ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2012; 3(4):764-769

ORIGINAL RESEARCH ARTICLE

A Study on *In Vitro* Interaction of Cephradine with Mango Juice at Lower pH

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Received 04 Mar 2012; Revised 15 July 2012; Accepted 24 July 2012

ABSTRACT

Cephradine is a first generation semi-synthetic cephalosporin antibiotic, is widely used in clinics for its activity against both Gram-positive and Gram-negative bacteria. It is indicated for the treatment of urinary tract infections, skin and skin structure infections, respiratory tract infections and otitis media. Interactions of cephradine with mango juice were investigated by UV-spectrophotometer in simulated gastric juice (pH 1.2&3.2). In this research work, Cephradine capsules were collected from drug shops. The samples were analyzed according to British Pharmacopoeia (BP) method 3. In this work in vitro dissolution studies were carried out in 900ml of acidic buffer (pH 1.2&3.2) in a dissolution tester with a speed of 51 rpm at 37±0.5°C for six hours. The absorbance was measured by using UV - spectrophotometer at a λmax of 254nm. Compare with the absorbance of drug and the drug in presence of mango juice simulated gastric juice (pH 1.2&3.2). The drug release kinetics was also measured. It is observed from the drug release profile that, there is no significant difference in the drug release curve of pH 1.2&3.2.

Key words: Cephradine, UV-spectrophotometer, Dissolution, Mango juice.

INTRODUCTION

Foods and therapeutic products are both used for well defined purposes. In simple terms food provides energy for sustenance, while therapeutic products are taken for managing ailments [2].

However, over the years roles of foods have changed considerably. Now, food no longer is seen as simply the provider of energy, but it is expected to provide physiological benefits for good health and productive lifestyles. Well managed combination of foods and therapeutic products plays important role in the prevention and treatment of many diseases, including a number of chronic diseases such as cancer, diabetes, hypertension, obesity. Most often food is combined with medicine to enhance the benefits of medicine - an additive and/or synergistic effect: food-therapeutic product synergism. At the most basic level, food is a complex mixture of chemicals with many functional groups; hence, they not only confer positive effects, but may also make negative contributions.

Cephradine is in a group of drugs called cephalosporin antibiotics. Cephradine fights bacteria in the body. Cephradine is used to treat infections caused by bacteria, including upper respiratory infections, ear infections, skin infections, and urinary tract infections [6]. Cephradine may also be used for other purposes not listed in this medication guide. Cephradine is the most commonly used antibiotic for prophylaxis in orthopaedic patients as it is safe and effective. We report a case of severe anaphylactic reaction to Cephradine in an elderly patient who had no history of allergic reactions to any drugs until then.

"PRAN" is currently the most well known household name among the millions of people in Bangladesh and abroad also. Since its inception in 1980, PRAN Group has grown up in stature and became the largest fruit and vegetable processor in Bangladesh. It also has the distinction of achieving prestigious certificate like ISO 9001:2000, and being the largest exporter of processed agro products. PRAN is the pioneer in Bangladesh to be involved in contract farming and procures raw material directly from the farmers and processes through state of the art machinery at our several factories into hygienically packed food and drinks products. The brand "PRAN" has established itself in every category of food and beverage industry and can boost a product range

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from Juices, Carbonated Drinks, Confectionery, Snacks, and Spices [4].

Figure 1: Lebac® (Cephradine) Capsule

Figure 2: Mango Juice (Frooto)

MATERIALS AND METHODS

Feature of Cephradine standard

Cephradine (compacted powder)
Potency: 99.14%
LOD- 4 %(NMT)
Origin: China
Collected from: Pharmik Laboratories Ltd.

Reagents used in this work

1. Hydrochloric acid,
2. Sodium hydroxide,
3. Citric acid,
4. Pottasium chloride,
5. Di-sodium hydrogen orthophosphate,
6. Potassium di-hydrogen orthophosphate.

