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IN VITRO INTERACTIONS OF CIPROFLOXACIN WITH SELECTED DRUGS AND EXCIPIENTS

B. K. Poudel, P. Thapa*

Department of Pharmacy, Kathmandu University, Dhulikhel, Nepal

*Corresponding address: pannathapa@ku.edu.np
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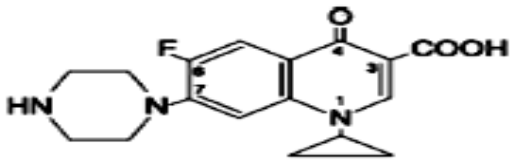
ABSTRACT
The present work comprises an interaction studies of ciprofloxacin, a quinolone antibiotic, with drugs (raw and market products) and excipients (raw and market products). For this, all the reaction conditions were simulated to gastric and intestinal environment. Drug-ciprofloxacin interactions were studied in USP Type II dissolution apparatus for three hours, aliquots of medium sampled out at an interval of 30 minutes. For excipients, fixed concentration of ciprofloxacin was mixed with varied ratio of excipients, shaken in an orbital shaker up to equilibrium time. The contents of ciprofloxacin in both processes were determined in UV spectrophotometer. The results revealed that both raw and market drugs: calcium hydroxide, aluminium hydroxide, magnesium hydroxide, sodium bicarbonate, calcium carbonate, marketed calcium carbonate tablets and marketed magnesium trisilicate suspension retarded the *in vitro* availability of ciprofloxacin in both simulated gastric and intestinal fluids. Further, binding of ciprofloxacin to talc, starch and microcrystalline cellulose was found to be non-linear but linear with activated charcoal and bentonite. While studying on two different formulations of activated charcoal, it was found that the maximum adsorption capacity for D-Tox capsules was 254.48 (simulated gastric fluid) to 232.63 (simulated intestinal fluid) and for D-Tox powder was 379.86(simulated gastric fluid) to 353.61 (simulated intestinal fluid) respectively. The effect of pH on binding to activated charcoal was not statistically significant. The binding of ciprofloxacin to drugs was found to be statistically significant and presumed to be due to chelation. The values of $T_{50\%}$ and $T_{90\%}$ increased drastically in both simulations, effect more pronounced in simulated intestinal fluid. Therefore, availability of ciprofloxacin can be affected by concurrent ingestion of aforementioned drugs or excipients.

Key words: ciprofloxacin, interaction, binding, adsorption

INTRODUCTION
The fluoroquinolones are a new series of synthetic antimicrobials with broad spectrum of activity, high potency, good bioavailability, large volume of distribution and a low binding to plasma proteins [1]. Ciprofloxacin, a fluoroquinolone, is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid. It is a faintish yellow to light yellow crystalline powder with a molecular weight of 331.4 [2]. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its chemical structure is shown below [2].



Ciprofloxacin oral tablet/suspension is rapidly and well absorbed from the GI tract, maximum serum concentrations are attained 1 to 2 hours after oral dosing [3].

In 2003, the patent for ciprofloxacin expired and since then, the number of prescriptions has more than doubled. In Nepal, it is one among the most prescribed antibiotics [4,5,6] and is being used extensively in different ailments concomitantly with other drugs and excipients. This incessant saturation of therapeutic markets with abundant ciprofloxacin formulations creates the need to compare and evaluate these agents using principles of dissolution and adsorption studies particularly in the absence of specific monograph. Drug interactions are one of the most important factors that should be considered in any preformulation study [7].

Several studies have been done on the interactions between fluoroquinolones and different drugs/excipients: Studies on the interaction and solubility of nalidixic acid on hydrophilic polymers & pharmaceutical additives including microcrystalline cellulose, ethyl cellulose, silicon dioxide and aluminium [8]; Ciprofloxacin hydrochloride binding with aluminium preparations and calcium polystyrene sulfonate [9]; Fluoroquinolones interaction with activated charcoal, kaolin and bentonite [10]; Complexation between norfloxacin and iron, zinc, aluminium, and magnesium ions respectively[11]; Reduction in absorption of levofloxacin by coadministration of aluminium hydroxide due to chelation [12]; Antacids (light magnesium carbonate, aluminium hydroxide and magnesium trisilicate) adsorption with lumefantrine *in-vitro* [13]; Plasma levels of ciprofloxacin reduction when taken with milk, yogurt and water due to binding with heavy metals, including calcium, to form an insoluble chelate [14]. Similarly, adsorption interaction between norfloxacin and pharmaceutical ingredients found binding capacities in following order: Activated Charcoal>Bentonite>Kaolin>Methyl Cellulose>Potato Starch>Talc [15]. Therefore, the aim of this study was to provide baseline information that would characterize the rate and extent of binding of the ciprofloxacin on some drugs and excipients which could guide in the choice of antidotes in the event of overdoses with the fluoroquinolones at one hand and at the other suggest clinicians and formulation scientists on possible interactions with ciprofloxacin.

MATERIALS AND METHODS

The simulated gastric and intestinal fluids, 0.1 N HCl and phosphate buffer pH 7.4 respectively, were prepared as per the pharmacopoeial methods [2]. Ciprofloxacin tablets and market products were bought from local pharmacy. Raw ciprofloxacin, drugs and excipients were obtained as gift sample from Lomus Pharmaceuticals Pvt. Ltd. All the solutions that were used in process were prepared fresh daily and were found to be stable at room temperature.

Procedure for excipients

The excipients [Activated Charcoal (AC), Bentonite, Maize Starch, Magnesium Stearate, Microcrystalline Cellulose (MCC-101) and Purified Talc (P. Talc)] were activated and freed from impurities by drying at 110°C for three hours in an oven. They were then cooled and stored in desiccator [10]. Magnesium stearate was excluded from studies because it crossed its melting point at that temperature. In order to make an intimate contact between solid liquid interfaces for the measurement of the uptake, various experimental arrangements have been generally employed by number of researchers. The simplest experimental set up, applied here, is shaking a definite weight of adsorbent with a solution of known concentration for an appropriate length of time to obtain equilibrium.

