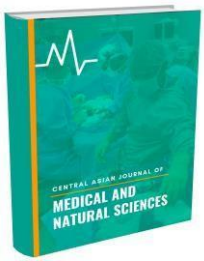

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Article

Evaluation Of Physicochemical Properties Of Cefdinir In Different Storage Conditions

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Abstract: Cefdinir is an antibiotic that belongs to the cephalosporin class of drugs. It is used to treat various bacterial infections such as pneumonia, acute bacterial exacerbations of chronic bronchitis, pharyngitis/tonsillitis, acute bacterial otitis media, and uncomplicated skin and skin-structure infections in both adults and children. It is available in the form of capsules and suspension and is sold under the brand name Sefarin®. The article aims to investigate changes in the physical properties of an oral Sefarin® suspension and analyzes the concentration of drug release, antimicrobial activity, and viscosity of samples after exposure to different temperatures in vitro. Three samples of oral (Sefarin®) suspension were reconstituted with distilled water and then stored under three different temperatures (at room temperature (25°C), in sunlight (45°C), and in a refrigerator (6°C)) for different periods. Three samples were analyzed after being stored in different conditions. The physical properties changed over time. Additionally, the percent concentration of a drug release decreased and there was a noted change in viscosity of the suspension and antimicrobial activity over time when stored at varying temperatures. In this study, we chose Sefarin ® suspension as an antibiotic to treat bacterial infections. We aimed to investigate the effect of different temperature conditions and storage periods on the concentration of drug release, antimicrobial activity, and viscosity of the dosage form. We observed that with an increase in temperature and time, the suspension lost a part of its activity and the dosage form viscosity decreased.

Keywords: Storage, Antibiotic susceptibility, Dissolution

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1. Introduction

Oral liquid dosage forms are liquid medications that are uniform in consistency. They can exist in different forms such as solutions, emulsions, and suspensions, and are composed of one or more active ingredients in a liquid base that is suitable for consumption[1]. Other substances may also be added to these medications, such as solubilizing agents, emulsifiers, stabilizers, suspending agents, thickening agents, and antimicrobial agents[2].

A pharmaceutical suspension is a mixture of insoluble solid particles within a liquid or semisolid vehicle[3]. These solid particles have a specific range of size and are prepared as dry powders that require reconstitution with a specified amount of vehicle before use. The main reason for producing suspensions is to ensure the stability of the medication. [11, 12]

The size of the particles in a dispersed phase is crucial and varies depending on the dosage form. For instance, the particle size in a suspension used for the ophthalmic

cavity should not exceed 10μ, while for an injectable suspension, the particle size should be small enough to pass through the needle of a syringe with ease. [13].

In the formulation of elegant pharmaceutical suspension, the particle size, thinking agent, suspending agent, and wetting agent are crucial factors to consider [14]. Water is the primary source of microbial contamination, making all medicinal products containing water susceptible to bacterial growth. Microbial and fungal sources may also come from naturally occurring additives[4]. The preservative activity may decrease due to its adsorption onto solid drug particles or its interaction with suspending agents. [15].

If a liquid preparation has a limited shelf life due to chemical or physical instability, suspensions can be made from dry powders or granules. The dry powder should be added to purified water and shaken until fully suspended[5]. For internal use, suspensions should be packed in plain amber bottles, while ribbed bottles should be used for external use. [16]

Antibiotics are drugs that destroy or inhibit the growth of bacteria. They are available for pediatric use as dry powders that can be reconstituted into oral suspensions. It is important to refrigerate the oral suspensions to preserve their potency and deliver optimal benefits to the patient. Stability testing is crucial for drug products as it provides information on how the quality of a drug substance varies with time[6].

This testing is influenced by different factors such as temperature, humidity, and light. In Iraq, antibiotics are the most commonly consumed drugs by patients at home. This study focuses on antibiotic suspensions as they require special storage conditions. [17].