They were all of analytical grade. One brands of cephradine capsule and the innovator brands with labeled contents of 500mg each were obtained from retail pharmacies in Chittagong city. The samples were checked for their production and expiry dates before purchasing.

Instrument Used in this Method

1. Electric balance
2. UV- Spectrophotometer
3. Dissolution Apparatus
4. Thermometer
5. pH Meter

DISSOLUTION RATE DETERMINATION

This was determined using the Pharma Test Dissolution Rate Testing Apparatus (Model D-63512, Hainburg). These studies were conducted at 37 ± 0.5^0C on an USP specification dissolution rate test type II apparatus (Paddle apparatus) with six section assembly according to the USP XXIII procedure with minor modification **(USP XXII and NF XVII, 1995).**

For in vitro dissolution studies simulated gastric medium (pH 1.2 & 3.2) and simulated intestinal medium (pH 6.8) were required.

Preparation of simulated gastric medium (pH 1.2)

1000ml buffer solution with pH 1.2 250 ml of 0.1 M HCl solution was taken in 1000ml beaker and 500ml 0.1M HCl solution were added into the 1000ml beaker. Adjust the pH 1.2 with adding distilled & demineralised water respectively. After adjusting the pH of the buffer solution the buffer solution were taken into1000ml volumetric flask.

Preparation of simulated gastric medium (pH 3.2)

1000ml buffer solution with pH 3.2 250 ml of 0.1 M HCl solution was taken in 1000ml beaker and 500ml 0.1M HCl solution were added into the 1000ml beaker. Adjust the pH 3.2 with adding distilled & demineralised water respectively. After adjusting the pH of the buffer solution the buffer solution were taken into1000ml volumetric flask.

Dissolution study statement

The dissolution study of Cephradine(Lebac®) were investigated firstly in the presence of tap water and then same investigation were performed in the presence of buffer solution pH 1.2 prepared by using both distilled and demineralised water. The dissolution study were investigated in the presence of buffer solution pH 3.2 prepared by using demineralised water.

The dissolution study of Cephradine(Lebac) were investigated in the presence of 250ml mango juice(Pran Frooto) and 650ml of buffer solution pH 1.2. Again dissolution studies of Cephradine (Lebac®) were investigated in the presence of 250ml mango juice 650ml of buffer solution pH 3.2.

Dissolution study description

According to the statement every time two capsules are places in the baskets, where one basket contain the the drug (cephradine capsule form) and another basket contain the drug with mango juice. First time drug was placed in tap water and demineralised water. Here one drug was placed in tap water and another was in demineralised water. Next time a drug was placed in buffer with pH 1.2 and another was in combined solution of 250ml mango juice and 650ml buffer pH 1.2.again a drug was placed in buffer with pH 3.2 and another was in combined solution of 250ml mango juice and 650ml buffer pH 3.2.again. The operation in the acid stages were carried out for 6 hours.Than the dissolution apparatus are switched on and the temperature was 37ºC and the rpm was 51.At every time interval 5ml solution were taken into test tube and the volume adjust by fresh media.The time interval were followings:-

0min, 5min, 10min, 20min, 30min, 45min, 60min, 90min, 135min, 195min, 285,min, 360min (upto 6 hours). From the test tube of each,1ml were taken into 100ml volumetric flask and it is diluted to 100ml with buffer. Than it was filtered, taken into cell and the released drug was assayed by using UV spectrophotometer at 254nm.