Primarily, the standard solution of ciprofloxacin (500 μg/ml) was prepared in 0.1 N HCl. 50 ml of this solution was added into volumetric flasks to which graded amounts of each AC, Bentonite, P.Talc, Maize Starch and MCC (25, 75, 150, 250 and 500 mg) were put separately. Similarly, 50 ml of 0.1N hydrochloric acid was added to equal graded amounts of adsorbents in volumetric flasks. The slurries were hand shaken thoroughly for 1 minute and then kept in an orbital shaker (Sonar) maintained at 100 rpm and 37 ± 0.2°C. Aliquots of the mixtures were withdrawn at separate time intervals, the equilibrium was found to attain within 15 minutes for activated charcoal and around 1 hour 45 minutes for other excipients. The slurries with 50 ml 0.1N HCl *(without ciprofloxacin)* treated in a similar way served as blanks for the absorbance measurements. For marketed AC (D-Tox powder and D-Tox capsules; 25, 50, 75, 100, 125 and 150 mg of AC was put in 50 ml of 500 μg/ml ciprofloxacin, medium being

simulated gastric or intestinal fluids and blanks were also prepared and shaken in similar fashion as described above. This was done to obtain a fit to Langmuir adsorption isotherm [16] in which AC:Ciprofloxacin ratios were 6:1, 5:1, 4:1, 3:1, 2:1, 1:1. The absorbance of all the solutions was measured at a maximum of 277 nm and 271 nm for simulated gastric fluid and simulated intestinal fluid respectively in UV visible spectrophotometer (Shimadzu UV-1601). The amounts of free drug remaining in solution at equilibrium in the presence of graded amounts of the excipients were determined hence the amount adsorbed was calculated. The procedure was repeated for each ciprofloxacin– excipient pair. Finally, linear form of Langmuir Adsorption Isotherm was used for linearization of experimental data by plotting C_f/Q against C_f.

$$\frac{Cf}{Q} = \frac{Cf}{Qm} + \frac{1}{KQm} \quad \text{......(1)}$$

Where,

- $Q\ [V(C_0 - C_f)\frac{1}{W}]$= Binding density (mg/g)
  Here, V is volume (L), W is weight (g), C_0 and C_f are initial and equilibrium drug concentrations respectively (mg/L)
- K= Langmuir modal parameter

The Langmuir constant/Binding constant/Maximum adsorption capacity, Q_m (mg of ciprofloxacin adsorbed per g of excipients) was evaluated from the slope of this linear equation [10, 16].

Procedure for drugs

For a solid dosage drug formulation to readily release its active ingredients effectively within the official specification, a number of independent variables such as uniformity of weight, hardness, friability, disintegration and assay that may affect its systemic activity must be assessed. These parameters were, therefore, preliminarily evaluated to ascertain the viability and suitability of the tablets for the dissolution studies.

In vitro release of Ciprofloxacin 500 mg tablets (with or without drugs pre-sieved through 80 mesh) was carried out in a six basket dissolution test apparatus (PLC dissolution test apparatus) with the following conditions:

Medium : 900ml; Simulated gastric or intestinal fluid
Temperature : 37±0.2^{o}C
Apparatus : USP- Type II (Paddle)
RPM : 50

The blanks were also prepared under similar conditions except for the use of Ciprofloxacin.
During dissolution studies, aliquots of the medium was pipetted out periodically at an interval of 30 minutes for 3 hours and dissolution fluid maintained by adding an equal amount of dissolution fluid withdrawn, which had previously been maintained at the same temperature in the same bath. The filtrate was suitably diluted and analyzed by UV Shimadzu Spectrophotometer

The percentage of drug release was calculated by comparing absorbance of the standard (Std) to that of the sample (Spl) using equation:

$$= \frac{\text{Spl Abs}}{\text{Std Abs}} \text{ x } \frac{\text{Std wt}}{\text{Std dil}} \text{ x } \frac{\text{Spl dil}}{\text{Spl wt}} \text{ x } \frac{\text{Std potency}}{100} \text{ x conversion factor}(0.8588) \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots(2)$$

The first order equation for dissolution of ciprofloxacin is-

$$K = \frac{2.303}{T} \log \left[\frac{a}{(a-x)}\right] \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(3)$$

The first order dissolution constants, $T_{50\%}$ and $T_{90\%}$, in presence of selected drugs in simulated gastric and intestinal fluids was calculated from rearrangement of first order equation as:

$$T_{50\%} = \frac{0.693}{K} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(4)$$

$$T_{90\%} = \frac{2.203}{K} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(5)$$

RESULTS AND DISCUSSION

Absorbance spectrum of ciprofloxacin showed λ_{max} at 277 nm and 271 nm for simulated gastric and intestinal fluids respectively (Fig. 1). Standard calibration curves for ciprofloxacin in simulated gastric and intestinal fluids showed good correlation with R^2 values of 0.9992 and 0.999 respectively (Figs. 2A, 2B).

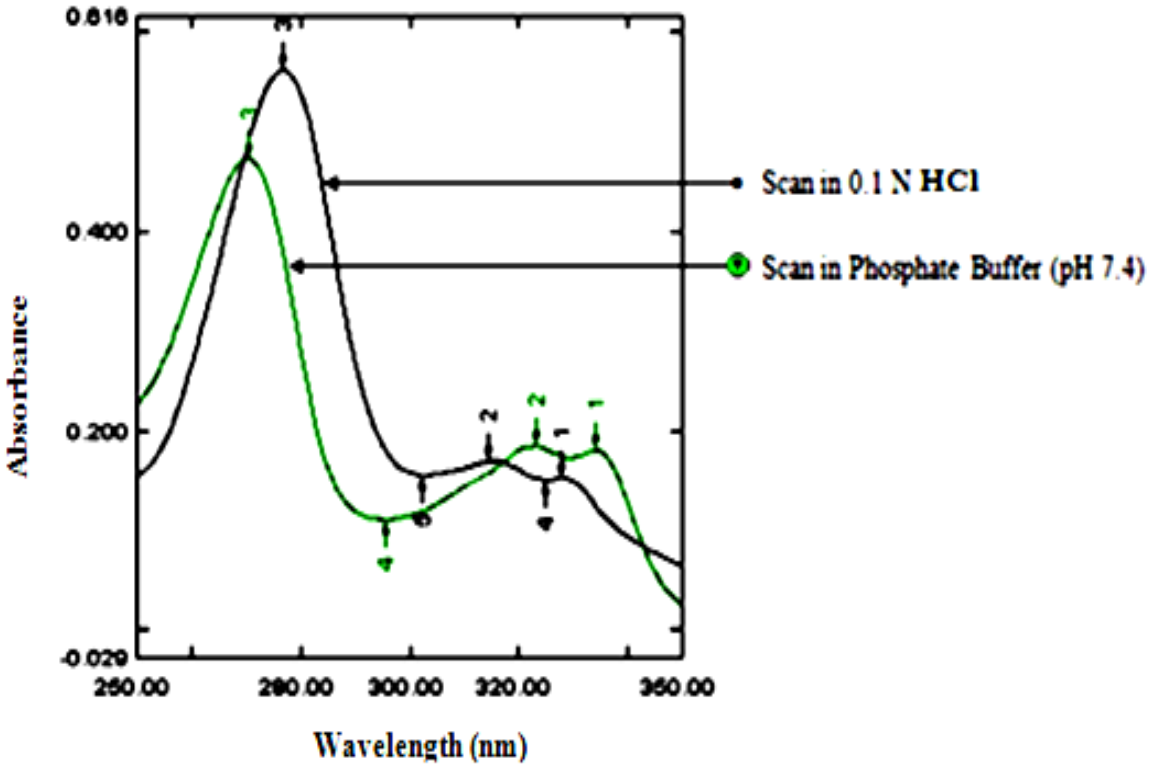


Figure 1 UV scans showing λ_{max} at 277 nm (simulated gastric fluid) and 271 nm (simulated intestinal fluid).

