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IN VITRO RELEASE KINETICS STUDY OF CEPHRADINE ALONE & ALONG WITH MANGO JUICE AT DIFFERENT PH - TRENDS FOR DRUG-NUTRIENT INTERACTIONS

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ABSTRACT
This present study focuses on Drug-Nutrient interactions. 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 (UTIs), skin and skin structure infections, respiratory tract infections and otitis media. Interaction of cephradine with mango juice were investigated by UV-spectrophotometer in simulated gastric & intestinal pH (1.2, 6.8 & 7.2). In this research work, cephradine capsules were collected from drug shops. The samples were analyzed according to British Pharmacopoeia (BP) method. In this work, in vitro dissolution studies were carried out in 900ml of acidic buffer (pH 1.2) and basic buffer (pH 6.8 & 7.2) 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. 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, 6.8, 7.2.

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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. 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. The later effect is of major concerns among the health practitioners and regulatory officials. Cephradine is in a group of drugs called cephalosporin antibiotics. Cephradine fights against 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. 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 from Juices, Carbonated Drinks, Confectionery, Snacks, and Spices.

Figure 1: Lebac® (Cephradine) Capsules

Figure 2: Mango Juice (Frooto)

MATERIALS & METHODS

Feature of Cephradine standard

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

Preparation of dissolution medium

Buffer solution of different pH were prepared and every time the pH were adjusted by pH meter. Simulated gastric medium pH(1.2)-(0.1N HCl), Simulated intestinal medium pH(6.8 & 7.2)-(Phosphate buffer) were prepared.

In Vitro dissolution study of Cephradine alone & in presence of mango juice

This was determined by using the Pharma Test Dissolution Rate Testing Apparatus (Model D-63512, Haiburg). These studies were conducted at 37±0.5^{0}C 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) and simulated intestinal medium (pH 6.8 & 7.2) were required. The dissolution study of Cephradine **(Lebac®)** were in the presence of buffer solution pH 1.2 prepared by using demineralised water. The dissolution study were investigated in the presence of buffer solution with pH 6.8 & 7.2 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 study of Cephradine (Lebac®) were investigated in the presence of 250ml mango juice 650ml of buffer solution pH 6.8 & 7.2. 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. 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 6.8 and another was in combined solution of 250ml mango juice and 650ml buffer pH 7.2 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 spectrophotometer (Shimadzu UV/Vis spectrophotometer 1700, Tokyo, Japan) at 254nm. The amounts of the drug present in the sample were calculated with the help of appropriate calibration curves constructed from reference standard. Drugs dissolved at specified time periods was plotted as percent release versus time (minutes) curve.

Kinetics analysis of release data

In Vitro drug release data were fitted to kinetic models such as zero-order, first-order, Higuchi equation. The correlation co-efficient (R^2) were also determined for the determination of the best fit release kinetics.

Zero-order kinetics

Zero-order (wagner, 1969) as cumulative amount of drug release versus time, **C= K0t**

Where, **K0** is the zero-order rate constant expressed in the units of concentration/time and **t** is the time in hours. A graph of concentration versus time would yield a straight line with a slope equal to **K0** .

First-order kinetics

First-order (Gibaldi and Feldman, 1967; Wagner 1969) as log cumulative percentage of the drug remaining versus time, **Log C= LogC0 – kt /2.303** .

Where,**C0** is the initial concentration of drug, **k** is the first-order rate constant and **t** is the time .

Higuchi Release Kinetics

Higuchi Kinetics (Higuchi, 1963-1964) as cumulative percentages of drug released versus square root of time, **Q= k t½**

Where, **k** is the constant reflecting the design variables of the system and **t** is the time in hours. Hence the drug release rate is proportional to the reciprocal of the square root of time.

