

INTERACTIONS BETWEEN SPARFLOXACIN AND ANTACIDS – DISSOLUTION AND ADSORPTION STUDIES

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ABSTRACT

Sparfloxacin is a broad-spectrum oral fluoroquinolone antimicrobial agent with a long elimination half-life, extensively used against both Gram-positive as well as Gram-negative microorganism. Concurrent administration of antacids and sparfloxacin decreases the gastrointestinal absorption of sparfloxacin and therapeutic failure may result. The present study was designed to evaluate the influence of some antacids on the availability of sparfloxacin. The release of sparfloxacin from tablets in the presence of antacids like sodium bicarbonate, calcium hydroxide, calcium carbonate, aluminum hydroxide, magnesium hydroxide, magnesium carbonate, magnesium trisilicate and magaldrate has been studied on BP 2003 dissolution test apparatus. These studies were carried out in simulated gastric and intestinal juices for three hours at 37°C.

The results confirmed that the dissolution rate of tablets was markedly retarded in the presence all of antacids studied, whereas magaldrate and calcium carbonate exhibited relatively higher adsorption capacities in simulated gastric juice and magnesium trisilicate and calcium hydroxide in simulated intestinal juice.

Keywords: Sparfloxacin, antacid, dissolution, drug interaction, adsorption.

INTRODUCTION

Sparfloxacin, 5-amino-1-cyclopropyl-7-(cis-3,5-dimethyl-1-piperazinyl)-6,8-di-fluoro-1-4-dihydro-4-oxo-3-quinocarboxylic acid, is a synthetic congener of nalidixic acid having broad spectrum of activity (Grady et al. 1997; Hoogkamp-Korstanje 1984), *in vitro* against Gram-positive and Gram-negative aerobic organisms and has little activity against anaerobes (PDR 1989; Abraham, 2003). The fluoroquinolone antibacterials are prone to many interactions with other drugs (Bruce G. Charles *et al.*, 1996). Drug interactions between sparfloxacin and antacids, containing divalent or trivalent ions, can lead to a significant decrease in GI absorption, bioavailability, and therapeutic effects (Hansten and Hom, 1997; Lomaestro and Bailie, 1995). In addition, these interactions can severely diminish the activity of sparfloxacin. The bioavailability of the drug is the proportion of the administered dose that reaches the systemic blood circulation.

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 (Deppermann and Lode, 1993). Coadministration of antacids, notably combinations of aluminum and magnesium hydroxide, 2 hour before to 6 hour after dosing, consistently reduces bioavailability by 30-90% (Polk 1989).

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 the mechanism responsible for the decreased absorption of the antibiotic in the presence of antacids.

In this work, 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 sparfloxacin, the present study was designed to monitor the drug in solutions and the formation of the complex species at the pH levels typical of the gastrointestinal tract. It involves the study of sparfloxacin in aqueous solutions containing antacids by combining the results of spectrophotometric and chromatographic (reversed-phase high performance liquid chromatography) techniques. The mechanism of interaction between antibiotic and antacids was also studied.

MATERIALS AND METHODS

Materials

Sparfloxacin base and sparfloxacin tablets (400mg) were gift from Abbott Laboratories Karachi, Pakistan. The

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antacids were of Pharmaceutical grade. All solid antacids were used after passage through a 170-mesh screen. Liquid or suspension antacids were used as such with out any pretreatment.

Equipment

The dissolution equipment (BP 2003) was manufactured to the B.P. 2003 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 using dissolution. The dissolution container was a flat bottom glass vessel with an internal diameter of 100mm and with a capacity of 1-liter dissolution fluid. The variable speed motor was modified to reduce unwanted vibrations by incorporation of 1000 230 μ F 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 ± 1 rpm throughout the experiment. The dissolution assembly was immersed in water bath at $37 \pm 0.1^\circ\text{C}$. Drug in each case was analyzed either by measuring the absorbance of aliquots at 290nm and 296nm for simulated gastric and intestinal juices on a UV/VIS (Shimadzu 1601) spectrophotometer, or by Reversed-phase High Performance Liquid Chromatographic (RP-HPLC) method. The chromatographic system Shimadzu comprised of 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 μ m particle size column at 37°C . The samples were introduced through a Rheodyne injector valve with a 20- μ L sample loop using the mobile phase acetonitrile-water (13:87, v/v) and pH was adjusted at 3.2 with 85% orthophosphoric acid. Mobile phase filtered through a 0.2 μ m 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 290 nm.