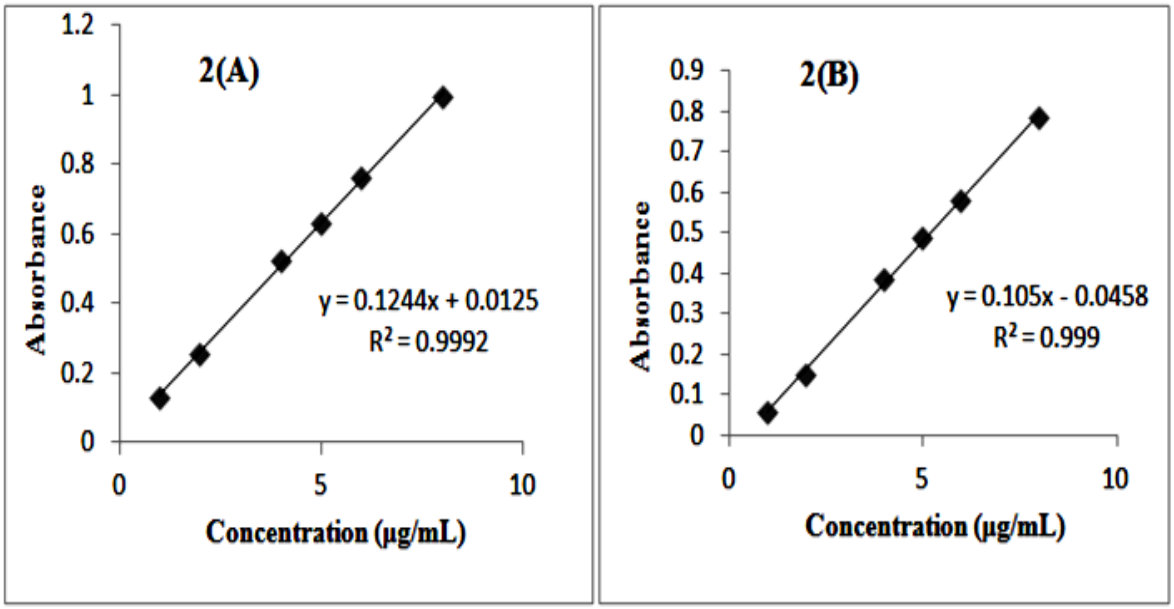


Figure 2 Standard calibration curves for ciprofloxacin in simulated gastric fluid 2(A) and simulated intestinal fluid 2(B) (n=4).

From this study, it was found that a substantial amount of drug was adsorbed by activated charcoal and bentonite (Figs. 3A, 3B; Table 2) while a little amount was adsorbed by purified talc, maize starch and MCC (Avicel pH 101) (Table 1). The binding of purified talc, maize starch and MCC was found to be non-linear (not shown here) as the relative adsorption of the ciprofloxacin to the charcoal did not correlate with the equilibrium concentration of ciprofloxacin as described in the Langmuir equation. However, the linear nature of adsorption isotherms for activated charcoal and bentonite shows that the binding process is due to monomolecular layer.

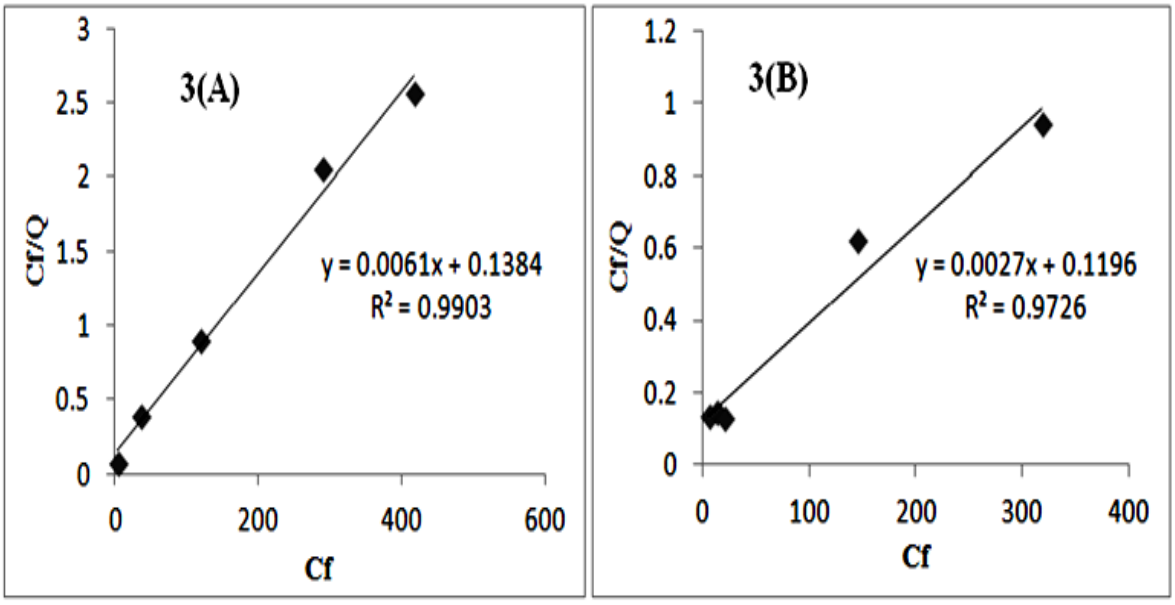


Figure 3 Adsorption of ciprofloxacin to raw bentonite 3(A) and to raw activated charcoal 3(B) in simulated gastric fluid (n=3).

