INTERACTIONS BETWEEN CIPROFLOXACIN AND ANTACIDS - DISSOLUTION AND ADSORPTION STUDIES

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SUMMARY

Ciprofloxacin is a fluorinated quinolone antibacterial agent extensively used against both Gram-positive and Gram-negative microorganisms. In certain polytherapy programs, ciprofloxacin can be administered with some antacids that could modify its dissolution rate and reduce its absorption leading to therapeutic failure. The aim of this study was to evaluate the influence of some antacids on the availability of ciprofloxacin. The release of ciprofloxacin from tablets in the presence of antacids, such as sodium bicarbonate, calcium hydroxide, calcium carbonate, aluminum hydroxide, magnesium hydroxide, magnesium carbonate, magnesium trisilicate and magaldrate was studied on BP 2002 dissolution test apparatus. These studies were carried out in simulated gastric and intestinal juices for 3 hours at 37°C. The results confirmed that the dissolution rate of tablets was markedly retarded in the presence of all the antacids studied. Magaldrate and calcium carbonate in simulated gastric juice exhibited relatively higher adsorption capacities, as did magnesium trisilicate and calcium hydroxide in simulated intestinal juice.

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KEY WORDS

ciprofloxacin, antacid, dissolution, drug interaction

INTRODUCTION

Ciprofloxacin, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl]-3-quinoline carboxylic acid, is a synthetic congener of nalidixic acid, having a broad spectrum of activity *in vitro* against Gram-positive and Gram-negative aerobic organisms /1,2/ with little activity against anaerobes /3,4/. Significant interactions with ciprofloxacin have been described /5/. These interactions reduce intestinal absorption after oral administration and may result in potentially serious problems via inhibition of various metabolic pathways. The bioavailability of a drug is the proportion of the administered dose that reaches the systemic blood circulation. Absorption from the gut can be altered by the presence of food, interactions with other drugs, etc. The availability of ciprofloxacin administered in tablet form is reported to be nearly the same as obtained with an aqueous solution /6/. Bergan *et al.* /7,8/ found the bioavailability of ciprofloxacin to be about 85%, but values as low as 70% have been reported /9/.

It is well established that antacids containing divalent or trivalent cations, such as Ca^{2+}, Mg^{2+}, or Al^{3+}, reduce oral absorption of fluoroquinolones by chelation in the gut /10/. Co-administration of antacids, notably combinations of aluminum and magnesium hydroxide, 2 hours before to 6 hours after dosing, consistently reduces bioavailability by 30-90% /11/. A number of mechanisms have been reported in the literature based on the changes in the pH of gastric fluid leading to degradation or depressed dissolution and absorption of the antibiotic. Chelation is also considered one mechanism responsible for the decreased absorption of the antibiotic in the presence of antacids.

In this study, we illustrated the effect of calcium hydroxide, calcium carbonate, magnesium hydroxide, magnesium carbonate, magnesium trisilicate, aluminum hydroxide, sodium bicarbonate, and a combination of aluminum and magnesium hydroxides and sulfates (magaldrate) on the dissolution of ciprofloxacin hydrochloride. The mechanism of interaction between the antibiotic and the antacids was also studied.

MATERIALS AND METHODS

Materials

Ciprofloxacin base and ciprofloxacin tablets (250 mg) were gifts from Ali Gohar Pharmaceutical Laboratories Ltd., Karachi, Pakistan. The antacids were of pharmaceutical grade. All solid antacids were used after passage through a 170-mesh screen. Liquid or suspensions of the antacids were used without any pretreatment.

Equipment

The dissolution equipment /12/ was manufactured to the B.P. 2002 /13/ standards, which included the dissolution motor and variable speed controller with a stainless steel basket assembly. The top of the basket was modified and replaced by a conical head in order to eliminate air entrapment during dissolution. The dissolution container was a flat bottom glass vessel with an internal diameter of 100 mm and with a capacity of 1 liter dissolution fluid. The variable speed motor was modified to reduce unwanted vibrations by incorporation of 1000 230 μF capacitor in the speed control circuit and was maintained within ±0.5% of the required speed.