Procedure for dissolution studies

Availability was obtained for sparfloxacin on the dissolution apparatus as detailed above. Simulated gastric juice (0.1N HCl) was prepared by taking 3.2g of pepsin and 7ml of 37% hydrochloric acid into 1L volumetric flask made up by distilled water whereas simulated intestinal juice was phosphate buffer of pH 6.8 prepared by weighing 6.8 g of potassium dihydrogen orthophosphate in 1L distilled water and adjusted the pH by sodium hydroxide. The dissolution fluids were 1000 ml of simulated gastric and intestinal juices. Samples of 5mL each were withdrawn periodically with an interval of 15 minutes for 180 minutes. The volume of dissolution fluid was maintained by adding an equal amount of dissolution fluid withdrawn, which had previously been maintained at the same temperature in the same bath.

In testing the effect of antacids on the dissolution, behaviour of the antibiotic 2g of antacid was added to the dissolution medium with 400mg tablet of sparfloxacin at the start of the experiment and aliquots were drawn similarly. The concentration of the antibiotic in solution was determined by diluting 5ml of aliquots into 25ml volumetric flask and made up by the same medium.

Adsorption studies

2 g of each antacid powder was weighed accurately in 25 ml Erlenmeyer flasks. Aqueous solution of sparfloxacin (10 ml of 20.4 μ g/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 μ m) and analyzed for the residual antibiotic content. The quantities of sparfloxacin 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

Sparfloxacin is a widely used broad-spectrum oral quinolone antibiotic. In many clinical situations, oral sparfloxacin has been used in place of intravenous antibiotics to facilitate the earlier discharge of patients and/or preventing the admission of patients. Like the tetracycline antibiotics, the interaction between oral sparfloxacin and antacids is a chelation reaction. As will be discussed, the antacids with which oral sparfloxacin 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 sparfloxacin molecule. The complex formed is an insoluble, non-absorbable compound.

The interactions between these antacids and sparfloxacin are particularly dramatic when the two agents are given simultaneously (Hansten and Hom, 1995). As shown in tables 1-2, the availability of sparfloxacin in simulated gastric and intestinal juices at different time intervals is reduced to 50% when it is mixed at the same time with aluminum and magnesium containing antacids. These reductions in sparfloxacin 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 sparfloxacin in 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

reaction and the time when 90 % of the molecules have been taken part in the reaction respectively.

First-order equation,

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

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

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

The $T_{90\%}$ of a first-order reaction is calculated similarly

$$T_{90\%} = \frac{2.303}{K} \log \left[\frac{1}{1/10} \right],$$

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

The $T_{50\%}$ and $T_{90\%}$ for a first-order reaction depend solely on the rate constant and is independent of the initial concentration of the reactant (Lund 1994). All the experiments were performed at least thrice. The results were satisfactorily reproducible as the deviations were within limits ($\pm 0.3\%$).

As can be seen from these profiles, the availability of sparfloxacin decreased in presence of all antacids studied in both simulated gastric and intestinal juices except sodium hydrogen carbonate, which decreased merely in simulated intestinal juice. These interactions occur regardless of the dosage form of antacids (i.e. liquid suspension or tablets).

In our studies, when sodium hydrogen carbonate 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 (changed from 1 to 1.4) that may be responsible for increased rate of dissolution as compared with other antacids in simulated gastric juice. While it did not happen in simulated intestinal juice, that's why there was a decreased rate of dissolution similar to other antacids i.e. 40.15 % and 52.06% after an interval of 90 minutes and at the end of experiment.