Table 1 Adsorption of ciprofloxacin to adsorbent excipients: Purified Talc, Starch, MCC

Adsorbents	Mean Absorbance±SD	Mean % Adsorbed ±SD	p value
Ciprofloxacin (5 µg/mL)	0.614±0.0002	-	-
Purified Talc (500 mg)	0.547±0.0001	0.108±0.0003 [.1075±.1095]	.000
Starch (500 mg)	0.554±0.001	0.0967±0.0025 [.0904±.1030]	.000
MCC (500 mg)	0.606±0.0004	0.0122±0.0003 [.0114±.0131]	.000

[*Mean difference was significant at 95% confidence limits]

Table 2 Binding constant, Q_m of ciprofloxacin to two formulations of activated charcoal (n=3)

Formulations	Simulations	Q_m
Powder		
	Gastric Fluid	379.86 [359.44; 400.28]
	Intestinal Fluid	353.61 [306.98; 400.24]
Capsule		
	Gastric Fluid	254.48 [230.22; 278.75]
	Intestinal Fluid	232.63 [219.19; 246.07]

The linear adsorption interactions of raw bentonite and activated charcoal showed maximum adsorption capacity, Q_m, to be 163.93 and 370.37 respectively (Figs. 3A, 3B). The adsorption studies with two commercial brands of activated charcoal, D-Tox powder and D-Tox capsules (equilibrium time of 15 minutes) showed that the maximum adsorption capacity (mg of drug per gram of adsorbent) for D-Tox capsules was 254.48 (simulated gastric fluid) to 232.63 (simulated intestinal fluid) and for D-Tox powder was 379.86 (simulated gastric fluid) to 353.61 (simulated intestinal fluid) respectively (Table 2, Figs. 4A, 4B, 5A, 5B). The effect of pH on binding of ciprofloxacin to activated charcoal was not statistically significant (Table 3). This complies with other *in vitro* studies done with other drugs [16, 17, 18].

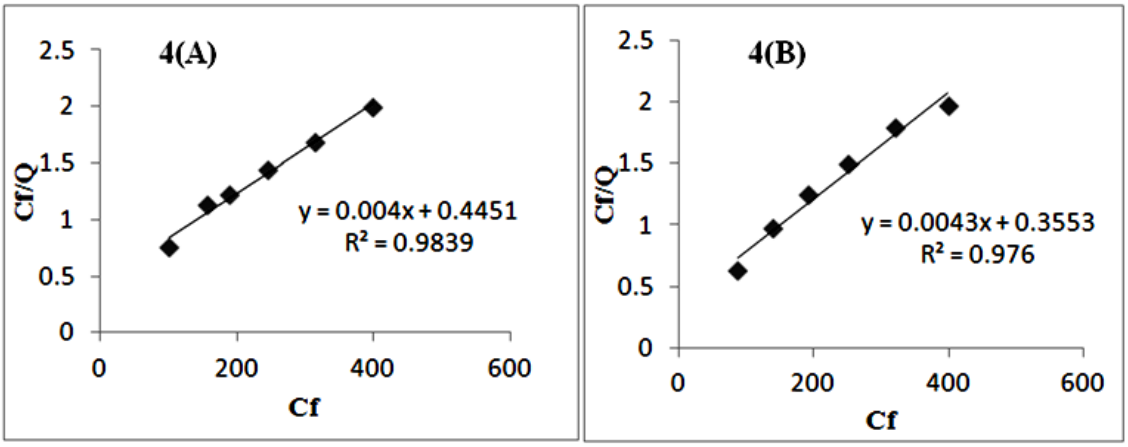


Figure 4 Adsorption of ciprofloxacin to D-Tox capsules in simulated gastric fluid 4(A) and in simulated intestinal fluid 4(B) (n=3).

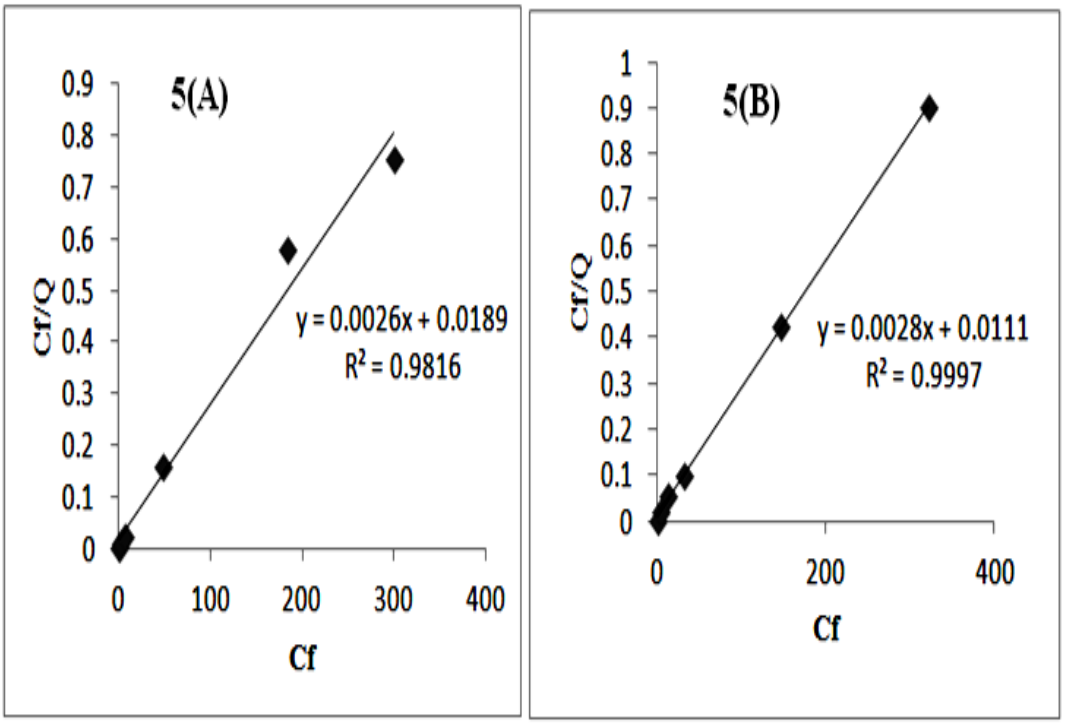


Figure 5 Adsorption of ciprofloxacin to D-Tox powder in simulated gastric fluid 5(A) and in simulated intestinal fluid 5(B) (n=3).

Table 3 Effect of pH on binding capacity (n=3)

Formulation	Mean Paired Difference	p value
Powder	26.25 [-2.19; 54.69]*	.058
Capsule	21.85 [-15.74; 59.44]*	.130

[*Mean difference was not significant at 95% confidence limits]

Talc is a non-adsorbent type of material made up of hydrous magnesium silicate, sometimes containing a small portion of aluminium silicate. This study revealed modest binding of ciprofloxacin to talc than that done by previous researchers [19]; the reason might be due to surface area and grade of talcum used in this study differs from that used by previous researchers. The binding capacity of talc for ciprofloxacin may be due to weak vander waals forces and the binding may be due to ion-exchange mechanism. Talcum, being basic in nature, can complex with ciprofloxacin thus removing it from solution. Further, talcum has magnesium ion in its structure which might have led to possible interaction with ciprofloxacin, as magnesium and other divalent/trivalent metals complex with fluoroquinolones, described in previous literatures [20, 21] and in this literature as well.

