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INFLUENCE OF MILK AND SOME SUDANESE MEALS ON THE DISSOLUTION OF CIPROFLOXACIN TABLETS

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الخلاصة:

ليكون العقار فعالاً، يجب أن يتحرر من شكل الجرعة الصيدلاني و يذوب بالكامل في السوائل المعوية ويكون مستقرًا كمحلول في السوائل المعوية ويعبر موانع الجهاز الهضمي إلى التوزيع المساريقي بدون أن يُؤيَض و يعبر الكبد إلى الجهاز الدوري بدون تغيير ويصل موقع أثره.

الغذاء أحد العوامل التي تتدخل في هذه العمليات و تأثير الأطعمة السودانية سيكون مختلفاً بسبب محتوياتها العالية من الدهون والبروتينات والألياف. هدفت هذه الدراسة لمعرفة أثر اللبن وبعض الأطعمة السودانية (الفول والقراصة بالدمعة والكسرة بالشرموط) على ذوبان حبوب السيبروفلوكساسين وعلى توفره الحيوي.

أخذ العقار في اللبن والأطعمة المذكورة لدراسة أثارها على ذوبانه، وباستعمال جهاز الذوبان الخلاط تم قياس ذوبان العقار ، بوجود الأطعمة كل على حده وذلك بواسطة مقياس طيفي للأشعة فوق البنفسجية والمرئية . وقد أخذت العينات كل خمس دقائق حتى الدقيقة الثلاثين وقورنت النتائج بذوبان العقار في وسط شبيهه بوسط المعدة الفارغة (حامض الهيدروكلوريك 0.1N).

وقد خلصت الدراسة إلى أن ذوبان السيبروفلوكساسين في الأطعمة السودانية المذكورة أقل بكثير من ذوبانه في اللبن – الذي يذكر أثره في تقليل ذوبان العقار في كثير من الدراسات على مستوى العالم- وأتى ترتيب الأطعمة السودانية المستعملة في الدراسة من حيث أثرها في ذوبان العقار الفول فالكسرة ثم القراصة بدءاً بالفول والذي دل على أن الأثر يتناسب طردياً مع مدى لزوجة الطعام .

وباستعمال حجمين مختلفين للفول أثبتت الدراسة أن أثر الطعام السالب في ذوبان السيبروفلوكساسين يحدث حتى لو أخذت الوجبات بكميات بسيطة. أي أن اللبن و الأطعمة السودانية تؤثر أثراً معنوياً على ذوبان عقار السيبروفلوكساسين حبوب وبالتالي وصوله لمكان عمله .

ABSTRACT

For a drug to be effective , it must be released from the dosage form , fully dissolved in the gastro-intestinal fluids , be stable as solution in the gastro-intestinal fluids, pass through the gastrointestinal barriers into the mesenteric circulation without being metabolized , pass through the liver into the systemic circulation unchanged and reach its site of action.

Food is one of the factors which interfere with these processes. The effect of Sudanese meals will be different due to their high contents of fats, proteins and fibers

This study aimed to determine the influence of milk and some Sudanese meals

(Foul –*Vicia faba* - , “Gorrassah with damaa” and “ Kissraa with sharmoot”)on the dissolution of ciprofloxacin HCl tablets and hence bioavailability.

The influence of milk and the mentioned Sudanese meals on the dissolution of ciprofloxacin was studied using paddle dissolution apparatus. The dissolution of the drug was measured in the presence of each meal individually using U.V - visible spectrophotometer. The samples were taken with 5 minutes intervals up to 30minutes The results obtained were compared to the results of the dissolution of this drug in simulated gastric fluid in fast state [0.1 N HCl].

The study revealed that the dissolution of ciprofloxacin in Sudanese meals is lower than its dissolution in milk- whose reduction of dissolution of ciprofloxacin was mentioned in a lot of studies world-wide. The order of the influence of Sudanese meals, used in the study, was foul

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followed by kissraa then gorrasah which showed that the influence was directly proportional to the viscosity of the meal. Using two different volumes of fowl, the study revealed that influence of meals on the dissolution of ciprofloxacin was significant even small amounts were used.

Key words

Ciprofloxacin, Dissolution, Sudanese meals.

INTRODUCTION

For a drug to be effective, enough amount of the dose needs to reach its site (s) of action and stays there long enough to be able to exert its pharmacological effect. This depends upon the route of administration, the form in which it is administered and the rate at which it is delivered (1).