Magnesium trisilicate, which is insoluble in both dissolution media, exhibited a significant retardation effect on the dissolution of sparfloxacin. After an interval of 90 minutes,

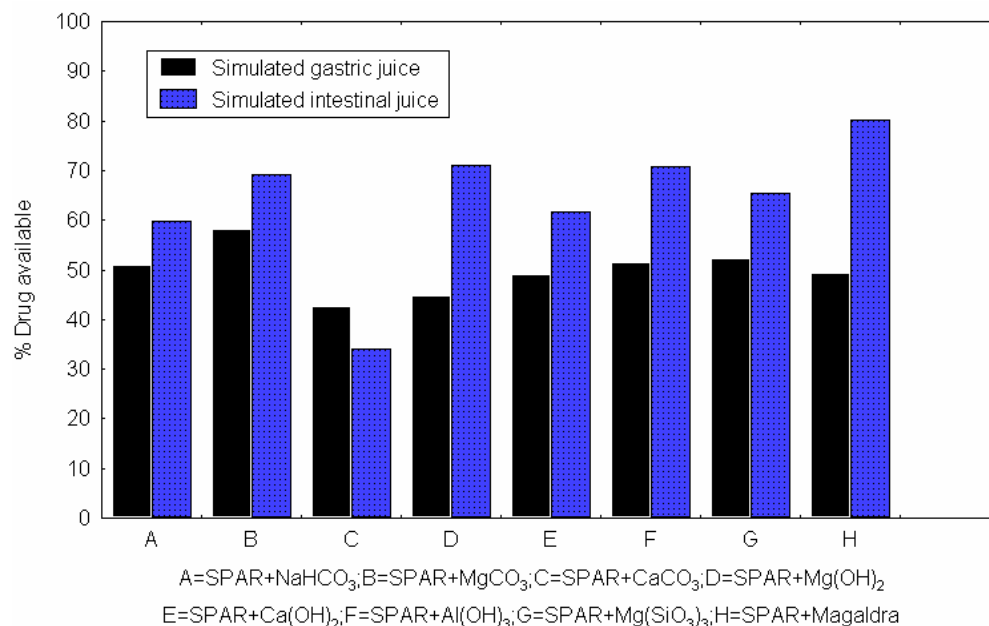


Fig. 1: Adsorption capacities of antacids for sparfloxacin

Table 1: Concentration of sparfloxacin (%) in presence of antacids at different time intervals in stimulated gastric juice at 296 nm

Sample	Time [min]												
	0	15	30	45	60	75	90	105	120	135	150	165	180
Sparfloxacin	14.65	89.38	90.48	90.85	90.85	91.22	91.22	91.22	93.41	95.25	97.08	99.64	100.01
Spar + Sodium bicarbonate	35.46	79.67	95.79	99.94	95.33	97.63	96.25	98.55	94.87	91.18	98.09	98.55	99.01
Spar + Calcium hydroxide	18.31	87.92	88.65	89.02	89.02	89.38	90.12	90.48	90.48	91.22	91.54	92.32	92.68
Spar + Calcium carbonate	15.75	53.85	13.92	56.05	56.41	57.15	58.25	58.61	58.61	58.61	58.60	58.61	58.61
Spar + Magnesium carbonate	15.19	46.51	48.35	48.35	49.27	50.20	49.74	50.66	51.58	52.96	52.96	53.88	53.88
Spar + Aluminum hydroxide	03.06	46.96	47.64	68.74	46.62	68.05	73.16	72.48	66.69	67.03	67.37	69.42	69.76
Spar + Magnesium hydroxide	07.36	56.18	58.95	62.17	65.39	64.47	68.16	68.62	68.62	69.08	69.08	70.00	70.46
Spar + Magnesium trisilicate	28.09	46.97	47.43	46.51	47.89	47.89	48.35	49.27	48.81	49.74	49.74	50.20	50.20
Spar + Magaldrate	21.09	62.95	72.48	68.39	78.60	67.71	74.86	76.56	77.24	77.24	77.58	77.58	77.92