Rotation of the basket assembly was fixed at 100 ± 0.5 rpm throughout the experiment. The dissolution assembly was immersed in a water bath at 37 ± 0.1°C. The drug in each case was analyzed either by measuring the absorbance of aliquots at 278 nm and 271 nm for simulated gastric and intestinal juices on a UV/VIS (Shimadzu 1601) spectrophotometer, or by a reversed-phase high performance liquid chromatographic (RP-HPLC) method. The Shimadzu chromatographic system was comprised of an LC 10AT VP pump, SPD 10A VP UV/VIS detector, and Communication Bus Module integrator (102). Separations were performed on a Shim-pack CLC-ODS 0.4 x 25 cm, 5-μm particle size column at 37°C. The samples were introduced through a rheodyne injector valve with a 20-μl sample loop using the mobile phase acetonitrile-water (13:87 v/v) and pH was adjusted to 3.2 with 85% orthophosphoric acid. The mobile phase was filtered through a 0.2-μm Millipore filter and degassed in an ultrasonic bath. The flow rate of the mobile phase was 1.5 ml/min and UV detection was performed at 278 nm.

Procedure for dissolution studies

Availability was obtained for ciprofloxacin hydrochloride on the dissolution apparatus as detailed above. Simulated gastric juice (0.1 N HCl) was prepared by taking 8.5 ml of 37% hydrochloric acid in a volumetric flask containing 1 l distilled water, and simulated intestinal juice was phosphate buffer pH 9 prepared by dissolving 17.4 g potassium dihydrogen orthophosphate in 1 l distilled water and adjusted the pH by sodium hydroxide. The dissolution fluid was 1,000 ml of simulated gastric or intestinal juice. Samples (5 ml) were withdrawn periodically with an interval of 15 min for 180 min. The volume of dissolution fluid was maintained by adding an equal amount of dissolution fluid to the fluid withdrawn, which had previously been maintained at the same temperature in the same bath.

In testing the effect of antacids on the dissolution behavior of the antibiotic, 2 g of antacid was added to the dissolution medium with a 250-mg tablet of ciprofloxacin at the start of the experiment and aliquots were drawn as above. The concentration of the antibiotic in solution was determined by diluting 5 ml of the aliquots in a 25 ml volumetric flask containing the same medium.

Adsorption studies

Two grams of antacid powders were weighed accurately in 25 ml Erlenmeyer flasks. An aqueous solution of ciprofloxacin (10 ml at 7.71 μg/ml concentration) was added to each flask. The flasks were shaken in a constant temperature bath at 37°C for 2 hours. It had been established previously that equilibrium was attained within this period. At the end of this time, aliquots were filtered through a Millipore filter (0.2 μm) and analyzed for the residual antibiotic content. The quantities of ciprofloxacin adsorbed were calculated by subtracting the equilibrium concentration from the initial concentration. No difference in concentration was found in samples to which antacid had not been added.

RESULTS AND DISCUSSION

Ciprofloxacin is a widely used broad spectrum oral quinolone antibiotic. In many clinical situations, oral ciprofloxacin has been used

in place of intravenous antibiotics to facilitate the earlier discharge of patients and/or to avoid the admission of patients. Like the tetracycline antibiotics, the interaction between oral ciprofloxacin and antacids is a chelation reaction. As discussed below, the antacids with which oral ciprofloxacin has been shown to interact are sodium bicarbonate, calcium hydroxide, calcium carbonate, aluminum hydroxide, magnesium hydroxide, magnesium carbonate, magnesium trisilicate and a combination of aluminum and magnesium hydroxides and sulfates (magaldrate). It is postulated that the multivalent cations complex with the 3-ketone and 4-carboxylic acid groups on the ciprofloxacin molecule. The complex formed is an insoluble, non-absorbable compound.

The interactions between these antacids and ciprofloxacin are particularly dramatic when the two agents are given simultaneously /14/. As shown in Tables 1 and 2, the availability of ciprofloxacin in simulated gastric and intestinal juices at different time intervals is reduced to 54% when it is mixed at the same time with aluminum- and magnesium-containing antacids. These reductions in ciprofloxacin availability by antacids may be due to the relative excess of aluminum and magnesium cations in a typical dose of antacid. The first-order dissolution constants, $T_{50\%}$ and $T_{90\%}$, of ciprofloxacin hydrochloride in the presence of various antacids in simulated gastric and intestinal juices are given in Table 3. These values are calculated from the first-order equation as the half-life of the reaction and the time when 90% of the molecules have taken part in the reaction, respectively:

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

where K is the first-order dissolution constant, log is the natural logarithm, T is time, a is the initial concentration of the drug and x is the concentration after dissolution.

