INFLUENCE OF TYPE AND NEUTRALISATION CAPACITY OF ANTACIDS ON DISSOLUTION RATE OF CIPROFLOXACIN AND MOXIFLOXACIN FROM TABLETS

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ABSTRACT

Dissolution rate of two fluoroquinolone antibiotics (ciprofloxacin and moxifloxacin) was analysed in presence/absence of three antacid formulations. Disintegration time and neutralisation capacity of antacid tablets were also checked. Variation in disintegration time indicated the importance of this parameter, and allowed evaluation of the influence of postponed antacid-fluoroquinolone contact. The results obtained in this study showed decreased dissolution rate of fluoroquinolone antibiotics from tablets in simultaneous presence of antacids, regardless of their type and neutralisation capacity.

KEY WORDS: dissolution, neutralization capacity, ciprofloxacin, moxifloxacin, antacid, interaction
INTRODUCTION

Fluoroquinolones (FQ) are broad spectrum antibacterial agents which chemically, may be regarded as weak substituted heterocyclic amino acids (1). Fluoroquinolones are very efficient against aerobic Gram-negative microorganisms but less efficient against Gram-positive microorganisms (2,3). These drugs are extremely useful for the treatment of a variety of infections, including urinary tract infections (4), soft tissue infections (5), respiratory infections (6), bone-joint infections, typhoid fever, sexually transmitted diseases (7), prostatitis (8), community acquired pneumonia, acute bronchitis and sinusitis (9). Also, a relatively new approach to the rational design of antitumour agents has been introduced based on some new quinolone molecules that display a novel mode of action (10). Ciprofloxacin and moxifloxacin are members of fluoroquinolone family which belong to third and fourth generation of these drugs, respectively (11,12,13).

In clinical practice, fluoroquinolones are often administered concomitantly with other drugs which may contain metal ions. The presence of metal ions from e.g. metal based antacids may significantly affect the activity of quinolones since they can readily bind several divalent or trivalent metal ions (14). Complexation alters solubility, lipophilicity, antimicrobial activity and protein binding capacity of quinolones. Solubility of all ionic quinolone complexes is much greater than that of molecular complexes which are only sparingly soluble (15).

Some metal–quinolone complexes show antimicrobial activity comparable to that or free quinolone but in some cases the activity is increased or lowered. Mg$^{2+}$ and Al$^{3+}$ were found to decrease the activity of quinolones (14).

Therefore, the aim of this study was to:

- determine disintegration time and neutralization capacity of tablets containing antacids,
- evaluate the influence of certain antacids on dissolution rate of fluoroquinolones during simultaneous administration,
- determine dissolution rate of fluoroquinolone formulations (ciprofloxacin and moxifloxacin tablets) tested alone or in combination with antacids, and on the basis of the results obtained evaluate the influence of antacids, concerning their neutralization capacity, on dissolution rate,
- evaluate the influence of postponed antacid-fluoroquinolone contact in dissolution media on dissolution rate of ciprofloxacin and moxifloxacin tablets.

MATERIALS AND METHODS

Reagents

The used reagents were all of analytical grade, unless otherwise stated. Ciprofloxacin hydrochloride monohydrate and moxifloxacin hydrochloride working standards were obtained from Merck (Darmstadt, Germany) and Bayer (Zürich, Switzerland), respectively.

Hydrochloric acid 37% was obtained from J.T. Baker (Deventer, Holland) and hydrochloric acid and sodium hydroxide titrimetric solutions (1.0 mol/dm$^3$) from Riedel-de Haën (Seelze-Hanover, Germany).

Tablet formulations

Three tablet formulations containing antacids were used. These antacid samples are marked as “M” (labelled strength: 666.6 mg Al(OH)$_3$ and 182.7 mg MgO), “G” (labelled strength: 450 mg Al(OH)$_3$, MgCO$_3$ jelly and 300 mg Mg(OH)$_2$), “R” (labelled strength: 500 mg hydrotalcite). For the fluoroquinolone antibiotics two tablet formulations were used: ciprofloxacin (labelled strength: 500 mg) and moxifloxacin (labelled strength: 400 mg).

Disintegration testing

The following disintegration test was performed: in each of six tubes, one tablet is placed. The assembly was suspended in the 1 litre beaker, containing 0.1 mol/dm$^3$ HCl, and operated (without disks). A suitable device maintained temperature of the liquid at 37±0.5°C. The test was provided using Pharma Test disintegration tester Type PTZ (Pharma Test, Hainburg, Germany).

Determination of neutralization capacity

Ten tablets containing antacid were weighed and the average tablet weight was determined. The tablets were ground to a fine powder, mixed to uniformity. The quantity of it, equivalent to the average tablet weight, was transferred to a 583 cm$^3$ beaker, diluted in 83 cm$^3$ of water and mixed on magnetic stirrer for two minutes (200 rpm). 50 cm$^3$ of 1.0 mol/dm$^3$ HCl titrimetric solution (Riedel-de Haën, Seelze-Hanover, Germany) was added after mixing. After the addition of the acid the mixing procedure continued (200 rpm), accurately timed, for 10 minutes. Excess hydrochloric acid was titrated with 1.0 mol/dm$^3$ NaOH titrimetric solution (Riedel-de Haën, Seelze-Hanover, Germany) to attain pH 3.5 stable for 15 seconds. The obtained result is expressed in mEq of acid neutralised/per tablet.