The binding of ciprofloxacin on microcrystalline cellulose, although in minute quantities, may be due to ionization of carboxyl groups on cellulose surface [22]. At low pH values, where the cellulose carboxy groups are predominantly in their non-ionized form, an increase in the added ionic strength causes a slight increase in the amount of drug adsorbed by microcrystalline cellulose. Even though this is hypothesized mechanism, the phenomenon

may be due to the fact that oxidized celluloses, such as microcrystalline cellulose have been shown to adsorb inorganic cations [23].

Similarly, the adsorption of ciprofloxacin onto maize starch, although in diminutive quantity, may be due to penetration and diffusion of the drug solution into the starch grains. The structure and porosity of the starch grains are important factors to be considered in the study of adsorption, as external and internal surfaces of the grains participate when adsorption is taking place in solution.

The higher binding of ciprofloxacin on excipients is desired at acidic pH because ciprofloxacin, a weak acid, is expected to remain in unionized form in acidic pH. Charcoal is non-polar adsorbent. At around neutral pH both H^+ and OH^- accumulates on charcoal surface resulting in most adsorption. In acidic pH range charcoal will have a net positive charge because of H^+ ions and so this might be the reason of adsorption of AC more in simulated gastric fluid than in simulated intestinal fluid (Table 2), this is because of high electrostatic attraction between the positively charged surface of charcoal and negative carboxyl group of COOH at the 3-position of ciprofloxacin. As the pH increases the negative charge on the adsorbent surface will increase because OH^- ions increase thus decreases the positively charged sites of charcoal that will cause repulsion of ciprofloxacin molecules through the basic piperazine functionality at the 7-position.

The rapid initial adsorption of ciprofloxacin is a surface phenomenon, due to anionic nature of ciprofloxacin, the vacant sites in the charcoal particles were filled up rapidly in the initial stages and followed a linear variation. Then a slow migration and diffusion of compound occurred and the rate of adsorption decreased drastically to reach the steady state (equilibrium). The higher binding to activated charcoal than to bentonite can be attributed to higher surface area of activated charcoal (Fig. 3B, Q_m=370.37; Fig. 3A, Q_m=163.93). A study has shown higher surface area results in more extensive adsorption *in vitro* [24].

In this study, rate of binding on bentonite was slower (equilibrium time-1 hour 45 minutes) than with activated charcoal (equilibrium time-15 minutes). Further binding on activated charcoal is presumed to be a surface phenomenon but to bentonite may be due to entrapment in the gel [10]. The adsorption experiments showed higher binding capacity of D-Tox powder than D-Tox capsules (Table 2), which can be attributed to the porosity of powder compared to granular nature of powder formulation of the capsules.

Like the tetracycline antibiotics, the interaction between oral ciprofloxacin and drugs is a chelation reaction. From this study, drugs (both raw and market products) with which oral ciprofloxacin interacts are sodium bicarbonate, calcium carbonate, aluminum hydroxide, magnesium hydroxide, calcium hydroxide and magnesium trisilicate (Figs. 6-9, Table 6, Table 7). It is postulated that the multivalent cations complex with the 4-keto and 3-carboxyl groups on the ciprofloxacin molecule and form an insoluble, non-absorbable compound. Metal complexes with active pharmaceuticals in which the drug molecules play the role of a ligand have been reported [25, 26].

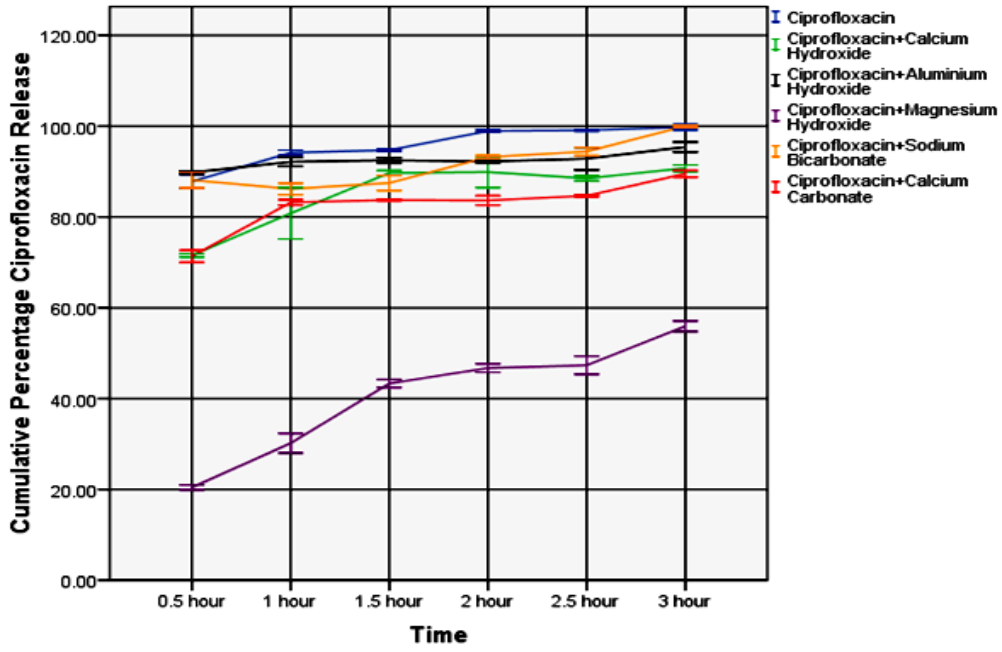


Figure 6 Cumulative percentage release of ciprofloxacin (500 mg tablets) alone or in presence of raw drugs (4 g each) in simulated gastric fluid (n=3).