The $T_{50\%}$ of a first order reaction is derived by rearrangement of the above equation. Since

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

$$T_{50\%} = \frac{2.303}{K} \log \left[\frac{1}{1/2}\right],$$

Therefore,

TABLE 1

Dissolution profiles (%) of ciprofloxacin (Cipro) in presence of antacids at different time intervals in stimulated gastric juice at 278 nm

	Time (min)												
	0	**15**	**30**	**45**	**60**	**75**	**90**	**105**	**120**	**135**	**150**	**165**	**180**
Ciprofloxacin	06.86	88.31	90.46	95.07	95.50	95.60	96.47	96.68	97.65	99.79	99.90	100	100
Cipro + sodium bicarbonate	02.69	80.94	95.51	98.07	94.29	98.20	96.32	98.20	96.18	92.94	98.34	98.47	98.61
Cipro + calcium hydroxide	13.19	86.81	87.34	89.49	89.60	90.13	95.50	95.61	95.61	95.71	95.71	95.82	95.93
Cipro + calcium carbonate	12.01	49.89	51.07	51.40	51.50	51.61	51.83	52.47	52.47	52.58	52.58	52.63	52.79
Cipro + magnesium carbonate	16.05	45.59	46.54	46.94	46.67	47.21	47.62	48.29	48.56	48.02	46.54	48.83	49.37
Cipro + aluminum hydroxide	02.66	68.57	68.71	85.54	76.57	84.70	85.33	86.49	83.86	84.00	84.56	86.95	87.09
Cipro + magnesium hydroxide	06.34	52.20	66.10	66.91	66.77	67.04	67.31	67.18	67.58	68.53	68.80	69.07	69.97
Cipro + magnesium trisilicate	21.18	42.89	43.16	43.57	43.70	44.11	43.84	44.51	44.78	45.05	44.92	45.32	45.46
Cipro + magaldrate	04.34	80.07	84.56	84.00	90.45	90.59	90.45	90.45	90.59	90.73	90.45	90.59	90.73

TABLE 2

Dissolution profiles (%) of ciprofloxacin (Cipro) in presence of antacids at different time intervals in stimulated intestinal juice at 271 nm

	Time (min)												
	0	**15**	**30**	**45**	**60**	**75**	**90**	**105**	**120**	**135**	**150**	**165**	**180**
Ciprofloxacin	12.62	30.43	36.32	40.81	49.22	69.98	73.62	90.45	98.03	99.99	100.21	100.41	100.97
Cipro + sodium bicarbonate	05.47	37.16	31.97	35.48	51.04	47.12	49.78	70.40	49.64	54.55	54.79	54.83	57.92
Cipro + calcium hydroxide	17.53	48.52	36.88	36.46	37.30	35.62	37.16	39.68	43.89	45.01	41.09	46.98	47.12
Cipro + calcium carbonate	08.13	43.19	36.74	41.51	40.95	41.65	41.65	69.18	46.84	53.29	51.18	49.64	62.94
Cipro + magnesium carbonate	10.58	34.78	30.43	31.41	25.10	43.61	40.67	31.55	39.40	32.67	39.26	36.60	43.89
Cipro + aluminum hydroxide	17.11	42.91	36.88	38.70	39.54	39.82	37.79	37.16	39.96	46.70	40.53	35.62	40.25
Cipro + magnesium hydroxide	02.80	34.92	31.55	28.32	25.52	27.62	29.03	30.57	30.57	37.86	32.39	31.41	37.86
Cipro + magnesium trisilicate	13.60	42.49	42.49	47.96	45.86	48.80	47.68	55.95	44.59	46.28	49.78	48.52	44.59
Cipro + magaldrate	09.39	38.70	35.34	36.74	38.00	34.64	36.04	40.11	40.25	42.35	42.35	42.63	43.61

TABLE 3

Various dissolution times and first-order dissolution constants of ciprofloxacin (Cipro) in the presence of some antacids

	Simulated gastric juice			Simulated intestinal juice		
	$T_{50\%}$ (min)	$T_{90\%}$ (min)	K (min^{-1})	$T_{50\%}$ (min)	$T_{90\%}$ (min)	K (min^{-1})
Ciprofloxacin	49.5	164.5	0.014	173.2	575.7	0.004
Cipro + sodium bicarbonate	30.1	100.1	0.023	173.2	575.7	0.004
Cipro + calcium hydroxide	40.7	135.4	0.017	86.6	287.8	0.008
Cipro + calcium carbonate	173.2	575.7	0.004	138.6	460.6	0.005
Cipro + magnesium carbonate	173.2	575.7	0.004	231	767.6	0.003
Cipro + aluminum hydroxide	63.0	209.3	0.011	346.5	1151	0.002
Cipro + magnesium hydroxide	115.5	383.8	0.006	693	2303	0.001
Cipro + magnesium trisilicate	231	767.6	0.003	231	767.6	0.003
Cipro + magaldrate	99.0	329	0.007	231	767.6	0.003

$$T_{50\%} = \frac{2.303 \log 2}{K} \quad \text{or} \quad T_{50\%} = \frac{0.693}{K}$$

