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Research Article

In vitro release kinetics study of Cefuroxime Axetil alone and along with Herbal Alkalizer-trends for herb-drug interactions

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ABSTRACT

The present study focuses on the Herb-Drug interactions. In treating Urinary Tract Infection (UTI) Cefuroxime Axetil is prescribed along with a herbal alkalizer as an adjuvant therapy. Herbal alkalizer is use to detoxify excretable urinary substances and thus reducing the irritation during micturation and also to reduce urinary obstruction in respective case. The samples were analyzed according to United States Pharmacopoeia (USP) methods. In this study the in vitro dissolution test and TLC (Thin Layer Chromatography) were performed. The dissolution studies include the determination of percent release of Cefuroxime Axetil alone and Cefuroxime Axetil in presence of Herbal alkalizer syrup. The study reveals that, the release of Cefuroxime Axetil in presence of Herbal alkailizer and Cefuroxime Axetil alone almost same. Different mathematical models were adopted to explore into the release kinetics. It was found from multiple coefficients (r2) that at simulated gastric medium of pH 1.2, acetate buffer of pH 4.5 and simulated intestinal media at pH 6.8, the release kinetics followed by drug alone and in presence of herbal related to Higuchi release kinetics. By evaluating TLC the possibility of drug interactions between Cefuroxime Axetil (CA) and Herbal alkailizer was not observed.

Keywords: Cefuroxime Axetil; Herbal alkalizer syrup; multiple coefficients (r2); Release kinetics; TLC.

INTRODUCTION

Drug interactions may be the result of the pharmacodynamic properties of the drugs that is the co-administration of a receptor antagonist and an agonist for the same receptor (Pleuvry, 2005). Drugs may interact with other drugs or any diet or dietary supplement taken at the same time. Cefuroxime Axetil is a of Class second generation cephalosporins which is commonly used in the treatment of AOM caused by Streptococcus pneumoniae, Haemophilus influenzae (including β-lactamase-producing strains), Moraxella catarrhalis (including β-lactamase-producing strains), or S. pyogenes (Marx and Fant, 1988; McLinn et al., 1988; Hebblethwaite et al., 1987 and Finn et al., 1985). This drug was commonly up taken by oral for administration (GlaxoSmithKline). On the other hand, herbal alkalizer is syrup which was available under the brand name of "Alkalith Syrup" and is commonly taken 2-3 teaspoons with cold water thrice a day (Web-1). This drug was used in the case of renal calculus, retention of urine, prostatic enlargement, dysuria, burning mictution and U.T.I. (Web-1). The herbal drug used in this research work was applied for curing Pyrexia, anuria, oliguria, amenorrhoea, hepatitis and obstructive jaundice. It is also very effective to clear the morbid substances from the kidney and urinary bladder. Basically it is an Anti-Pyretic, Anti-Obstructive & Diuretic.

Drug interactions occur not only by the effects of a different drug but also by some other factor. John and Philip were mentioned Drug-herb interactions along with other available standard interactions mechanism (John and Philip, 2004). Herbal medicines follow modern pharmacological principles. Drug-herbal interactions can occur at the pharmaceutical, pharmacodynamic or pharmacokinetic (PK) levels (Beijnen and Schellens, 2004) but most of the interactions occur at PK level (Brazier and Levine, 2003) that involves changes in absorption, distribution, metabolism and excretion of the conventional drug, which in turn determine the bioavailability of the drug.

Furthermore, the use of herbal drugs worldwide is increasing day to day. Experts suggest that natural substances are not always safe. Everything we put in our

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mouth has the potential to interact with something else. The medication that is taken by mouth travels through the digestive system in much the same way as food and herbs taken orally do. So, when a drug is mixed with food or another herb (like alkalizer), alteration of absorption or molecular modification might occur, which might lead to unwanted and harmful effects. As more and more people discover new herbs, there is more and more potential for the abuse of these herbs and the patients may end up in serious problems which drive us to take an initial screening for detecting interactions between Cefuroxime Axetil and Herbal Alkalizer since these two drugs were frequently taken by general peoples in a daily time manner. Here, in this study we have seen release kinetics of Cefuroxime Axetil alone and along with Herbal Alkalizer with response to their multiple coefficients (r^2) and TLC examination which might play an important role in more understanding of these Herb-Drug interactions.

MATERIALS & METHODS

Preparation of dissolution medium

Simulated gastric medium pH 1.2 (0.1 N HCl), acetate buffer pH 4.5(0.1 M Acetic acid solution + 0.1 M Sodium acetate solution) and simulated intestinal medium pH 6.8(Sodium Hydroxide 25%+ 0.1 N Hydrochloric acid + 1.2 ml o-phosphoric acid) were prepared.