RESULTS & 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 average of Concentration / Absorbance were also calculated to determine the release kinetics. Data are shown at **Table 1 .**

Table 1:

Conc. (mg/ml)	Absorbance	Conc. /Absorbance	Average
0.001	0.072	0.0138	
0.002	0.102	0.0196	
0.003	0.182	0.0164	
0.004	0.264	0.0151	
0.005	0.315	0.0158	
0.006	0.387	0.0155	0.0211
0.007	0.423	0.0165	

0.008	0.498	0.0160	
0.009	0.543	0.0165	
0.01	0.611	0.0163	

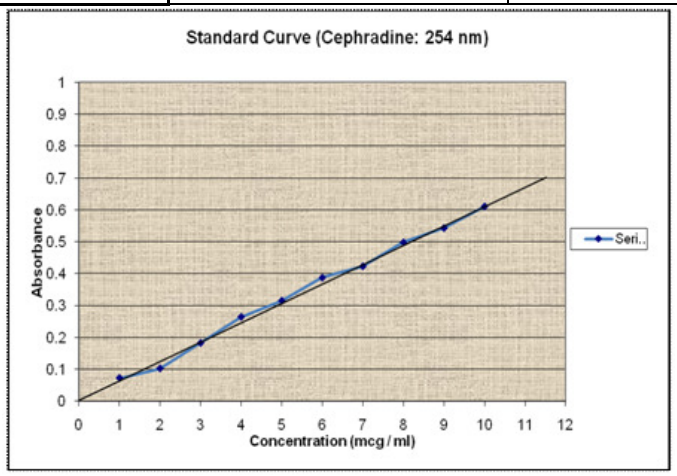


Figure 3 : Standard Curve of Cephradine (blue line) represents the measured absorbance were plotted against the respective concentrations of the standard solutions which give a straight line in the concentration range of 1 to 10µg/ml (0.001-0.01 mg/ml).

Release kinetics evaluation

To investigate the release kinetics of Cephradine alone & Cephradine in presence of Mango juice we performed dissolution study, and from the multiple co-efficient value (R^2) we determined the release mechanism of Cephradine alone & Cephradine in presence of Mango juice. Oral administration of Cephradine & concomitant administration of Cephradine with Mango juice might brings some relative changes in release kinetics of Cephradine. The release kinetics of drug alone & drug in presence of Mango juice shows slight/no significant changes with the change of pH, there are summarized at table 2,3 & figure 4, 5, 6 respectively. It is observed that percent release of the drug is increased up to 90 minutes and than decreased again by time (pH 1.2) . As well as the concentration of drug in experimental medium. Hence the percent remain and log of percent remain decreased. Again, percent release of the drug is increased up to 90 minutes and than increased grossly again by time (pH 6.8 & 7.2). From the comparison study of the % release and log % of drug remaining of Cephradine alone & Cephradine in presence of Mango juice, it is clear that there was no undesirable and objectionable changes occur hence both Cephradine & Mango juice can be taken concomitantly due to less in variation in aspect of release of drug from dosage form at different environment. Finally we can say that, since the % release of Cephradine alone & Cephradine in presence of Mango juice was not significantly changed, which gives us an idea we can take Cephradine & Mango Juice concurrently. There will be no hazardous effect from each other.

Table 2: Comparison of percent of Cephradine (CEP) release alone and in presence of mango juice (Frooto) (M) at different pH

Time(Minutes)	**% of drug release**					
	CEP (pH 1.2)	**CEP+M (pH 1.2)**	**CEP (pH 6.8)**	**CEP+M (pH 6.8)**	**CEP(pH 7.2)**	**CEP+M (pH 7.2)**
0	0.24556	1.47337	1.2350	2.1613	3.2934	3.6022
5	1.96450	2.57841	1.7496	2.4700	3.3963	3.9109