Table 2: Concentration of sparfloxacin (%) in presence of antacids at different time intervals in stimulated intestinal juice at 290 nm

Sample	Time [min]												
	0	15	30	45	60	75	90	105	120	135	150	165	180
Sparfloxacin	12.69	35.39	36.75	41.17	45.60	58.19	64.99	77.24	93.24	97.32	99.02	99.70	100.04
Spar + Sodium bicarbonate	02.04	30.96	27.90	29.26	43.55	41.17	40.15	42.53	43.21	52.06	47.98	51.38	52.06
Spar + Calcium hydroxide	17.35	35.05	36.07	35.73	35.73	35.73	38.45	39.13	43.21	43.21	40.83	46.96	47.30
Spar + Calcium carbonate	26.20	58.87	70.78	73.84	70.44	72.14	71.12	72.82	70.10	67.37	72.48	72.84	73.16
Spar + Magnesium carbonate	09.86	29.94	27.22	27.22	23.14	43.55	37.09	29.94	35.39	30.96	33.34	34.03	37.43
Spar + Aluminum hydroxide	17.35	36.75	34.03	35.05	36.75	35.73	38.45	31.30	36.41	43.21	35.05	34.37	38.79
Spar + Magnesium hydroxide	03.06	27.22	26.20	25.18	22.46	25.52	27.22	27.90	27.22	29.26	29.94	28.58	30.28
Spar + Magnesium trisilicate	13.95	37.43	41.17	41.85	44.57	44.91	47.64	43.55	43.89	44.23	47.98	48.32	48.32
Spar + Magaldrate	09.18	30.62	31.64	34.03	36.41	31.98	33.68	38.45	38.79	39.13	38.45	43.89	43.89

47% of the drug was present in the solution that was consistent up to 180 minutes. The $T_{50\%}$ and $T_{90\%}$ values of sparfloxacin, in presence of magnesium trisilicate, were found to be 6.24 minutes and 7.85 minutes respectively in both media.

In case of aluminum hydroxide, 63 % of the drug was present in simulated gastric juice after half interval of the experiment and at the end of the experiment, 69.7 % was there in dissolution medium. In simulated intestinal juice the

availability of the drug was 38.45 % after 90 minutes and that was consistent up to 180 minutes. When aluminum hydroxide and magnesium trisilicate were added to the dissolution media, they remained in suspension and undissolved state. There are two possibilities for the slow rate of dissolution, either due to increase in pH or adsorbent properties of these two antacids. According to earlier reports (Arayne and Sultana 1993), from the pH studies it is quite clear that pH is not a major factor for prolonged dissolution behavior. The chelating effect of sparfloxacin with Mg^{2+}

Table 3: Various dissolution times and first-order dissolution constants of sparfloxacin in presence of antacids

Sample	Simulated gastric juice			Simulated intestinal juice		
	T _{50%}	T _{90%}	K _{296 nm}	T _{50%}	T _{90%}	K _{290 nm}
Sparfloxacin	4.92	6.53	0.014	6.19	7.80	0.004
Spar + Sodium bicarbonate	4.35	5.96	0.025	6.23	7.84	0.003
Spar + Calcium hydroxide	4.92	6.53	0.014	5.40	7.01	0.009
Spar + Calcium carbonate	6.01	7.62	0.004	5.61	7.22	0.007
Spar + Magnesium carbonate	6.90	8.51	0.002	6.64	8.25	0.002
Spar + Aluminum hydroxide	5.70	7.31	0.006	6.59	8.20	0.002
Spar + Magnesium hydroxide	5.68	7.29	0.006	7.092	8.70	0.001
Spar + Magnesium trisilicate	6.24	7.85	0.003	6.30	7.91	0.003
Spar + Magaldrate	5.91	7.52	0.005	6.43	8.04	0.003

Table 4: Adsorption capacities of antacids towards sparfloxacin in simulated gastric and intestinal juices