In vitro-dissolution study of Cefuroxime Axetil alone and in presence of herbal alkalizer

Dissolution studies were conducted according to USP method (USP XXII) using apparatus II paddle at a speed of 50 rpm and the temperature was maintained at 37± 0.5°C. The total duration of dissolution was 6 hours in which the tablets were subjected to simulated gastric media (pH 1.2), acetate buffer media (pH 4.5), and simulated intestinal media (pH 6.8) in every separate experiment. After the medium was placed in the vessels, paddle rotation was started and the system was allowed to equilibrate for 15 min. From the prepared medium, 900 ml of simulated gastric medium (0.1 N pH 1.2 HCl) was placed in each vessel (n=6) and the apparatus was assembled. 500 mg of Cefuroxime Axetil tablets (Local market) & Herbal Alkalizer according to daily dose were weighed and placed in the vessels. 5 ml sample were collected at 0 min, 10 min, 20 min, 30 min, 40 min, 50 min, 60 min, 90 min, 120 min, 150 min, 180 min, 210 min, 240 min, 270 min, 300 min, 330 min, and 360 min and at the same time 5 ml of fresh dissolution mediums were added to maintain the volume constant . After filtration and appropriate dilution, the sample solution was analyzed at a wavelength of 278 nm Cefuroxime Axetil by spectrophotometer (Shimadzu UV/Vis spectrophotometer 1700, Tokyo, Japan) at 37± 0.5°C with 50 rpm. The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time (minutes) curve.

By the above same method for simulated gastric medium (pH 1.2), the dissolution test for acetate buffer (pH 4.5) and simulated intestinal medium (Buffer pH 6.8) were also performed.

Method of Thin Layer Chromatography (TLC)

To assess herbal-drug interactions, we performed TLC as an initial screening process. The drug-herbal interaction study was performed using silica gel-coated TLC (Thin layer Chromatography) plates and a mixture of chloroform: methanol: toluene (4:2:2 v/v) as a mobile phase. The stationary phase used was pre-coated silica gel 60F 254. Activation of plates was done in an oven at 50°C for 5 min. Working standard of cefuroxime axetil (10 mg) was weighed accurately and diluted with methanol to obtain the final concentration of 100 µg/ml of drug. The content of twenty tablets was ground to fine powder. Weight equivalent to 25 mg of cefuroxime axetil was transferred to conical flask and dissolved in methanol. The solution was sonicated for 15 min. The extracts were filtered through Whatmann filter paper No. 41 and residue was washed with methanol. The extracts and washing were pooled and transferred to a 250 ml volumetric flask and volume was made with methanol. Required dilutions were made to get 100 µg/ml of Cefuroxime Axetil. An UV lamp (Analtech-EA-160S) provided the source of radiation.

Kinetics analysis of release data

In vitro drug release data were fitted to kinetic models such as zero-order, first-order, and Higuchi equation. The multiple coefficients (r^2) were also determined for the determination of best fit release kinetics.

Zero-Order Kinetics

Zero order (Wagner, 1969) as cumulative amount of drug released versus time, $C = K_0 t$

Where, K0 is the zero-order rate constant expressed in 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 K_0 and intercept the origin of the axes.

First order kinetics

First order (Gibaldi and Feldman, 1967; Wagner, 1969) as log cumulative percentage of drug remaining versus time, $Log C = Log C_o - k t / 2.303$, where C_0 is the initial concentration of drug, k is the first order constant, and t is the time.

Higuchi Model

Higuchi's model (Higuchi, 1963) as cumulative percentage of drug released versus square root of time. $Q = K t 1 / 2$, where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Table 1: Comparison of percent of Cefuroxime Axetil (CA) release alone and in presence of herbal drug (diuretic) (H) at different pH

