessed for their organoleptic properties since they play a determinant role in patient's compliance; even though, the change in this parameter does not mean that the active ingredient is unstable because these properties could also change due to excipients incompatibility. Therefore, all formulated syrups were routinely examined for their appearance. No signs of change in color, smell, or precipitation were observed in any of the formulated syrups during the period of this study except for F3, which showed a change in organoleptic properties after one month of storing in both storage conditions. The pH is a very important parameter for chemical stability of liquid formulations. pHs were assessed for the obtained syrups and found to be unchanged during the study except for F3 that showed the worst stability. Regarding the stability assay of paracetamol in the prepared syrups which was stored at room temperature and accelerated conditions; F4 showed the best stability at both conditions, paradoxically, F3 showed the worst stability. In fact, the quality and source of the used honey played a key role in the stability of paracetamol since the content of honey depends on the source or place of nutrition of bees. In addition, F3 was the cheapest one, and this may suggest poor quality or being adulterated. In fact, the microbial contamination results of F3 showed signs of contamination when compared to other formulas (F1, F2, and F4).

The obtained results of this study suggest that paracetamol-honey based syrup is difficult to be produced in large scale since it showed limited chemical stability as reported previously. However, manufacturers, who are eager to produce this product, should perform more studies to find the best source of honey that gives acceptable stability results that permit to commercialize it industrially. Moreover, community pharmacists could benefit from F4 formulation to produce this kind of syrup, especially as personalized formulation for parents who are eager to offer special products that have nutritional value and hepatic protection action against paracetamol overdosing. However, pharmacists should aware of recommending this kind of formulation for children under 1 year of age because of infant botulism bacterial spores that affect baby's nerves and muscle.[23]

CONCLUSION

In this study, paracetamol-honey based syrup was successfully prepared. F4 showed the highest chemical stability, whereas F3 was the worst. In general, paracetamol stability was limited and accordingly cannot be prepared in large scale formulations. Furthermore, the study showed that stability of the honey-based syrup is highly dependent on the quality of honey used. Pharmacist as well as pharmaceutical industry could benefit from F4 formulation to produce this kind of syrup to achieve an antitussive formulation with antipyretic activity and nutritional value. Moreover, the presence of honey could counteract the paracetamol-induced hepatotoxicity.

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