Similarly,

$$T_{50\%} = \frac{2.303}{K} \log \left[\frac{1}{1/10}\right],$$

$$T_{90\%} = \frac{2.303 \log 10}{K} \quad \text{or} \quad T_{90\%} = \frac{2.203}{K}$$

Thus $T_{50\%}$ and $T_{90\%}$ for a first-order reaction depend solely on the rate constant and are independent of the initial concentration of the reactant /15/. All experiments were performed at least thrice. The results were satisfactorily reproducible as the deviations were within limits of ±0.3%.

As can be seen from these profiles, the availability of ciprofloxacin hydrochloride was decreased in the presence of all antacids studied in both simulated gastric and intestinal juice, except with sodium bicarbonate and calcium hydroxide, which decreased merely in simulated intestinal juice. These interactions occurred regardless of the dosage form of antacids (i.e. liquid suspension or tablets).

In our studies, when sodium bicarbonate was added to the dissolution medium in simulated gastric juice, the concentration of hydrogen ion decreased due to evolution of CO_2, which led to an increase in pH (change from 1 to 1.4) that may be responsible for the increased rate of dissolution as compared with other antacids in simulated gastric juice. This did not happen in simulated intestinal juice.

Magnesium trisilicate, which is insoluble in both dissolution media, exhibited a significant retardation effect on the dissolution of ciprofloxacin. After an interval of 90 minutes, 44% of the drug was present in the solution that was consistent up to 180 minutes. The $T_{50\%}$ and $T_{90\%}$ values of ciprofloxacin in the presence of magnesium trisilicate were found to be 231 min and 767 min, respectively, in both media.

In the case of aluminum hydroxide, 85% of the drug was present in the simulated gastric juice after the half time of the experiment, and at the end of the experiment 87% was present in the dissolution medium. In simulated intestinal juice the availability of the drug was 37.7% and 40.2% after 90 and 180 minutes. When aluminum hydroxide and magnesium trisilicate were added to the dissolution media, they remained undissolved in suspension. There are two possibilities for the slow rate of dissolution, either due to an increase in pH or absorbent properties of these two antacids. According to Arayne *et al.* from pH studies /16/, it is quite clear that pH is not a major factor for prolonged dissolution behavior. The chelating effect of ciprofloxacin with Mg^{2+} and Al^{3+} may be responsible for the prolonged and incomplete dissolution.

From the results listed in Tables 1 and 2, it is apparent that the availability of ciprofloxacin decreased in the presence of calcium and magnesium carbonate (in a concentration of 0.2 % w/v). In the presence of even lower levels of antacid, calcium carbonate also reduced ciprofloxacin availability; the amount dissolved after 90 min was 51.8% and after 180 min 52.8% with comparatively high values of $T_{50\%}$ and $T_{90\%}$.

In the case of magnesium carbonate, merely 47.6% of the drug was present in simulated gastric juice after an interval of 90 min and 49.4% at the end of the experiment, with $T_{50\%}$ and $T_{90\%}$ values of 173 and 575 min, respectively, while in simulated intestinal juice the availability of the drug after intervals of 90 and 180 min was 40.6% and 43.9%, respectively.

The availability of ciprofloxacin in presence of calcium hydroxide was 95% at $T_{50\%}$ and remained constant until the end of the experiment in simulated gastric juice, whilst it was 37.1% and 47.2% at 90 and 180 minutes, respectively, in simulated intestinal juice.

Magnesium hydroxide, that is soluble in simulated gastric juice, exhibited an insignificant effect on the availability of ciprofloxacin. After an interval of 90 min, 70% of the drug was present in solution, which was consistent up to the end of the experiment in gastric juice, whereas in simulated intestinal juice 29% and 37% was present, respectively.

Magaldrate, a combination of aluminum and magnesium hydroxides and sulfates, showed an insignificant effect on the availability of ciprofloxacin in simulated gastric juice. After an interval of 15 minutes, 80% of the drug was present in simulated gastric juice and remained constant until the end; while in simulated intestinal juice, there was a significant retardation in the availability of the drug. At $T_{50\%}$, 36% of the drug was available in the medium and at 180 min 43% of the drug had been recovered.