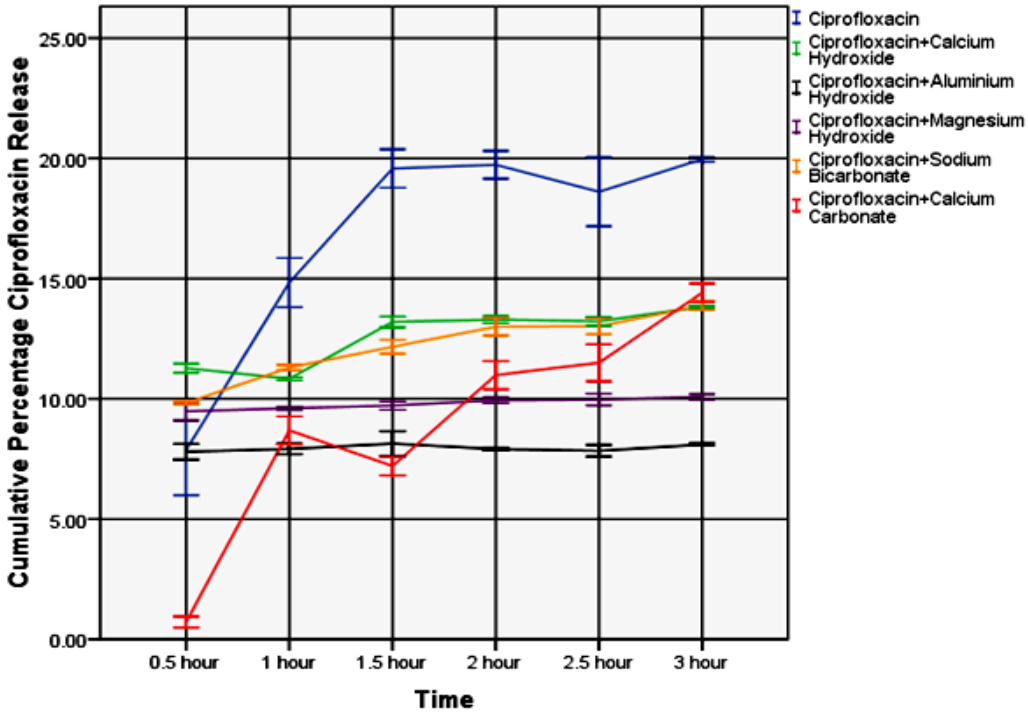


Figure 7 Cumulative percentage release of ciprofloxacin (500 mg tablets) alone or in presence of raw drugs (4 g each) in simulated intestinal fluid (n=3).

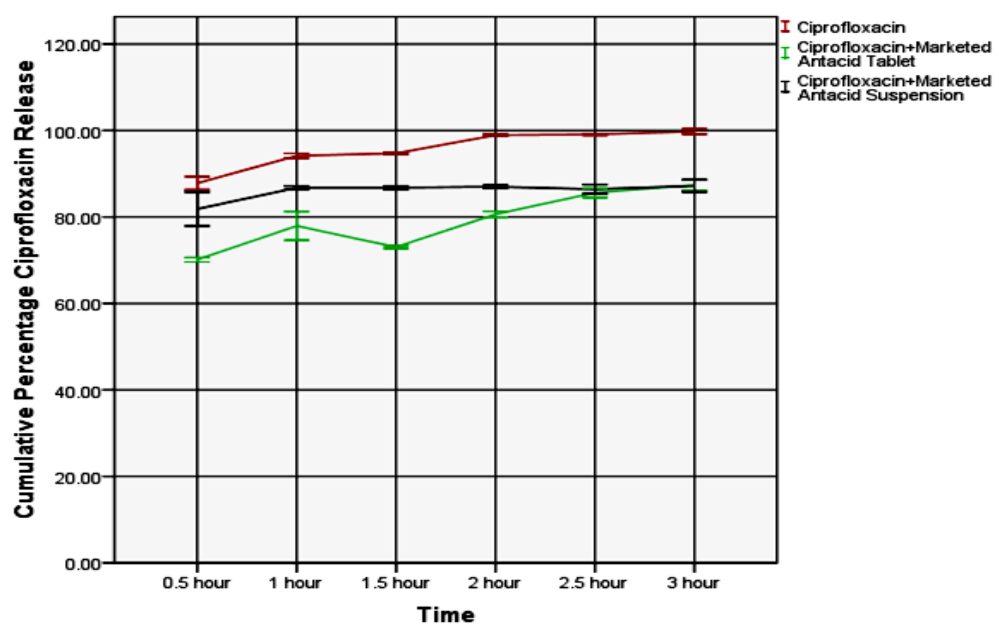


Figure 8 Cumulative percentage release of ciprofloxacin (500 mg tablets) alone or in presence of marketed antacid tablet (calcium carbonate) and suspension (magnesium trisilicate), both 1 g equivalents, in simulated gastric fluid.

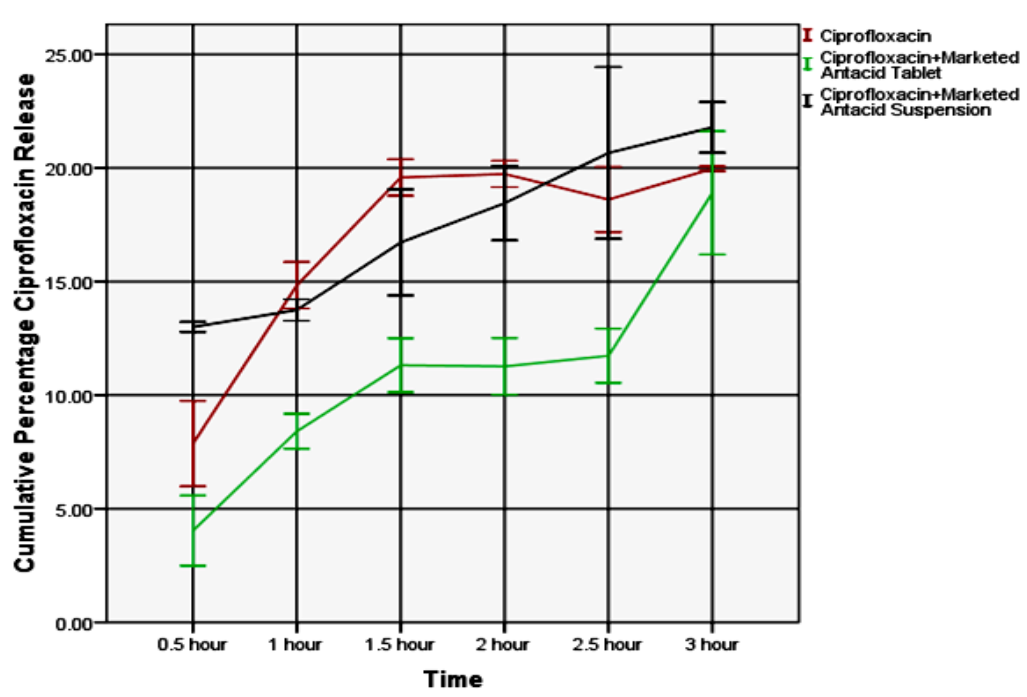


Figure 9 Cumulative percentage release of ciprofloxacin (500 mg tablets) alone or in presence of marketed antacid tablet (calcium carbonate) and suspension (magnesium trisilicate), both 1 g equivalents, in simulated intestinal fluid.