Cefdinir is a third-generation cephalosporin that is semisynthetic and has a broad spectrum of activity against Gram-positive and Gram-negative bacteria. It is known for its potent antimicrobial activity and excellent therapeutic action, making it a favorable choice compared to other antimicrobial agents. Cefdinir is classified as BCS Class IV due to its low solubility and permeability[7]

[28,29]

Currently, it is available in two dosage forms - capsules and suspension forms. However, due to its crystalline nature, it is difficult to formulate it into tablet dosage forms. ([20]

A calibration curve was created for a drug by preparing buffer solutions according to the United States Pharmacopoeia monographs. To create 0.1 N hydrochloric acid (HCL), HCL was added to a sufficient amount of distilled water to produce 1000 ml. The concentration of the material was read using a UV spectrophotometric method using the Shimadzu 1650 pc, Japan, after serial dilution in HCL. Cefdinir was prepared by appropriately diluting the standard stock solution and scanning it in spectrum mode from 400 nm to 200 nm[8].

The purpose of this study is to investigate the efficacy of the drug and its antibacterial effect at different storage temperatures for varying lengths of time to ensure stability after reconstitution.

2. Materials and Methods

Cefdinir powder was supplied by Hubei Widely Chemical Technology Co., Ltd. Cefdinir suspension, known as Sefarin®, is available as dry powders for reconstitution, containing 125mg/5ml and was purchased from a registered pharmacy. It was manufactured by Pharma International Company in Amman, Jordan. Ethanol 70% and sodium chloride 0.9% w/v were purchased from Iora Lifecare in India, while HCL, Muller Hinton agar, and Nutrient agar were purchased from Hi Media in India. The clinical isolates of Staphylococcus aureus, Proteus mirabilis, and Streptococcus pyogenes are multi-drug resistant and were supplied by a local hospital in Baghdad, Iraq[9].

Equipment

UV-visible spectrophotometer (UV-1800, 240V, Japan), dissolution apparatus (Vanguard, USA), viscometer (Brookfield, LVDVE, USA), digital viscometer, Japan, and autoclave (Hamburg, Germany)[10].

Method

Preparation of calibration curve

A calibration curve was created for a drug by preparing buffer solutions according to the United States Pharmacopoeia monographs. To create 0.1 N hydrochloric acid (HCL), HCL was added "Add enough distilled water to reach 1000 ml. The concentration of the material was read using a UV spectrophotometric method using the Shimadzu 1650 pc, Japan, after serial dilution in HCL. Cefdinir was prepared by appropriately diluting the standard stock solution and then scanning it in spectrum mode from 400 nm to 200 nm[11].

Preparation of sample

Three samples of oral Cefdinir suspension (Sefarin)® (125mg/5ml) were freshly reconstituted with distilled water and then stored under three different stress conditions - at room temperature (25°C), in sunlight (45°C), and in a refrigerator (6°C). Samples of the suspension were taken at four different intervals (zero time, 3 days, 10 days, and 3 months). These samples were then analyzed for their physical properties (such as odor and color), the amount of drug release using a dissolution apparatus, the drug viscosity using a viscometer, and the antibacterial properties using Muller Hinton Agar.

Characterization of the sample

The samples are analyzed for physical properties (visual odor, color)[12].

Dissolution study

A dissolution study was conducted using the USP dissolution apparatus type II. In this study, 5 ml of a suspension was placed in a dissolution vessel filled with 900 ml of 0.1 N hydrochloric acid (HCl) and stirred at a speed of 50 rpm. The method was carried out at 37°C as per the standards of the British Pharmacopoeia. The suspension was stirred for 10 minutes, after which 5 ml of the sample was withdrawn using a syringe. The same volume of the dissolution medium was added to the vessel after each withdrawal[13].
Each sample was then measured and transferred into a clean cuvette. After dilution, each sample was assayed spectrophotometrically at 281 nm to determine the cefdinir content. This process was repeated for each stored sample at different time intervals[14].