Thus, it is clear that the availability of ciprofloxacin can be retarded by small amounts of antacids containing polyvalent cations. Although it has previously been suggested that antacids decrease the availability of other antibiotics by raising the pH of the medium /17/ and the dissolution rate is markedly reduced at high pH values, there was no significant enhancement in pH (to 1.0 pH unit) by the addition of these antacids in the dissolution medium.

On the other hand, ciprofloxacin was found to be strongly adsorbed on various antacids. Figure 1 is derived from the Langmuir equation /18/, and studied by RP-HPLC, that may be written as:

$$\frac{c}{x/m} = \frac{1}{ab} + \frac{c}{b}$$

where c is the equilibrium concentration of the solute, x/m is the amount of the solute adsorbed per unit weight of the adsorbent, and a and b are constants. It is evident that all the antacids adsorbed ciprofloxacin to different extents. Magaldrate and calcium carbonate in simulated gastric juice exhibited relatively higher adsorption capacities, 96% and 81%, while in simulated intestinal juice magnesium trisilicate and calcium hydroxide exhibited higher adsorption capacities, 98% and 94%, respectively. The adsorption capacities of the antacids are also listed in Table 4, which shows that calcium hydroxide has maximum capacity to adsorb the drug in simulated gastric juice and magaldrate in simulated intestinal juice.

It is thus obvious that antacids containing polyvalent cations can retard the availability of ciprofloxacin. These studies indicate that ciprofloxacin is strongly adsorbed by antacids; magnesium trisilicate, calcium carbonate, and magaldrate exhibited relatively high adsorp-

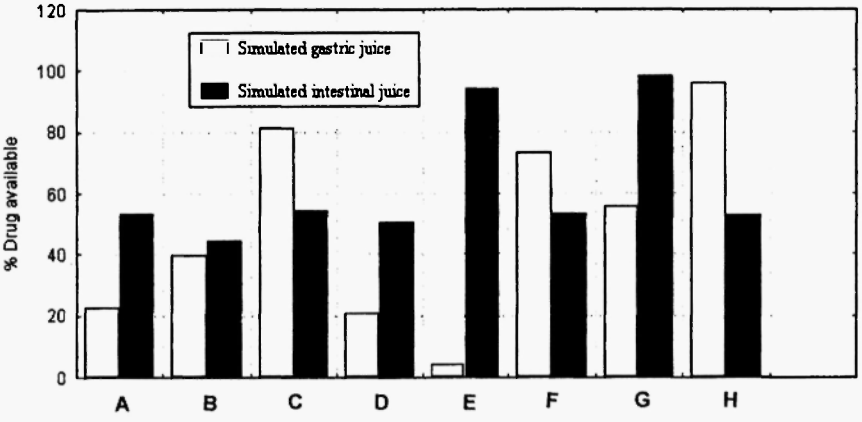

Fig. 1: Adsorption capacities of antacids for ciprofloxacin obtained from HPLC.

TABLE 4

Adsorption capacities of antacids towards ciprofloxacin in simulated gastric and intestinal juices obtained by UV spectrophotometric studies

Antacid	Adsorption capacity for ciprofloxacin [mg (mmol)/g]	
	Simulated gastric juice 278 nm	Simulated intestinal juice 271 nm
Sodium bicarbonate	599 (0.0146)	520 (0.0132)
Magnesium carbonate	491 (0.0120)	532 (0.0135)
Calcium carbonate	258 (0.0063)	540 (0.0137)
Magnesium hydroxide	581 (0.0142)	490 (0.0124)
Calcium hydroxide	734 (0.0179)	540 (0.0137)
Aluminium hydroxide	284 (0.0069)	555 (0.0141)
Magnesium trisilicate	341 (0.0083)	216 (0.0054)
Magaldrate	141 (0.0034)	614 (0.0156)

tion capacities. The adsorption of ciprofloxacin by antacids may be responsible for the marked retardation of availability of ciprofloxacin.

CONCLUSION

The availability of oral ciprofloxacin can be affected by the concurrent ingestion of antacids containing multivalent cations. The most dramatic ciprofloxacin interactions are with antacids containing aluminum cation. However, significant interactions have been seen with antacids containing magnesium and calcium cations. It is important to avoid taking ciprofloxacin concurrently with multivalent cation-containing medications. It is imperative to be aware of these interactions because they may affect ciprofloxacin availability to the extent that it may compromise the patient's outcome.

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