Table 6 Effect of drugs on dissolution behavior of ciprofloxacin in simulated gastric fluid (n=3)

Ciprofloxacin-Drugs Pair	Mean Paired Difference with Ciprofloxacin	p value
Ciprofloxacin - Calcium Hydroxide	10.55 [6.46; 14.63]*	.001
Ciprofloxacin-Aluminium Hydroxide	3.26 [-.120; 6.65]*	.045
Ciprofloxacin - Magnesium Hydroxide	55.08 [45.81; 64.34]*	.000
Ciprofloxacin - Sodium Bicarbonate	4.18 [.374; 8.00]*	.037
Ciprofloxacin - Calcium Carbonate	13.06 [1.079; 10.28]*	.000
Ciprofloxacin - Antacid Tablet	16.62 [13.06; 20.19]*	.000
Ciprofloxacin – Antacid (Mg-Trisilicate) Suspension	9.74 [6.63; 12.86]*	.000

*Different from each other at significance level 0.05

Table 7 Effect of drugs on dissolution behavior of ciprofloxacin in simulated intestinal fluid (n=3)

Ciprofloxacin-drugs Pair	Mean Paired Difference with Ciprofloxacin	p value
Ciprofloxacin - Calcium Hydroxide	3.94 [.0295; 7.85]*	.049
Ciprofloxacin-Aluminium Hydroxide	8.81611 [3.91; 13.71]*	.006
Ciprofloxacin - Magnesium Hydroxide	6.97722 [2.17; 11.77]*	.014
Ciprofloxacin - Sodium Bicarbonate	4.56556 [.934; 8.19]*	.023
Ciprofloxacin - Calcium Carbonate	7.84778 [5.25; 10.44]*	.001
Ciprofloxacin - Antacid Tablet	5.82089 [2.81; 8.82]*	.004
Ciprofloxacin - Antacid (Mg-Trisilicate) Suspension	-.62889 [-3.68; 2.42]	.620

*Different from each other at significance level 0.05

The binding of ciprofloxacin to selected drugs was found to be statistically significant (Table 6, Table 7) and presumed to be due to chelation. The values of $T_{50\%}$ and $T_{90\%}$ increased drastically in both simulations, effect more pronounced in simulated intestinal fluid (Table 8).

Table 8 First Order Dissolution Rates of Ciprofloxacin at 37 ± 0.2°C

	Simulated Gastric Fluid			Simulated Intestinal Fluid		
	$T_{50\%}$ (hr)	$T_{90\%}$ (hr)	K	$T_{50\%}$ (hr)	$T_{90\%}$ (hr)	K
Ciprofloxacin	0.450	1.43	1.5395	14.43	45.89	0.0480
Ciprofloxacin – $Ca(OH)_2$	3.890	12.36	0.1781	70.00	222.5	0.0099
Ciprofloxacin – $Al(OH)_3$	2.220	7.06	0.3120	216.56	688.4	0.0032
Ciprofloxacin – $Mg(OH)_2$	3.150	10.01	0.2200	256.66	815.9	0.0027
Ciprofloxacin–$NaHCO_3$	0.757	2.40	0.9147	40.76	129.5	0.0170
Ciprofloxacin – $CaCO_3$	0.758	2.41	0.9140	15.19	48.31	0.0456
Ciprofloxacin – $CaCO_3$ Tab	1.910	6.10	0.3610	22.50	71.52	0.0308
Ciprofloxacin – Antacid Susp	7.080	22.52	0.0978	15.13	48.10	0.0458

Table 9 Effect of pH on dissolution behavior of Ciprofloxacin 500 mg tablets (n=3)

Sample	Mean Paired Difference	p value
Ciprofloxacin	78.98 [78.04; 79.91]*	.000
Ciprofloxacin+Calcium Hydroxide	72.58 [69.48; 75.69]*	.000
Ciprofloxacin+Aluminium Hydroxide	84.53 [83.71; 85.35]*	.000
Ciprofloxacin+Magnesium Hydroxide	30.87 [24.91; 36.82]*	.000
Ciprofloxacin+Sodium Bicarbonate	79.36 [77.39; 81.33]*	.000
Ciprofloxacin+Calcium Carbonate	73.76 [72.78; 74.74]*	.000
Ciprofloxacin+Marketed Antacid Tablet	68.17 [66.25; 70.09]*	.000
Ciprofloxacin+Marketed Antacid(Mg-Trisilicate) Suspension	68.60 [67.22; 69.98]*	.000

*Different from each other at significance level 0.05

From this study, it is found that the effect of pH on dissolution behavior was significant with ciprofloxacin alone or in combination with drugs (Table 9). The cumulative percentage release of ciprofloxacin alone significantly differed with release in presence of all the drugs tested, in both the pHs, most prominent effect seen with magnesium hydroxide and calcium carbonate. To further extrapolate this finding, marketed antacids (calcium carbonate tablets and magnesium trisilicate suspension), that are given 1 g and 20 ml respectively per therapy, were tested with ciprofloxacin 500 mg tablet at both simulated gastric and intestinal fluids and the dissolution study showed significant retardation in ciprofloxacin release (Table 6, Table 7, Fig. 8, Fig. 9). This is also in coherence with previous studies where ciprofloxacin had significant interactions with aluminium preparations and calcium polystyrene sulfonate [9, 27]. While testing on magnesium trisilicate suspension in simulated intestinal fluid, it was found that during the first initial hours, the dissolution markedly increased and then later on it declined (Fig. 9) and because of which p value was found to be higher (Table 7) and values of $T_{50\%}$ and $T_{90\%}$ are only 15.13 and 48.10 hr respectively (Table 8). This was due to the liquid nature of suspension which enhanced the dissolution at first, but after certain time it declined because of binding of ciprofloxacin to magnesium ions. The release of ciprofloxacin in simulated intestinal fluid in this study was only around 20% even after 3 hours' dissolution studies (Fig.7, Fig. 9), which was in par with dissolution studies done on ciprofloxacin [28] but contradicts similar studies done in the past [27].

It can be postulated that such interactions occurred due to binding of metal containing drugs with ciprofloxacin which is consistent to similar studies done with variety of drugs and cations [20, 21, 27, 29]. Furthermore, this study shows that rate of release of ciprofloxacin, alone or in combination, is faster in acidic environment than in basic environment (Fig. 8, Fig. 9).

The physical parameters of ciprofloxacin tablets under study have been shown in Table 10 which complies with pharmacopeial specifications.

Table 10 Physical parameters of ciprofloxacin tablets under study:

Physical parameters	Tablet (500 mg)
Average weight of 20 tabs (mg)	680.15±4.80
Hardness of 6 tabs (kg/cm^2)	13.84±1.26
Friability (%)	0.023%
Disintegration test	142 seconds
Assay (%)	98.38%

Therefore, the availability of oral ciprofloxacin can be affected by the concurrent ingestion of drugs containing multivalent cations (irrespective of dosage forms) or when taken with adsorbent excipients like talc, starch, MCC, activated charcoal and bentonite. Further, these multivalent cation containing drugs, activated charcoal (capsules or powders) and bentonite can be taken in event of ciprofloxacin overdose. Furthermore, occurrence of such interactions (ciprofloxacin-drugs or ciprofloxacin-excipient) could impair the clinical efficacy of ciprofloxacin and reduce their bioavailability. Until and unless, this complex is broken down *in vivo* both the drugs would remain unavailable. A considerable time gap between administrations of these drugs and/or excipients may avoid such interactions.