Therefore, for a drug which is administered orally to be completely bioavailable, the entire dose must move from the dosage form to the systemic circulation (2). Any factor which adversely affects either the release of the drug from the dosage form, its dissolution into gastric fluids, its permeation through and stability in the gastrointestinal barrier or its in the hepatic portal circulation will influence the bioavailability exhibited by that drug from the administered dosage form in which it was administered (1).

Many factors have been found to influence the rate and extent of absorption, hence the time course of a drug in plasma and therefore at its site (s) of action and one of these factors is the presence of food.

Dissolution rate is a critical step in the performance of a drug as well as the dosage form, because absorption and hence, bioavailability of the drug depends on the dissolved state of the drug. This step has been found to be affected by food(3).

The Sudanese meals and drinks are different from those of the others, world wide, due to their high contents of fibers, proteins and carbohydrates which may markedly influence the effectiveness of drugs.

Many studies have been done in these respects. It was found that there is a significant reduction in chloroquine bioavailability following co-administration with the Sudanese beverages Aradaib, Karkadi and Lemon (4).

The comparison of glycaemic and insulin responses to six traditional Sudanese meals show differences of clinical importance, and could form a basis for dietary advice to diabetic subjects in Sudan and countries sharing similar food traditions (5).

Ciprofloxacin hydrochloride is a synthetic broad spectrum antimicrobial agent for oral administration. Ciprofloxacin hydrochloride, USP, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1-cyclopropyl-6 fluoro-1, 4-dihydro-4-oxo-7(1-piperazinyl)-3-quinolinecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8 (6).

Its empirical formula is **C₁₇ H₁₈ FN₃ O₃.HCl.H₂ O**.

Ciprofloxacin is the commonly used drug in treating enteric fever and urinary tract infections in Sudan, both have high incidence in the country.

The dose regimen of ciprofloxacin, which is twice a day, leads patients to take it after breakfast and supper, OR, after the morning and evening tea.

The objective of this study is to determine the influence of milk and some Sudanese meals on the dissolution of ciprofloxacin HCl tablets.

Materials and Methods

Materials:Ciprofloxacin hydrochloride powder was supplied by Amipharma Pharmaceutical

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laboratory, BN. CPH/1602011, MFD. 2/2006, and Exp. 2/2011.

Amiciprox tablets (Ciprofloxacin hydrochloride 500mg), BN. TFX-58, MFD. 8/2006, and Exp. 8/2008, Amipharma Pharmaceutical laboratories, Sudan.

Hydrochloric acid 35-38% , LOBA chemic, India. **Equipment:**Digital tablet dissolution test apparatus model DA. 6D USP standards, Veego scientific Devices, Mubai, India. Electronic balance (readability = 0.0001gm) model AR 2140, Adventurer, OHAUS, USA. U.V. visible spectrophotometer, Genway 6305 England.

Double bed deionizer, Aquoion, TBD, India. Filter papers (0.1mm), GEM.

Food – Mixer, Molinex, France. The Sudanese meals used are: 'Foul meal' *Vicia faba* (Fava bean, bread, salt cumin and sesame oil).

'Gorrassah by Damaah:- (baked corn flour and yeast with lamb meat curry).

'kissrah by molah sharmoot' – (Sorghum baked sheath with spicy beef meat curry).

Methods:The methods were adopted as stated in: the Laboratory Manual of Physical Pharmaceutics (3), the Science of Dosage Form Design (2), the FDA guidance for industry (7), and the British Pharmacopoeia (6).

Preparation of 0.1N Hydrochloric Acid (6):

Eight hundreds and fifty ml of deionized water were measured and transferred into a 1000 ml volumetric flask. 8.5 ml of concentrated hydrochloric acid were added slowly to the water and shaken. Finally the volume was completed to the mark to get the 0.1N hydrochloric acid.

Standard plot for ciprofloxacin hydrochloride (3)

Preparation of Ciprofloxacin HCl Stock solution (1mg/ml)

One hundred mg of ciprofloxacin HCl were weighed accurately and transferred into a 100 ml volumetric flask, 0.1N HCl was added and shaken thoroughly to dissolve the ciprofloxacin HCl , finally the volume was made up to 100 ml.

A series of five dilute solutions, with the concentrations 2, 3, 4, 5 and 6 µg/ml were prepared from the stock solution prepared.

The absorbencies of the solutions were determined using UV–visible spectrophotometer at 276 nm and reported. The absorbencies were measured for each concentration in triplicate and the means were obtained. The data of absorbencies versus concentrations were plotted using excel work sheet.