Time(minutes)	% of drug release					
	CA[a] (pH1.2)	CA+H[b](pH1.2)	CA[a] (pH4.5)	CA+H[b] (pH4.5)	CA[a](pH6.8)	CA+H[b] (pH6.8)
0	0.6416	0.7532	0.6416	0.6695	0.6416	0.6695
10	26.1961	28.7069	28.6929	29.8786	29.1811	31.050
20	31.6082	35.4860	32.0546	31.3851	30.4086	31.3572
30	33.0589	36.0719	31.8175	35.0397	30.7713	34.0075
40	33.5611	37.4389	33.0478	36.0301	31.5524	34.6212
50	34.8723	37.5784	33.1566	36.4625	31.4409	35.2071
60	35.6255	37.8853	33.9517	36.7973	32.6126	35.6813
90	35.8487	38.3037	34.1191	37.1599	32.8358	35.7650
120	36.0719	38.6106	34.6212	37.4668	33.0031	36.2114
150	36.2114	38.9175	35.1792	37.7458	33.3937	36.5183
180	36.5183	39.3918	35.6813	38.2479	33.7006	36.7973
210	37.0204	39.8102	35.8487	38.4432	34.0075	37.1878
240	37.4110	40.1450	36.0719	38.7222	34.4538	37.6063
270	37.5226	40.3961	36.5183	38.9454	35.0676	37.9132
300	37.8853	40.8703	36.8530	39.3918	35.4024	38.1642
330	38.2200	41.2609	37.4668	39.7823	35.6534	38.5269
360	38.5269	42.0699	38.5548	40.0892	36.0719	38.9454

[a]CA = Cefuroxime Axetil; [b]CA+H= Cefuroxime Axetil in herbal diuretics

Table 2: Comparison of log of percent of drug remaining (Cefuroxime Axetil (CA) alone and in presence of herbal diuretics at different PH

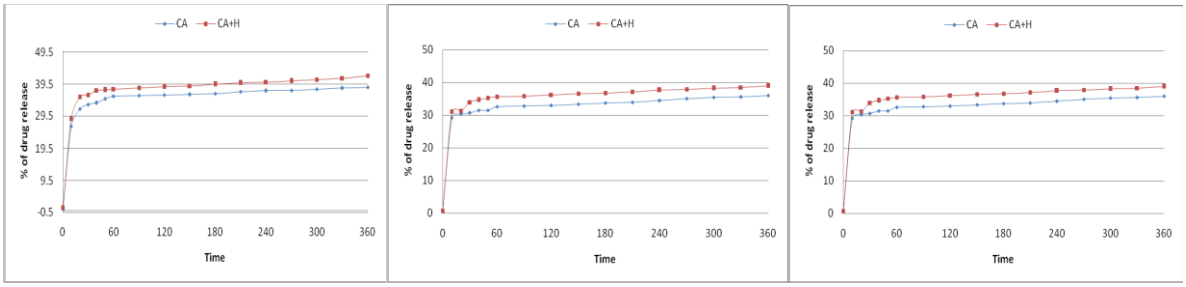
Time(minutes)	Log of % of drug remaining					
	CA[a] (pH1.2)	CA+H[b] (pH1.2)	CA[a] (pH4.5)	CA+H[b] (pH4.5)	CA[a] (pH6.8)	CA+H[b] (pH6.8)
0	1.9972	1.9967	1.9972	1.9970	1.9972	1.9970
10	1.8680	1.8530	1.8531	1.8458	1.8501	1.8385
20	1.8350	1.8096	1.8321	1.8364	1.8425	1.8365
30	1.8256	1.8056	1.8336	1.8126	1.8402	1.8194
40	1.8224	1.7963	1.8257	1.8059	1.8353	1.8154
50	1.8137	1.7953	1.8250	1.8030	1.8360	1.8115
60	1.8087	1.7931	1.8198	1.8007	1.8285	1.8083
90	1.8072	1.7902	1.8187	1.7982	1.8271	1.8077
120	1.8056	1.7880	1.8154	1.7961	1.8260	1.8047
150	1.8047	1.78591	1.8117	1.7941	1.8235	1.8026
180	1.8026	1.7825	1.8083	1.7906	1.8215	1.8007
210	1.7991	1.7795	1.8072	1.7892	1.8194	1.7980
240	1.7964	1.7771	1.8056	1.7873	1.8165	1.7951
270	1.7957	1.7752	1.8026	1.7857	1.8124	1.7929
300	1.7931	1.7718	1.8003	1.7825	1.8102	1.7912
330	1.7908	1.7689	1.7961	1.7797	1.8085	1.7886
360	1.7886	1.7629	1.7884	1.7775	1.8056	1.7857