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REFERENCES

[1] Hattab A, Adsorption of Some Fluoroquinolones on Selected Adsorbents. *MSc Thesis*. An-Najah National University, Nablus, Palestine, 2010.
[2] Indian Pharmacopoeia Commission. *Indian Pharmacopoeia* (2010), Government of India, Ministry of Health and Family Welfare Delhi: Controller of Publications.
[3] Cardinal Health, Ciprofloxacin Hydrochloride Tablet http://medlibrary.org/lib/rx/meds/ciprofloxacin-hydrochloride (August 29, 2012), 2012.
[4] Kumar J, Shaik MM, Kathi MC, Deka A, Gambhir SS, Prescribing indicators and pattern of use of antibiotics among medical outpatients in a teaching hospital of Central Nepal, *Journal of College of Medical Sciences-Nepal,* 6 (2010) 7.
[5] Das BP, Sethi A, Rauniar GP, Sharma SK, Antimicrobial utilization pattern in outpatient services of ENT department of tertiary care hospital of Eastern Nepal, *Kathmandu University Medical Journal,* 3 (2005) 370.
[6] Dawadi S, Rao BS, Khan GM, Pattern of antimicrobial prescription and its cost analysis in respiratory tract infection. *Kathmandu University Journal of Science, Engineering and Technology*, 1 (2005) 1.
[7] Al-Nimry SS, Assaf MS, Jalal MI, Najib MN, Adsorption of Ketotifen onto some pharmaceutical excipients, *International Journal of Pharmaceutics,* 149 (1997*)* 115.
[8] Othman S, Muti H, Shaheen O, Awidi A and Al- Turk W, Studies on the Adsorption and Solubility of Nalidixic acid, *International Journal of Pharmaceutics,* 41 (1988) 197.
[9] Toyoguchi T, Ebihara M, Ojima F, Hosoya J & Nakagawa Y, *In vitro* Study of the Adsorption Characteristics of Drugs, *Biological Pharmaceutical Bulletin,* 28 (2005) 841.
[10] Eboka CJ and Afolabi BA, *In-vitro* Adsorption of Fluoroquinolones on Some Pharmaceutical Adsorbents, *Tropical Journal of Pharmaceutical Research,* 5 (2006) 533.
[11] Campbell NRC, Kara M, Hasinoff BB, Haddara WM & Mckay DW, Norfloxacin interaction with antacids and minerals, *British Journal of Clinical Pharmacology,* 33 (1992) 115**.**
[12] Tanaka M, Kurata T, Fujiswa C, Ohshima Y, Aoki H, Okazaki O, and Hakusui H, Mechanistic Study of Inhibition of Levofloxacin Absorption by Aluminum Hydroxide, *Antimicrobial Agents and Chemotherapy,* 37 (1993) 2173.

[13] Babalola C, Ajayi O, Kotila O and Ameh S, *In-vitro* interaction studies of lumefantrine with antacids, *Pharmacie Globale*, 3 (2012) 1. www.pharmacie-globale.info (September 5, 2012)
[14] Welling PG, Effects of food on drug Absorption, *Annual Reviews of Nutrition*, 16 (1996)383.
[15] Singh GN, Gupta RP, Adsorption characteristics of norfloxacin to pharmaceutical additives, *Drug Development and Industrial Pharmacy*, 14 (1988)1845.
[16] Hoegberg LCG, Angelo HR, Christophersen AB, Christensen HR, Effect of ethanol and pH on the adsorption of acetaminophen (paracetamol) to high surface activated charcoal, *in vitro* studies, *Journal of Toxicology-Clinical Toxicology*, 40 (2002) 59.
[17] Teubner DJ, Absence of ice-cream interference with the adsorption of paracetamol onto activated charcoal, *Emergency Medicine*, 12 (2000) 326.
[18] Bailey DN & Briggs JR, The effect of ethanol and pH on the adsorption of drugs from simulated gastric fluid onto activated charcoal, *Therapeutic Drug Monitoring*, 25 (2003) 310.
[19] Ibezim EC, Ofoefule SI, Ejeahalaka CNC, Orisakwe, OE, *In vitro* adsorption of ciprofloxacin on activated charcoal and talc, *American Journal of Therapy*, 6 (1999) 199.
[20] Arayne MS, Sultana N and Hussain F, Interactions between Ciprofloxacin and Antacids-Dissolution and Adsorption studies, *Drug Metabolism and Drug Interactions*, 21 (2005) 117.
[21] Hussain F, Arayne, MS and Sultana N, Interaction between Sparfloxacin and Antacids Dissolution and Adsorption Studies. *Pakistan journal of Pharmaceutical Sciences*, 19 (2006) 16.
[22] McBurney LF, High Polymers in Cellulose and Cellulose- Derivatives, 5 (1954) Wiley, New York.
[23] Franz M and Peck E, *In vitro* adsorption–desorption of fluphenazine dihydrochloride and promethazine hydrochloride by microcrystalline cellulose, *Journal of Pharmaceutical Sciences*, 71 . (1982) 1193.
[24] Cooney DO, *In Vitro* Adsorption of Phenobarbital, Chlorpheniramine Maleate, and Theophylline by Four Commercially Available Activated Charcoal Suspensions, *Clinical Toxicology*, 33 (1995) 213.
[25] Eboka CJ and Okeri HA, Aqueous Solubility of Ciprofloxacin in the Presence of Metal Cations, *Tropical Journal of Pharmaceutical Research*, 4 (2005) 349.
[26] Edrissi M, Razzaghi, N & Madjidi B, Interaction of Mefenamic Acid with Cobalt (II) Ions in Aqueous Media: Evaluation *via* Classic and Response Surface Methods, *Turkish Journal of Chemistry*, 32 (2008) 505.
[27] Sultana N, Arayne MS & Hussain F, *In vitro* monitoring of ciprofloxacin antacids interactions by UV & HPLC, *Pakistan Journal of Pharmaceutical Sciences*, 18 (2005) 23.
[28] Kyriacos SB, Boukarim C, Safi W, Mroueh M, Maroun AB, El-Khoury G and Hehayeb R, *In Vitro* Testing of Ciprofloxacin Formulations and Preliminary Study on BCS Biowaiver, *Journal of Food and Drug Analysis*, 17 (2009) 78.
[29] Sultana N, Arayne MS, Shakeb SB, Haroon U & Rizvi S, *In vitro* drug interaction studies of atorvastatin with ciprofloxacin, gatifloxacin, and ofloxacin, *Medicinal Chemistry Research*, 19 (2010)717.