Linearity was detected by both correlation coefficient and visual inspection of the calibration curve.

The dissolution rate studies:

As described in (2,3&7)

Nine hundred ml of 0.1N HCl were measured and transferred into the dissolution flask (OR 900ml pure water OR milk OR 900ml of the meal and HCl as described in

table 1) , the temperature was maintained at $37 \pm 0.5^\circ\text{C}$, the ciprofloxacin HCl tablet was placed at the bottom of the dissolution flask and the paddle was rotated at 50 rpm

Ten ml samples with 5 minutes intervals were withdrawn up to 30 minutes and transferred into beakers appropriately labeled. Immediately 10 ml of 0.1N HCl acid was placed into the dissolution flask.

All the samples were filtered using GEM filter paper , diluted with 0.1N HCl acid to suitable dilutions to help in reading the absorbencies since Beers Lambert law (absorbencies are directly proportional to concentration) is applied in very dilute solutions , then dilution factors were calculated.

The absorbencies were measured in triplicates using the UV–visible spectrophotometer at 276 nm

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and the means were recorded.

Calculations and graphs

The concentration of ciprofloxacin HCl dissolved at specified times were calculated using the slope obtained from the standard plot.

RESULTS AND DISCUSSION:

Calibration curve of ciprofloxacin HCl

Calibration curve for ciprofloxacin was constructed using excel work sheet and 0.1N HCl as a solvent. Table (2) Showed the mean absorbencies taken at 276 nm for five concentrations of ciprofloxacin HCl. Linearity was detected by both visual inspection of the curve (Figure 1) and correlation coefficient (Regression 0.996, Intercept 0.012 & Slope 0.1553).

The slope of the calibration curve was used to calculate the concentrations of the drug dissolved at specified times as described in the section of calculations.

Dissolution of ciprofloxacin HCl tablet in different media

Percentage of ciprofloxacin HCl dissolved at different times in different media were shown in Table (3) and the dissolution profile was shown in Figure (2).

In Figure (2), the dissolution of ciprofloxacin HCl tablet was better in water compared to that in HCl (The simulated gastric fluid). This may be partly due to the fact that ciprofloxacin is a salt of quinolone carboxylic acid and the pH of water is higher compared to that of HCl which leads to the increased dissolution of ciprofloxacin since weakly acidic drugs dissolve better in basic medium than acidic one (8).

It was clear that there was a significant influence of the Sudanese food on the dissolution of ciprofloxacin even more than the dissolution of the drug in milk due to complexation with minerals found in milk, which is a well defined food interaction with ciprofloxacin (9).

The complexation in milk seemed to begin after the first 15 min which explained the immediate reduction in the percentage of the drug released at 20 min.

The reduction in dissolution of ciprofloxacin in the used food may also be explained by the viscous environment which resulted from the presence of food. (2).

It seemed from Figure (2) that the order of Sudanese meals regarding viscosity or heaviness was fowl, kissrah and then gorrasah in ascending order.

This order was consistent with the results since the consistency of milk is light compared to that of fowl, then kissrah and gorassah.

Complexation was not excluded in kissrah and gorrasah. The immediate reduction in the percentage released was also noticed with them after 20 min.

But there was no sudden reduction of the drug dissolved in fowl. This can be explained by that kissrah and gorrasah are rich in minerals compared to fowl since they contained tomato and onion.

Dissolution of ciprofloxacin HCl tablet in two volumes of fowl:

The reason for choosing two different volumes of fowl (Table 4) was that sometimes patients used to take drug with a light meal.

But the results (Figure 3) showed that the dissolution was reduced in both volumes. Although the curve of 150 ml volume was regular first, compared to that of 300 ml volume, but finally the results were the same since they overlapped after 25min.

This can be explained by that the viscosity of fowl reduces dissolution even if it is in small amount

Conclusions

Ciprofloxacin is highly affected by the Sudanese meals even higher than by the dietary products,

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therefore it must be administered on empty stomach.

Dissolution of drugs is better in large volume of water.

Food will affect the dissolution of the drug (if it has an effect) even if the food is in small amount.

Recommendations

1-Patients should be advised to take their medications with plenty of water as possible since sufficient water is necessary for drug dissolution.

2-Post-marketing studies on the effect of local meals on the bioavailability of drugs especially new ones must be done continuously.