[a]CA = Cefuroxime Axetil; [b]CA+H= Cefuroxime Axetil in herbal diuretics

RESULTS AND DISCUSSION

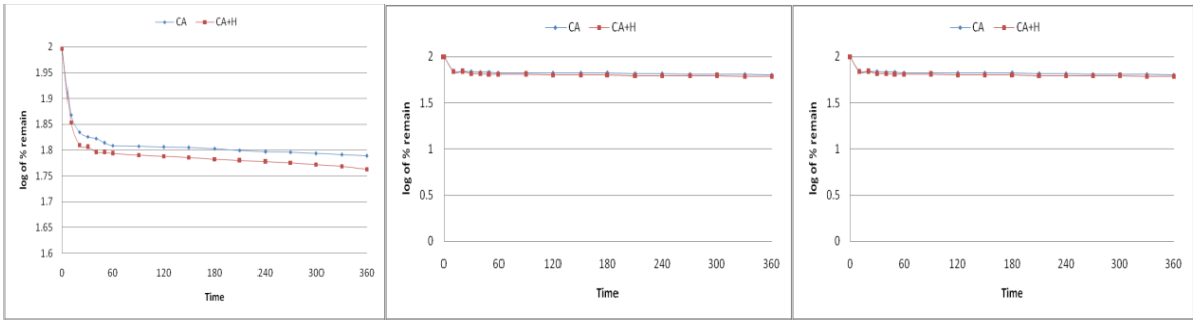
To investigate the release kinetics of Cefuroxime Axetil alone and Cefuroxime Axetil with Herbal Alkalizer we performed dissolution study, and from multiple coefficients we determined release mechanism of Cefuroxime Axetil alone and Cefuroxime Axetil with Herbal Alkalizer. Oral administration of Cefuroxime Axetil alone and concomitant administration of Cefuroxime Axetil with Herbal Alkalizer might brings some relatives change in release kinetics of Cefuroxime Axetil.

The release kinetics of drug and drug in presence of herbal shows no significant change with the change of pH, these are summarized in the tables-1 and 2 and Fig. 1, 2 and 3. Similarly, same thing was happening while we have seen the Log of % remaining of drug versus time. Here at the beginning the Log of % remaining of drug was the most. But it was the lowest after 360 minutes (6 hours). Again same thing was occurring while the drug was dissolved with herbal at different pH. This is the gist of tables 1 and 2 and Fig. 1, 2 and 3. The comparison study of percent (%) release



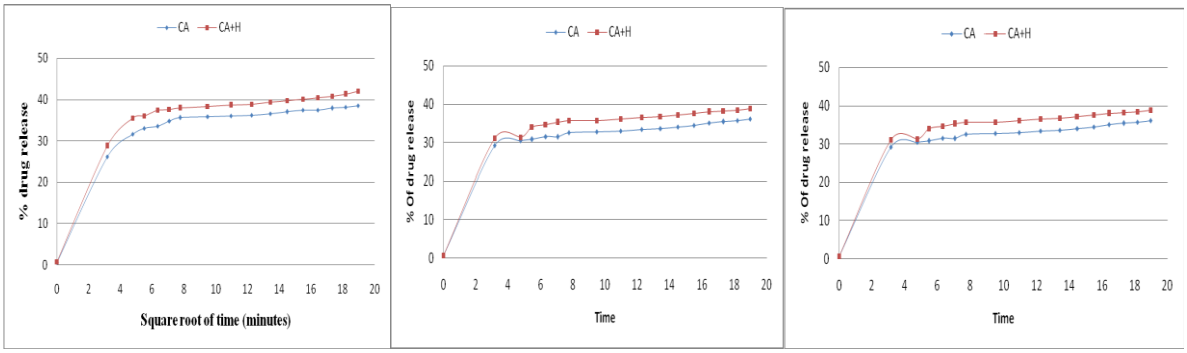
(A) (B) (C)

Figure 1: Zero order rate kinetics profiles of Cefuroxime Axetil alone (blue line) and in presence of Herbal Alkalizer (red line) at pH-1.2 (A), pH-4.5, (B) and pH-6.8 (C). Here the blue line appears below the red line. Thus the percent release of Cefuroxime Axetil in presence of herbal is slightly more at different pH



(A) (B) (C)

Figure 2: First Order Rate Kinetics for Cefuroxime Axetil (CA) alone (blue line) and in presence of Herbal Alkalizer (HA) (red line) at simulated buffer of pH 1.2(A), pH 4.5 (B) and pH 6.8 (C). There is no significant difference in log of percent (%) remaining since the one curve superimpose to each other when the Cefuroxime Axetil (CA) alone and in presence of Alkalizer (HA)



(A) (B) (C)

Figure 3: Higuchi Release kinetics profiles of Cefuroxime Axetil alone (blue line) and in presence of Herbal Alkalizer (HA) (red line) at pH 1.2 (A), pH 4.5 (B), and pH 6.8 (C). Here the blue line appears below the red line. Thus the percent release of Cefuroxime Axetil in presence of Herbal Alkalizer (HA) is more in case of Higuchi kinetics at pH 1.2, 4.5 and 6.8

and Log of % remaining of Cefuroxime Axetil alone and in presence of Herbal Alkalizer has been assembled in the tables 1and 2. From these results we have also find that these two drugs can be taken concomitantly, because there is no significant variation. That infer we can say that, since the percent (%) release of Cefuroxime Axetil was not significantly changed in presence of Herbal comparing to Cefuroxime Axetil alone, which gives us an idea that if we take this two drug concurrently there will be no hazardous effect from each other.