Antibiotic susceptibility

Bacterial isolates (Staphylococcus aureus, Streptococcus pyogenes, and Proteus mirabilis) were spread on Muller Hinton agar to test their susceptibility to cefdinir. A 6 mm pore was made on each plate and 50 microliters of reconstituted cefdinir suspension were inoculated into the pore for each isolate. The plates were then incubated for 24 hours at 37°C. Antibacterial activity was determined by measuring the diameter of the inhibition zone around the pore. An inhibition zone diameter greater than 9 mm was considered effective. The study was conducted on reconstituted suspension samples that had been exposed to different temperatures for different time intervals [22, 23].

Viscosity study

The viscosity (digital viscometer, Brookfield, lvdve, U.S.A) of the stored samples will be measured at the beginning of reconstituting the suspension and three months after it is exposed to different temperatures using a digital rotational viscometer, spindle number 4, and at different RPM[14].

3. Results

Calibration curve

Figure 1 shows the calibration curve for cefdinir in 0.1 N HCl. The spectrum showed a sharp peak at 281 nm, and the calibration curves of cefdinir at different concentration ranges were recorded at the wavelength of 281 nm. A linear relationship emerged. It is used to calculate the percent drug release in the dissolution studies shown below.

The Effect of Storage Conditions on Physical Properties.

The physical properties of three samples were examined after being stored in different conditions. The results showed that the odor and color of these samples were changed. No change was observed in the physical properties of the sample stored in the refrigerator (6°C) for 3 months compared to the sample stored at a temperature of 45°C. However, a slight change was noted in the smell of the suspension with a clear change in color from pink to light pink for the sample stored at room temperature (25°C). This is shown in Figure 2[15].

The Effect of Storage Conditions on the Dissolution Test.

The results of a home study have shown that the percent concentration of a drug reduced over time when stored in different temperature conditions. The study involved reconstituting a suspension and then monitoring its stability in three simulated storage conditions. The absorbance values were used to determine the drug's concentration at different time intervals.

The storage of cefdinir syrup at three different temperatures revealed that not all three storage conditions maintained the stability of the reconstituted suspension during testing. The refrigerated sample showed stability for the first seven days, whereas the samples kept at room temperature (22-25°C) preserved the suspension for three days before degradation was observed on the seventh day. The samples kept at a temperature of 25-40°C showed the least level of stability, with degradation observed after three days.

Figure 3 shows that the reconstituted samples lost their stability with full degradation after three months. (30)

Antibacterial susceptibility

The antibacterial activity of the suspension has shown varying results among different formulas, with different saving times and conditions. The tests were conducted at room temperature (25°C), in the refrigerator (6°C), and outdoors (45°C). Different inhibition zones were observed with different isolates, which are mentioned below:

1. For Staphylococcus aureus isolate

After zero time, the inhibition zone is measured to be 40 mm. Following three days, the inhibition zone of different suspension formulas was recorded under various storage conditions - room temperature, 6°C (refrigerator), and 45°C (outdoor). The inhibition zone remained the same throughout the experiment. Even after 10 days of different storage conditions, the inhibition zone did not change. It was noticed that the change occurred after being stored for a long period, specifically three months. This result suggests that the active component in the suspension is highly stable and not affected by different environmental conditions.

2. For Proteus Mirabilis isolate

After no time, the inhibition zone for the different samples was 49 mm. However, after 3 days, the inhibition zone decreased to 42 mm for the 3 samples that were stored at room temperature (25°C), in a refrigerator (6°C), and outdoors (45°C). After 10 days of storage, the inhibition zone of the same isolate decreased further to 41 mm. This difference in the inhibition zone can be explained by the isolate's ability to become more resistant to the antibiotic Cephalosporin, and its activity decreases over time.