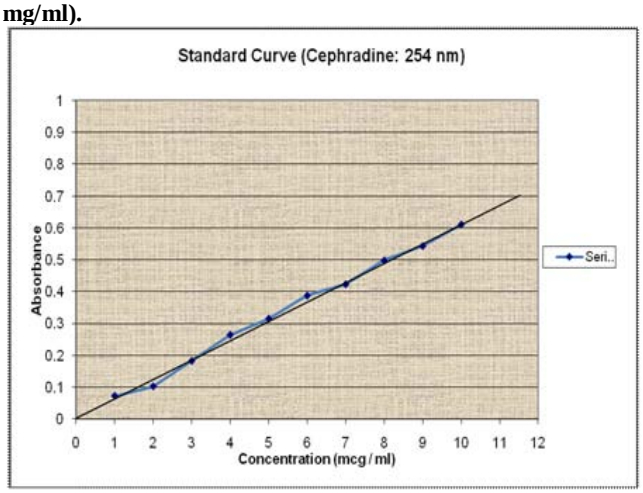
RESULTS AND DISCUSSION

The absorbances of standard Cephradine solution under a concentration range of 1 to 10µg/ml (0.001 to 0.01 mg/ml) where the averages of Concentration / Absorbance were also calculated to determine the release kinetics. Data are shown at **Table 1.**

Table 1: The absorbance's of standard Cephradine solution under a specified concentration

Conc (mg/ml)	Absorbance	Conc/ Absorbance	Average
0.001	0.072	0.013888889	
0.002	0.102	0.019607843	
0.003	0.182	0.016483516	
0.004	0.264	0.015151515	
0.005	0.315	0.015873016	
0.006	0.387	0.015503876	0.021182606
0.007	0.423	0.016548463	
0.008	0.498	0.016064257	
0.009	0.543	0.016574586	
0.01	0.611	0.016366612	

Figure 3: Standard Curve of Cephradine (blue line) represents the measured absorbance were plotted against the respective concentrations of the standard solutions which give a straight line in the concentration range of 1 to 10µg/ml (0.001-0.01 mg/ml).



Dissolution test of Cephradine in presence of juice (250ml) in pH 1.2(650ml)

The dissolution tests of cephradine in presence of juice were conducted & collected the absorbance of the dissolute solution after every 5 minutes. All the respected value are shown at **Table 2**

Table 2: The dissolution tests of cephradine in presence of juice

Time (minutes)	Absorbance	C_t	% release	% Remain	log of % remain
0	0.012	0.0008185	1.4733783	98.52662164	1.993553592
5	0.021	0.0014324	2.5784121	97.42158787	1.988655204
10	0.03	0.0020463	3.6834459	96.3165541	1.983700936
20	0.045	0.0030695	5.5251688	94.47483114	1.975316124
30	0.061	0.00416093	7.48967333	92.51032666	1.966190214
45	0.08	0.00545695	9.8225224	90.17747759	1.955098083
60	0.156	0.0106410	19.153918	80.8460813	1.907658974
90	0.152	0.01036821	18.662792	81.33720742	1.910289258
135	0.112	0.0076397	13.751531	86.24846862	1.935751393
195	0.076	0.0051841	9.3313962	90.66860371	1.957456928
285	0.098	0.0066847	12.032589	87.96741005	1.944321806
360	0.189	0.012892061	23.2057092	76.7942908	1.885328934

Form the table it is found that percent release of the drug is increased up to 90 minutes and then decreased again by time, as well as the concentration of drug in experimental medium. Hence the percent remain and log of percent remain decreased. The graphical representation of rate kinetics are shown at (**Fig 4, 5 & 6)** respectively.

Figure 4: Zero order plot of release kinetics of Cephradine

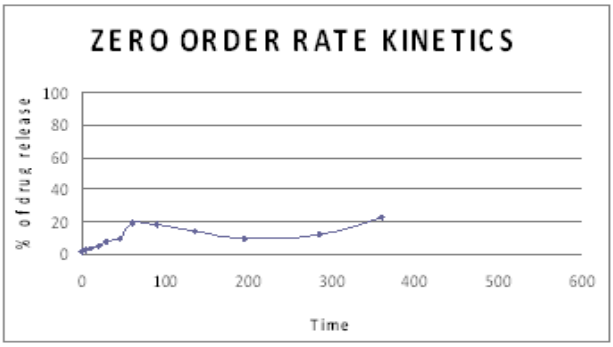
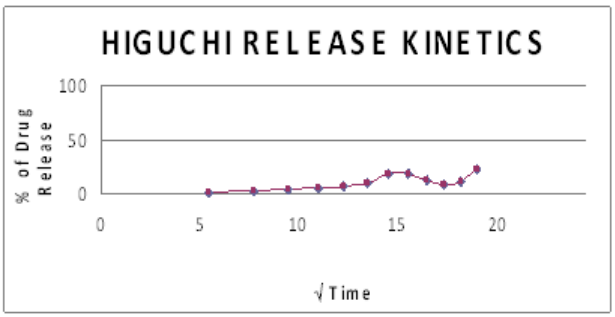