3-Leaflets should contain information about the effect of food on the drug (if there is any) and it is better to be written in an understandable language or contain drawings which are understandable by patients.

4-Further studies to understand the exact mechanisms for the effect of food on drugs should be done.

5-Pharmacists should play their role in counseling.

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Table 1: The Different Media used in the dissolution tests of ciprofloxacin HCl tablets

| No. of test | Drug used | Medium used |
|-------------|--------------------------|-------------------------|
| 1 | Ciprofloxacin HCl tablet | 900ml (deionzied water) |
| 2 | Ciprofloxacin HCl tablet | 900mg HCl |
| 3 | Ciprofloxacin HCl tablet | 150ml fowl + |

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| | | |
|---|--------------------------|-----------------------------|
| | | 750ml HCl |
| 4 | Ciprofloxacin HCl tablet | 300ml foul + 600ml HCl |
| 5 | Ciprofloxacin HCl tablet | 450 ml milk + 450 ml HCl |
| 6 | Ciprofloxacin HCl tablet | 300 ml kissrah + 600ml HCl |
| 7 | Ciprofloxacin HCl tablet | 300ml gorrassah + 600ml HCl |

Table 2: Calibration curve of ciprofloxacin HCl in 0.1N HCl

| Concentration (µg/ml) | Absorbance |
|-----------------------|------------|
| 2.0 | 0.311 |
| 3.0 | 0.454 |
| 4.0 | 0.583 |
| 5.0 | 0.767 |
| 6.0 | 0.931 |

Table 3: Cumulative percentage of ciprofloxacin HCl tablet dissolved in different media

| Time (min) | Water | HCl | Foul | Milk | Kissrah | Gorrassah |
|------------|-------|-------|-------|-------|---------|-----------|
| 5 | 9.1% | 2.2% | 3.9% | 5.5% | 2.2% | 1.8% |
| 10 | 40.8% | 30.9% | 4.9% | 16.1% | 2.6% | 1.8% |
| 15 | 49.2% | 40.2% | 5.2% | 16.7% | 3.9% | 1.2% |
| 20 | 52.2% | 45.3% | 9.1% | 7.8% | 6.3% | 1.6% |
| 25 | 61.2% | 47.9% | 10.1% | 10.9% | 5.4% | 1.4% |
| 30 | 73.5% | 59.4% | 10.1% | 15.3% | 10.5% | 3.4% |

Table 4: Cumulative percentage of ciprofloxacin HCl tablet dissolved in two different volumes of foul (150ml and 300ml)

| Time (min) | %age of ciprofloxacin In Foul (150ml) | %age of ciprofloxacin In Foul (300ml) |
|------------|---------------------------------------|---------------------------------------|
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| | | |
|----|-------|-------|
| 5 | 1.3% | 3.9% |
| 10 | 5.3% | 4.9% |
| 15 | 8.5% | 5.2% |
| 20 | 9.9% | 9.1% |
| 25 | 9.9% | 10.1% |
| 30 | 10.1% | 10.1% |