3. For Streptococcus pyogenes isolate

The following information was gathered from measuring the inhibition zone of various samples under different storage conditions. Initially, the inhibition zone was 52mm. After 3 days, the inhibition zone of samples stored at room temperature, in a refrigerator (at 6oC), and outdoors (at 45oC) decreased to 50mm. After 10 days, samples stored at 25oC and 6oC showed a decrease in the inhibition zone to 40mm, while the outdoor sample remained at 50mm. This discrepancy in results may be attributed to the antibiotic's ability to affect the isolate, which could be due to physical changes in the formula's texture

Viscosity study

It was observed that the viscosity of the suspension is affected by the temperature at which it is stored for an extended period. The higher the temperature, the lower the viscosity of the syrup. Specifically, when the syrup was kept at 45 degrees, the viscosity decreased in comparison to the samples stored in the refrigerator or at room temperature. This difference is illustrated in the figure (4).

4. Discussion

The Effect of Storage Conditions on Physical Properties

We observed that the suspension's color changed from pink to brown, and it emitted a foul smell due to the effects of high temperature. These changes were only noticeable after storing the sample for three months at 45°C. It's important to note that the long storage period at a high temperature caused these changes in the sample.

The Effect of Storage Conditions on the Dissolution Test

Based on the results of the dissolution test, we observed that the concentration of drug release varied with time and was affected by temperature. Initially, when the sample was stored at room temperature and in the refrigerator for the first ten days after being reconstituted, we noticed that the concentration was not affected. However, during this period, we observed an effect on the sample stored at 45°C. The effect of temperature was more pronounced after the sample had been stored for a longer period. The concentration of drug release decreased with longer storage times and at higher temperatures.

Antibacterial susceptibility

1. **For *Staphylococcus aureus* isolate**

   After testing the culture isolate, it was observed that sefarin's antibacterial activity remained unaffected even when stored in a cool, dry place for an extended period.

2. **For *Proteus Mirabilis* isolate**

   After culturing this isolate, we observed a decrease in antibacterial activity, especially when stored at high temperatures.

3. ***For Streptococcus pyogenes* isolate**

   Antibacterial activity decreases at high temperatures when this isolate is stored.

   Viscosity study

   After storing the sample for a long time at different temperatures (25°C and 45°C), we observed a change in suspension viscosity.

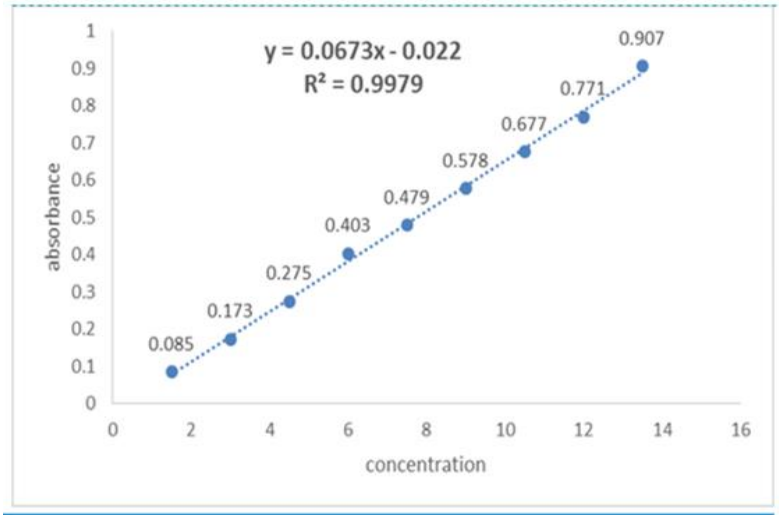

Figure 1. Calibration Curve Of Cefdinir

Figure 2. Shows How The Physical Properties Of A Material Change As The Temperature Changes. The Graph Illustrates The Relationship Between Temperature And These Properties.