Figure 5: First order plot of release kinetics of Cephradine

Figure 6: Higuchi plot of release kinetics



Release parameters of cephradine capsules in presence of juice(250ml) in pH 1.2(650ml)

Parameters	Zero order	First order	Higuchi
R^2	0.545231637	0.47787719	0.82326676

The R-squared value is highest in case of Higuchi release kinetics

Dissolution test of Cephradine in presence of juice(250ml) in PH 3.2(650ml)

The dissolution test of cephradine in presence of juice was conducted and collects the absorbance of the dissolute solution after every 5 minutes. All the respected value are shown at **Table 3**

Table 3: Dissolution test of Cephradine in presence of juice (250ml) in PH 3.2(650ml)

Time(minutes)	Absorbance	C_t	% release	% Remain	log of % remian
0	0.004	0.00027284	0.491126121	99.50887388	1.997861811
5	0.018	0.00122781	2.210067542	97.78993246	1.990294146
10	0.027	0.0018417	3.315101314	96.68489869	1.985358646
20	0.039	0.00266026	4.788479675	95.21152032	1.9786895
30	0.058	0.00395629	7.121328748	92.87867125	1.967915994
45	0.067	0.00457020	8.226362519	91.77363748	1.962717945
60	0.081	0.00552516	9.945303941	90.05469606	1.954506365
90	0.101	0.00688940	12.40093454	87.59906546	1.942499473
135	0.124	0.00845828	15.22490974	84.77509026	1.928268261
195	0.148	0.0100953	18.17166646	81.82833354	1.912903707
285	0.162	0.01105033	19.89060788	80.10939212	1.903683436
360	0.172	0.01173245	21.11842318	78.88157682	1.896975583

Form the table it is found that percent release of the drug is increased by time, as well as the concentration of drug in experimental medium. Hence the percent remain and log of percent remain decreased.