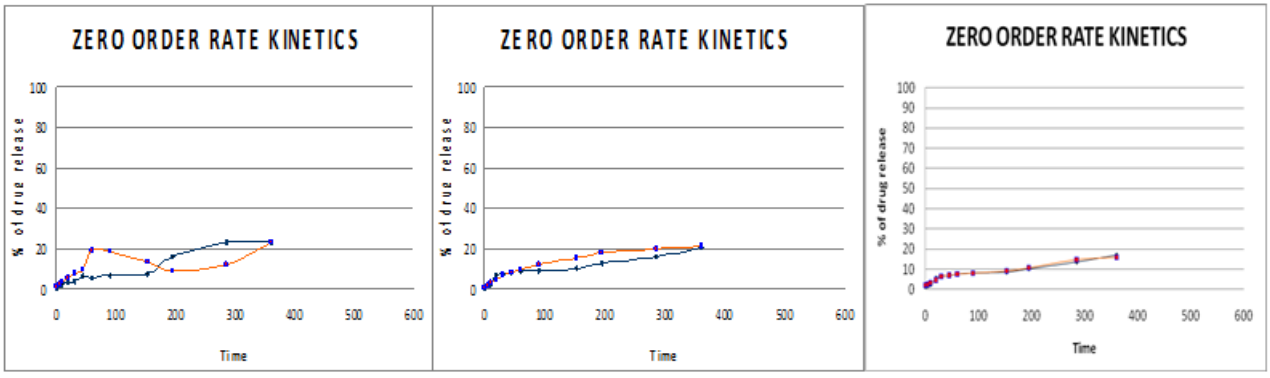
10	2.33284	3.68344	2.3671	3.2934	4.4255	4.4255
20	3.43788	5.52516	5.5577	4.6314	4.7343	4.6314
30	3.80622	7.48967	6.5869	6.5869	5.4548	5.8664
45	6.38463	9.82252	6.7927	6.9986	6.6898	6.5869
60	5.89351	9.1539	7.5132	7.6161	6.8956	6.9986
90	7.24411	18.6627	8.1307	8.1307	7.3073	7.6161
135	7.61245	13.7515	8.5424	9.1599	7.9248	9.1599
195	16.0843	9.33139	10.1891	10.7037	8.6453	9.9833
285	22.9601	12.0325	13.5855	14.7176	13.5855	13.2767
360	23.2057	23.2057	17.0848	15.8497	16.9819	16.7760

CEP= Cephradine ; CEP+M= Cephradine in Mango juice

Table 3: Comparison of log of percent of drug remaining (Cephradine (CEP)) release alone and in presence of mango juice (Frooto) (M) at different pH)

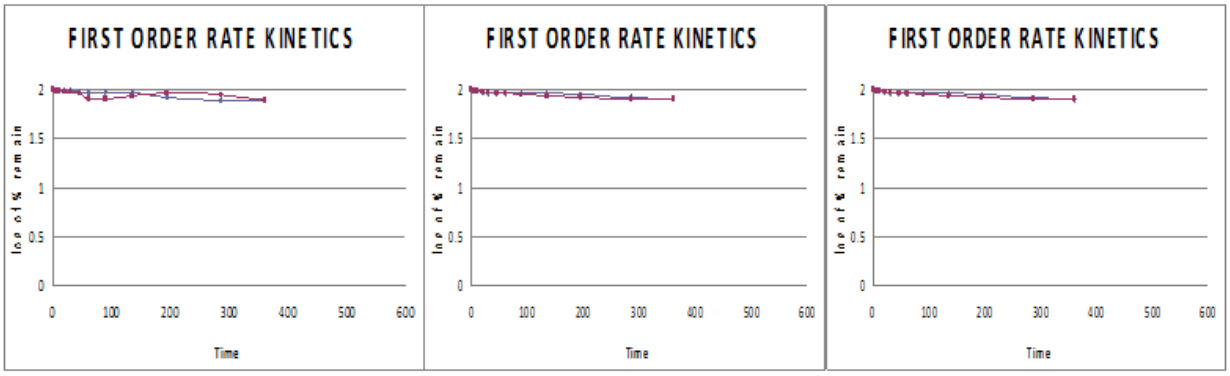
Time(Minutes)	**Log % of drug remaining**					
	CEP (pH 1.2)	**CEP+M (pH 1.2)**	**CEP (pH 6.8)**	**CEP+M(pH6.8)**	**CEP (pH 7.2)**	**CEP+M(pH 7.2)**
0	1.9989	1.9935	1.9946	1.9905	1.9854	1.9840
5	1.9913	1.9886	1.9923	1.9891	1.9849	1.9826
10	1.9897	1.9837	1.9895	1.9854	1.9803	1.9803
20	1.9848	1.9753	1.9751	1.9794	1.9789	1.9794
30	1.9831	1.9661	1.9704	1.9704	1.9756	1.9737
45	1.9713	1.9550	1.9694	1.9684	1.9699	1.9704
60	1.9736	1.9076	1.9660	1.9655	1.9689	1.9684
90	1.9673	1.9102	1.9631	1.9631	1.9670	1.9655
135	1.9656	1.9357	1.9612	1.9582	1.9641	1.9582
195	1.9238	1.9574	1.9533	1.9508	1.9607	1.9543
285	1.8867	1.9443	1.9365	1.9308	1.9365	1.9381
360	1.8853	1.8853	1.9186	1.9250	1.9191	1.9202