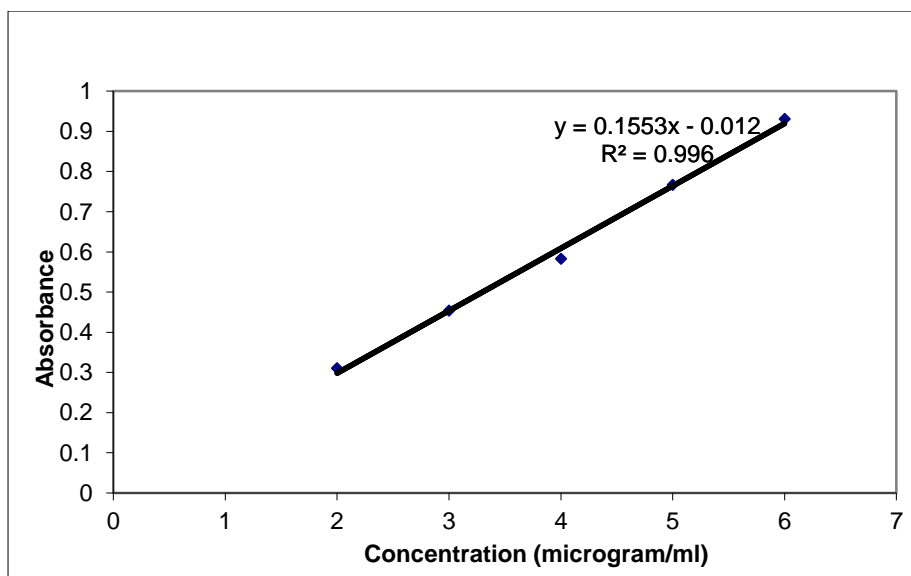


Figure 1 : Calibration Curve of Ciprofloxacin HCl in 0.1N HCl

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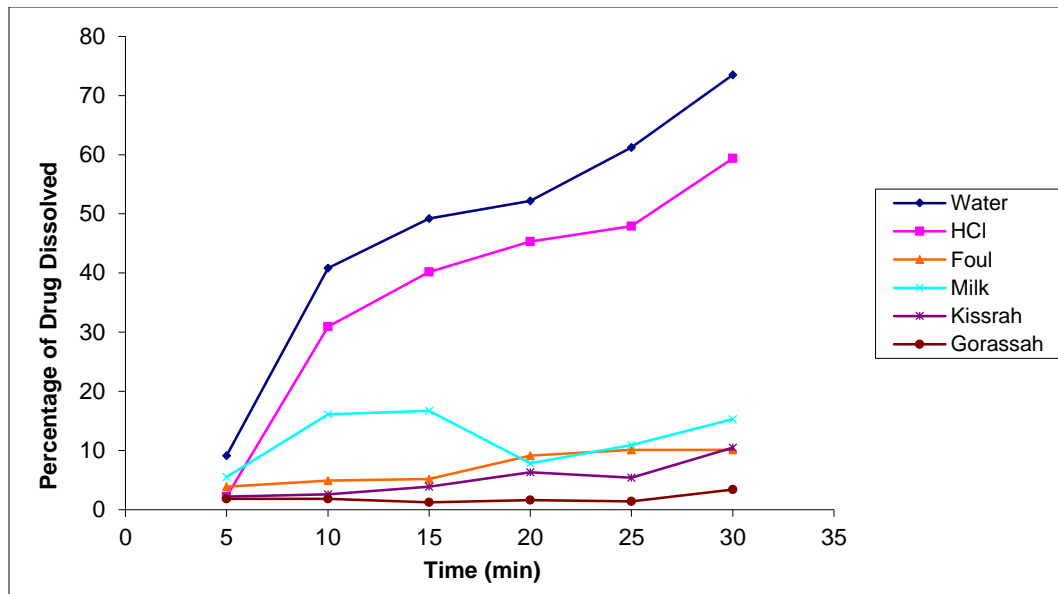


Figure 2: Dissolution Profile of ciprofloxacin HCl tablet in different media

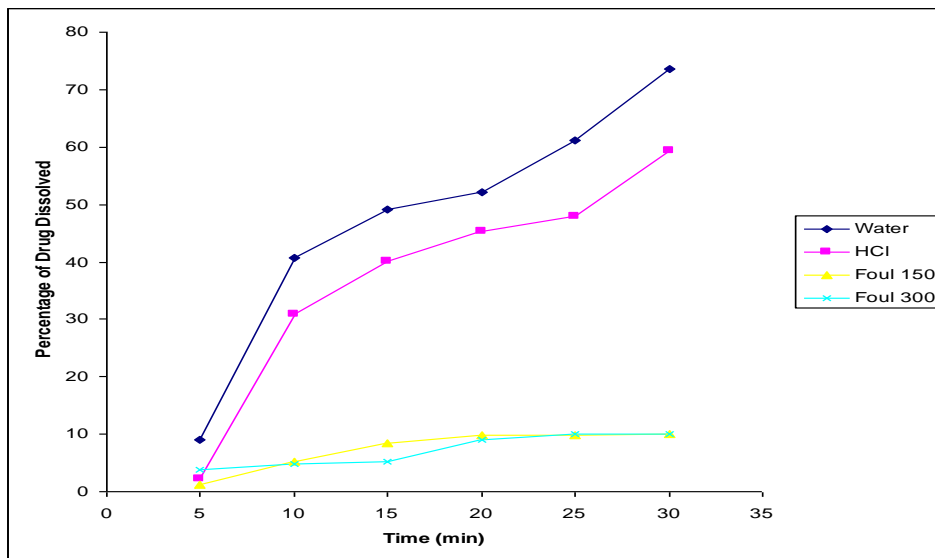


Figure 3 : Dissolution Profile of Ciprofloxacin HCl Tablet in two volumes of Foul (150 and 300 ml)