Antacid	Adsorption capacity [mg (mmol)/g] for sparfloxacin	
	Simulated gastric juice 296 nm	Simulated intestinal juice 290 nm
Sodium bicarbonate	125(0.0104)	212(0.0130)
Magnesium carbonate	139(0.0116)	224(0.0138)
Calcium carbonate	117(0.0097)	230(0.0142)
Magnesium hydroxide	122(0.0101)	194(0.0119)
Calcium hydroxide	107(0.0089)	230(0.0142)
Aluminium hydroxide	123(0.0102)	229(0.0141)
Magnesium trisilicate	102(0.0085)	110(0.0067)
Magaldrate	118(0.0098)	260(0.0160)

and Al³⁺ may be responsible for the prolonged and incomplete dissolution.

From the results listed in tables 1-2, it is quite apparent that the availability of sparfloxacin decreased in presence of calcium and magnesium carbonate (in a concentration of 0.2% W/V). In presence of even lower levels of antacids calcium carbonate also reduced sparfloxacin availability; the amount dissolved after 90 minutes was 71.12% and after 180 minutes 73.16 % with comparatively high values of T₅₀ and T₉₀.

In magnesium carbonate case, merely 49.74 % of the drug was present in simulated gastric juice after an interval of 90 minutes and 53.88 % of the drug was present at end of the experiment with T₅₀ and T₉₀ values of 6.9 and 8.51 minutes, respectively. While in simulated intestinal juice, the availability of the drug after intervals of 90 and 180 minutes was 37.09 and 37.43 %, respectively.

The availability of sparfloxacin in presence of calcium hydroxide was 90.12 % at half of interval and remained consistent until end of the experiment in simulated gastric juice, whilst 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 sparfloxacin. After an interval of 90 minutes, 768.16 % of the drug was present in solution, which was consistent up to end of the experiment, while in simulated intestinal juice 27.22 and 30.28 % was present respectively. This higher drug content is also indicative of formation of magnesium chelate.

Magaldrate, a combination of aluminum and magnesium hydroxides and sulfates showed effect on availability of sparfloxacin in simulated gastric juice. After an interval of 90 minutes, 74.86 % of the drug was present in simulated gastric juice and remained consistent till the end, while in simulated intestinal juice there was significant retardation in the availability of the drug. At half of the time, 33.68 % of the drug was available in the medium and in 180 minutes, only 43.89 % of the drug could be recovered.

Thus, it is clear that the availability of sparfloxacin can be retarded by small amounts of antacids containing polyvalent cations. Although it had previously been suggested that antacids decrease the availability of other antibiotics by raising the pH of the medium (Arayne et al. 2005) 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, sparfloxacin was found to be strongly adsorbed on various antacids. Figure 1 is derived from the Langmuir equation (Frenning and Stromme, 2003) 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 from the studies that all antacids adsorbed sparfloxacin to different extents. Magaldrate and calcium carbonate in simulated gastric juice exhibited relatively higher adsorption capacities that is to say 96% and 81% in that order, even as in simulated intestinal juice. Magnesium trisilicate and calcium hydroxide exhibited higher adsorption capacities that is 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 sparfloxacin. These studies indicate that sparfloxacin is strongly adsorbed on antacids; magnesium trisilicate, calcium carbonate, and magaldrate exhibited relatively higher adsorption capacities. The adsorption of sparfloxacin by antacids may be responsible for the marked retardation of availability of sparfloxacin.

CONCLUSIONS

The availability of oral sparfloxacin can be affected by the concurrent ingestion of antacids containing multivalent cations. It is imperative to be aware of these interactions because they may so greatly affect sparfloxacin availability that it may compromise the patient's outcome. The effects of these interactions can be significantly reduced by administering antacid doses several hours before or after giving the fluoroquinolone drug. If an antacid is absolutely required, adjunctive therapy, such as an H_2 receptor antagonist or a proton pump inhibitor, may be used to replace the antacid in the treatment of peptic ulcer disease. When patients use antacid products, particularly magnesium-aluminum hydroxide antacids, they should be encouraged to avoid taking the antacid within two hours after a fluoroquinolone dose or six hours prior to the next antimicrobial dose.

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