CEP= Cephradine ; CEP+M= Cephradine in mango juice



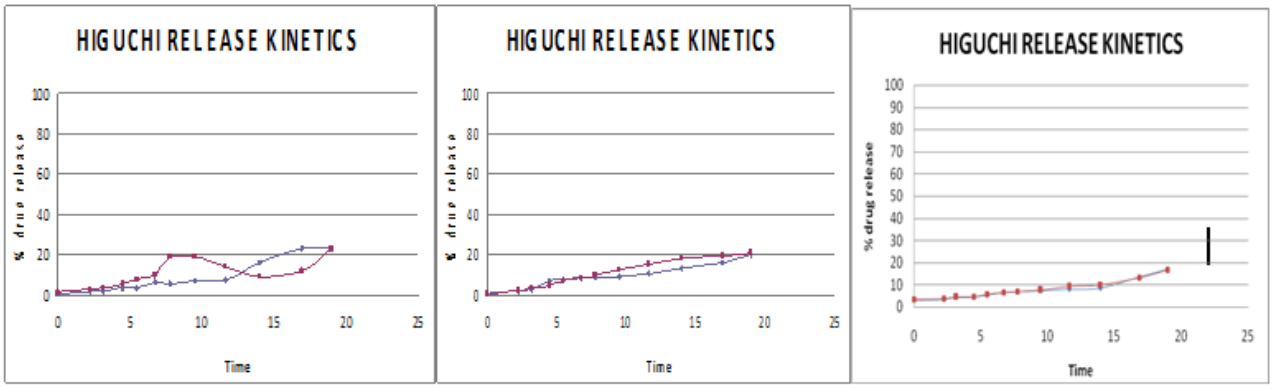
(A) (B) (C)

Figure 4: Zero order rate kinetics profiles of Cephradine alone (blue line) and in presence of Mango Juice (red line) at pH-1.2 (A), pH-6.8, (B) and pH-7.2 (C). Here the blue line appears below the red line. Thus the percent release of Cephradine in presence of Mango Juice is slightly more at different pH



(A) (B) (C)

Figure 5: First Order Rate Kinetics for Cephradine alone (blue line) and in presence of Mango Juice (red line) at simulated buffer of pH 1.2(A), pH 6.8 (B) and pH 7.2 (C). There is no significant difference in log of percent (%) remaining since the one curve superimpose to each other when the Cephradine alone and in presence of Mango Juice



(A) (B) (C)

Figure 6: Higuchi Release kinetics profiles of Cephradine alone (blue line) and in presence of Mango Juice (red line) at pH 1.2 (A), pH 6.8 (B), and pH 7.2 (C). Here the blue line appears below the red line. Thus the percent release of Cephradine in presence of Mango Juice is more in case of Higuchi kinetics at pH 1.2, 6.8 and 7.2.

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 order 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, 6.8, 7.2

Sample	correlation coefficients (R^2) pH 1.2		
	Zero Order	**First Order**	**Higuchi**
CEP	0.9619	0.3673	0.9256
CEP+M	0.5452	0.4778	0.8232
	correlation coefficients (R^2) pH 6.8		
CEP	0.8563	0.1756	0.9664
CEP+M	0.8602	0.3767	0.9901

	correlation coefficients (R^2) pH 7.2		
CEP	0.7612	0.2453	0.9132
CEP+M	0.5132	0.4524	0.9725

CEP= Cephradine ; CEP+M= Cephradine in mango juice

From **table 4** it was seen that Cephradine alone and Cepharadine in presence of Mango juice at pH 1.2 indicates that the Correlation Coefficients was 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. Again from table it was seen that Cephradine alone and Cepharadine in presence in simulated intestinal medium at pH 6.8 indicates that the Correlation Coefficients is close to 1 in case of Higuchi plot than Zero Order and First Order kinetics. Higuchi release kinetics predominates in simulated intestinal medium of pH 6.8.

CONCLUSION

The percent release data suggest that, in the simulated gastric medium (pH 1.2), simulated intestinal medium (pH 6.8 & 7.2) 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 (pH 1.2), simulated intestinal medium (pH 6.8 & 7.2)

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

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