Figure 7: Zero order plot of release kinetics of Cephradine

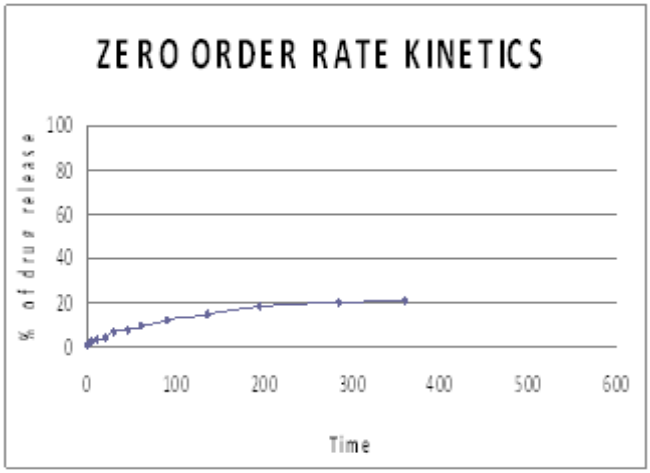


Figure 8: First order plot of release kinetics of Cephradine

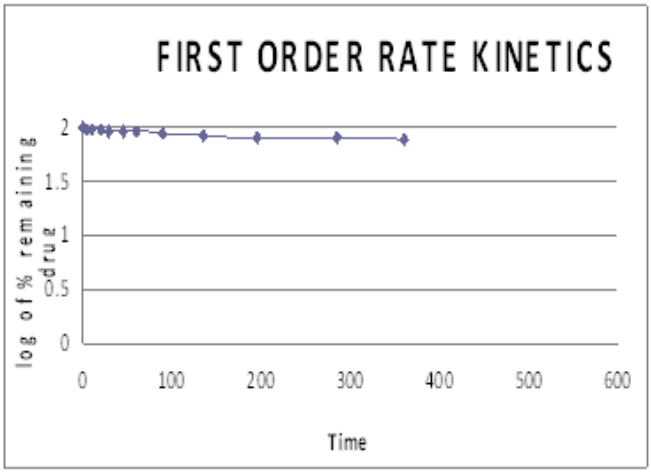
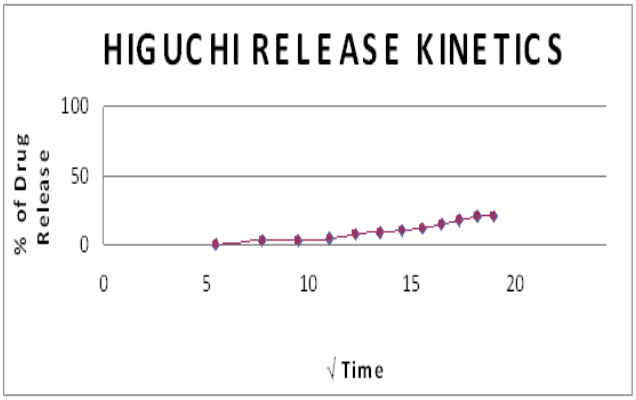


Figure 9: Higuchi plot of release kinetics



Release parameters of Cephradine capsules at in presence of juice(250ml) in PH 3.2(650ml)

Parameters	Zero order	First order	Higuchi
R^2	0.860280793	0.37678758	0.99018821

The R-squared value is highest in case of higuchi release kinetics

Determination of release mechanism from correlation coefficients (R^2):

From the drug release data of cephradine in presence of mango juice were treated in different kinetics orders such as Zero Order Plot, First Order Plot and Higuchi Plot and their correlation coefficients were determined to identify their release mechanism.

Table 4: Correlation coefficients determination data for pH 1.2

Sample	correlation coefficients (R^2)		
	Zero order	First order	Higuchi
Cephradine	0.961991564	0.367350838	0.925652992
Cephradine+ Mango juice	0.545231637	0.477877192	0.82326676

(Table 4) shows that Cephradine in the presence of Mango juice at pH 1.2.Indicates that the Correlation Coefficients is close to 1 in case of Higuchi plot than Zero Order and First Order Kinetics. So Higuchi release kinetics predominates in simulated gastric medium of pH 1.2.

Table 5: Correlation Coefficients determination data for pH 3.2

Sample	correlation coefficients (R^2)		
	Zero order	First order	Higuchi
Cephradine	0.856321083	0.175630601	0.966493533
Cephradine+ Mango juice	0.860280793	0.37678758	0.99018821

(Table 5) shows that Cephradine in the presence of Mango juice in simulated Gastric medium at pH 3.2 indicates that the Correlation Coefficients is close to 1 in case of Higuchi plot that Zero Order and First Order kinetics. Higuchi release kinetics predominates in simulated gastric medium of pH 3.2.

CONCLUSION

The percent release data suggest that, in simulated gastric medium (pH1.2 and 3.2), the percent release of Cephradine not increased significantly. It is also seen that in different pH the percent release neither increased nor decreased when Cephradine is taken with the Mango juice. From the Correlation coefficients determination data it is seen that, Correlation Coefficients (R^2) is close to 1 in case of Higuchi plot. So Higuchi release kinetics predominates in simulated gastric medium of pH 1.2 and 3.2.

It is also observed from the release kinetics profile (Zero order, First order, Higuchi), both lines are close to each other and there is no significant distance between two lines. Both the lines appear in between 0-20 percent of drug release. Hence, we can reveal that, on the basis of our present study if the patients take Cephradine and Mango juice at a time, no harmful effect will occur.

ACKNOWLEDGEMENT

I author grateful to Pharmik Laboratories Ltd. for providing the Standard sample of Cephradine for this research work

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