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

From The drug release data of Cefuroxime Axetil (CA) and Cefuroxime Axetil in presence of Herbal (Alkalizer) 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.

Cefuroxime Axetil (CA) tablets and Cefuroxime Axetil in presence of Herbal Alkalizer (H) in simulated gastric

Table 3: Correlation coefficients determination data for pH 1.2, 4.5 and 6.8

Sample	Correlation Coefficients (R^2) pH 1.2		
	Zero order	First order	Higuchi
CA[a]	0.2938	0.3420	0.5001
CA+H[b]	0.2818	0.3345	0.4812
	Correlation Coefficients (R^2) pH 4.5		
CA[a]	0.2919	0.3444	0.4845
CA+H[b]	0.2772	0.3265	0.4767
	Correlation Coefficients (R^2) pH 6.8		
CA[a]	0.2689	0.3138	0.4548
CA+H[b]	0.2631	0.3099	0.4540

[a]CA = Cefuroxime Axetil; [b]CA+H= Cefuroxime Axetil in herbal diuretics

Table 4: Determination of Drug- Herbal Interaction using the TLC method

Samples	Distance travelled by Samples	Distance travelled by Mobile Phase	Reference (Rf)[a] Values
Standard Cefuroxime Axetil	8.5 cm[b]	14.8 cm[b]	0.57
Cefuroxime Axetil (CA) drug	8.3 cm[b]	14.8cm[b]	0.56
Mixture of Cefuroxime Axetil(CA) with Herbal	8.3 cm[b]	14.8 cm[b]	0.56

[a]Rf= Ratio of Front; [b]cm= centimeter

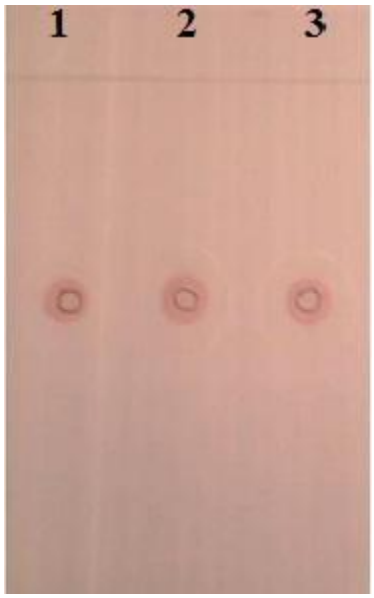


Figure 4: Thin Layer Chromatography (TLC) plate. Thin Layer Chromatography (TLC) showed in lane 1(Commercial Cefuroxime Axetil); lane 2 (Standard Cefuroxime Axetil) and in lane 3 (Cefuroxime Axetil with Herbal Alkalizer). In each case the concentration of spotting solution was 100 µg/ml

medium at pH 1.2 (Table-3) indicates that the Correlation Coefficients (R^2) was close to 1 in case of Higuchi plot than First order and Zero order kinetics. So Higuchi release kinetics predominates in simulated gastric medium of pH 1.2.

Thin Layer Chromatography (TLC)

TLC studies were performed to assess any interaction between the drug and the Herbal. The data obtained suggested that there was no interaction between the drug and the herbal because the R_f values of both the drug and the drug–herbal solutions were nearly similar as shown in table-4 and Fig. 4.

The TLC plate has shown that there is no difference in R_f values among Standard Cefuroxime, Cefuroxime Axetil tablets and mixture of Cefuroxime Axetil with Herbal Alkalizer which is shown Fig. 4, from which we can assumed that there is no complexation was occurred between these two drugs.

CONCLUSION

The percent release data suggest that, in the simulated gastric medium (pH 1.2), simulated acetate medium (pH 4.5) and simulated intestinal buffer (pH 6.8) the percent release of Cefuroxime Axetil not increased significantly. It was also seen that in different pH mediums, the percent release neither increased nor de-

creased when Cefuroxime Axetil is taken with the Herbal Drug (Alkalizer). It was also observed from the R_f values, where we see that the R_f values are too close to each other, which means there is no interaction if we take Cefuroxime Axetil with the Herbal Drug (Alkalizer). Hence, we can say that on the basis of our present study if the patient takes these two drugs concomitantly no harmful effect will occur.

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