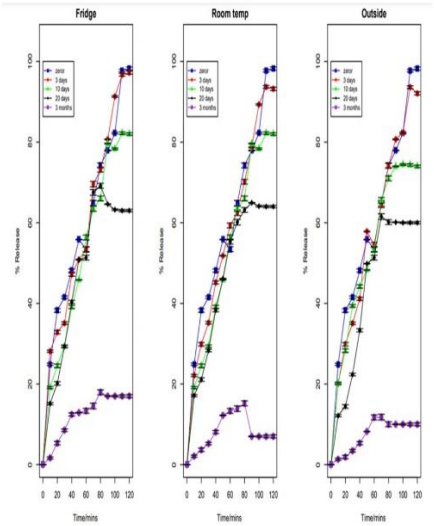

Figure 3. Dissolution Of Sefarin ® Suspension Within 3 Months Under Different Storage Media

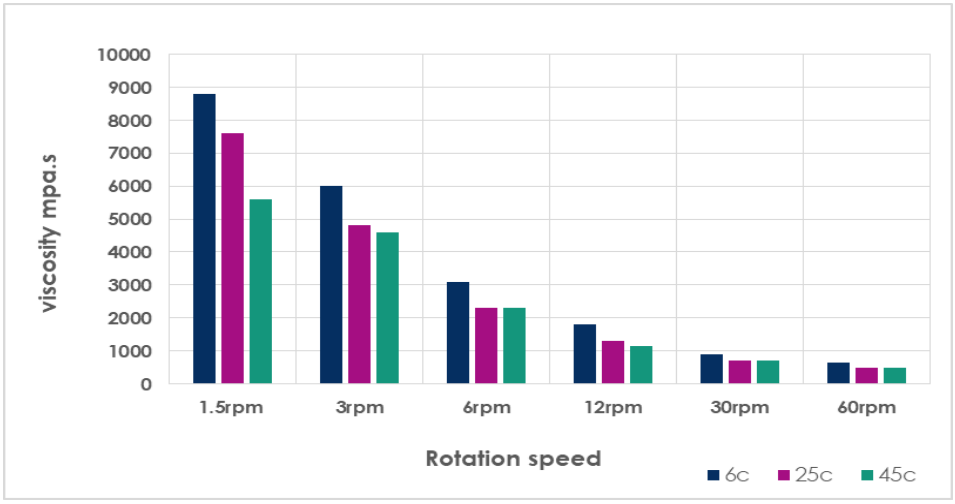

Figure 4. Shows The Viscosity Measurements For Three Samples Stored At Different Temperatures For Three Months.

Table 1. Shows The Inhibition Zones Of Staphylococcus Aureus Isolates With Different Formulas And Saving Times

Saving days	**Formula-type inhibition zone Measured in mm**			
		8ºC Refrigerator	**25ºC** Room temperature	**45ºC** outdoor
	zero time	40		
	3 days	40	40	40
	10 Days	40	40	40
	3 months	36	36	33

Table 2. Shows The Inhibition Zone Of Proteus Mirabilis Isolates With Different Formulas And At Varying Saving Times

Saving days	**Formula-type inhibition zone Measured in mm**			
		6ºC(refrigerator)	**25ºC**(room temperature)	**45ºC**(outdoor)
	zero time	49		
	3 days	42	42	42
	10 Days	41	41	41
	3months	33	34	30

Table 3. Shows The Inhibition Zone Of Streptococcus Pyogenes Isolates With Different Formulas And Saving Times

S a v	**Formula-type inhibition zone Measured in mm**

		6ºC(refrigerator)	25ºC(room temperature)	45ºC(outdoor)
	zero time	52		
	3 days	50	50	50
	10 Days	40	40	50
	3 months	35	30	28

4. Conclusion

Sefarin® is an antibiotic that is commonly used in Iraq to treat bacterial infections in various parts of the body such as the eye, nose, lungs, skin, and urinary tract. It belongs to the class of medicines called cephalosporin antibiotics. However, it has been observed that there is a significant change in its effectiveness if it is not stored in the right conditions. If the patient stores it outside the fridge or at room temperature, it might affect the bioavailability of the drug. Patients must be educated on the proper storage and administration of the drug to ensure it reaches the right site of action and to avoid any physical or chemical changes that may occur to the final product. Moreover, additional instructions should be followed as provided by the drug company to avoid the negative impact of light and moisture on the drug's efficacy.

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