In vitro dissolution assay

The dissolution tests of ciprofloxacin and moxifloxa-
cin coated tablets \( (n=6) \) were performed using USP apparatus 2 \( (n=6) \). Van Kel VK 7010 dissolution tester, at a stirring speed of 50 rpm (Van Kel, Cary, NC, USA). Dissolution profiles were determined at \( 37\pm0.5^\circ\text{C} \) in \( 900 \text{ cm}^3 \) of \( 0.1 \text{ mol/dm}^3 \) hydrochloric acid solution, \( \text{pH}=1.0 \). The paddle was positioned to extend to exactly 2.5 cm above the flask bottom.

Samples aliquots \( (5 \text{ cm}^3) \) were collected using graduated syringe after 30 minutes. Prior to use, the dissolution medium was equilibrated at \( 37^\circ\text{C} \) overnight to deaerate medium. The suitability of the paddle apparatus was checked using the USP prednisone and salicylic acid calibrators -calibrators for system suitability test of basket and paddle dissolution apparatus (16). One tablet of the corresponding quinolone (ciprofloxacin or moxifloxacin) was placed in each filled flask \( (6 \text{ tablets per run}) \) when establishing the dissolution profiles of quinolones in the absence of cations. These profiles were used to generate reference profile. To evaluate the influence of the different cations on the quinolone dissolution kinetics, the corresponding cation preparation was added to each flask at the same time as the quinolone formulation.

These samples were filtered using a "blue ribbon paper-391" (Munktell & Filtrak GmbH, Bärenstein, Germany) and quantified by UV/VIS spectrophotometric analysis (Shimadzu UV-1700, Kyoto, Japan).

Standard curves of absorbance versus concentration (in eight points) were constructed using solutions of:

\( \diamond \) ciprofloxacin hydrochloride monohydrate (dissolution medium- \( 0.1 \text{ mol/dm}^3 \) HCl, pH=1.0; previously degassed, ranging in concentration from \( 0.000075 \text{ mg/cm}^3 \) to \( 0.015 \text{ mg/ cm}^3 \); \( y = 120.510366x + 0.015705; \ r^2 = 0.998524 \)). UV absorbance of each standard solution was measured spectrophotometrically at 276 nm.

\( \diamond \) moxifloxacin hydrochloride (dissolution medium- \( 0.1 \text{ mol/dm}^3 \) HCl, pH=1.0; previously degassed, ranging in concentration from \( 0.0002 \text{ mg/ml} \) to \( 0.004 \text{ mg/ cm}^3 \); \( y = 100.084681x + 0.009209; \ r^2 = 0.999813 \)). UV absorbance of each standard solution was measured spectrophotometrically at 295 nm.

Absorbance versus concentration plots were linear over these concentration ranges and were used to determine percent of drug dissolved in the dissolution experiments.

**RESULTS AND DISCUSSION**

The results of disintegration testing are summarised in Table 1, neutralisation capacity determination in Table 2, and in vitro dissolution assay in Tables 3-4 (which show the amount of the dissolved drug-ciprofloxacin or moxifloxacin without/with antacid addition).

Values of dissolved moxifloxacin exceeding 100 % are well within the deviation range for content uniformity allowed for solid preparations by both US and European Pharmacopoeias (±10%) (17, 18).

| Antacid formulation | Disintegration time |
|---------------------|--------------------|
| "M"                | ≥ 2 hours          |
| "G"                | ≤ 7 minutes        |
| "R"                | ≤ 40 seconds       |

**TABLE 1. Disintegration time of antacid tablet formulations**

| Antacid formulation | Neutralisation capacity (mEq acid/tablet) |
|---------------------|------------------------------------------|
| "M"                | 23.25                                    |
| "G"                | 21.63                                    |
| "R"                | 13.60                                    |

**TABLE 2. Neutralisation capacity values for antacid tablet formulations**

| Sample | Ciprofloxacin (500 mg) without antacid | Ciprofloxacin (500 mg) + M | Ciprofloxacin (500 mg) + G | Ciprofloxacin (500 mg) + R |
|--------|---------------------------------------|---------------------------|---------------------------|---------------------------|
| 1      | 93.61                                 | 96.44                     | 90.68                     | 68.68                     |
| 2      | 94.77                                 | 96.28                     | 87.60                     | 78.15                     |
| 3      | 97.21                                 | 97.34                     | 83.76                     | 80.52                     |
| 4      | 98.54                                 | 95.08                     | 86.74                     | 75.11                     |
| 5      | 99.86                                 | 95.91                     | 88.66                     | 76.59                     |
| 6      | 97.61                                 | 96.25                     | 89.41                     | 79.01                     |

χ \( 96.9320 \) 96.2175 87.8083 76.3346
S.D. 2.3424 0.7344 2.4120 4.1996
R.S.D 2.42 0.76 2.75 5.50

**TABLE 3. Amount of dissolved ciprofloxacin from tablet formulation without/with antacid addition**
Conclusion

According to the results obtained in this study, we can conclude that dissolution rate of ciprofloxacin and moxifloxacin was downsized by simultaneous application of antacids. This influence was more pronounced in the case of ciprofloxacin, than in the case of moxifloxacin tablets. Also, similar relationship was found in decreased dissolution rate of ciprofloxacin tablets compared to moxifloxacin (2.3 vs. 2.4) using the same antacids ("M", "G" and "R"), under the same testing conditions. It can be assumed, that it is a consequence of similar mechanism of interaction which is not dependent of structural differences between ciprofloxacin and moxifloxacin.

Regardless of the type and neutralization capacity of analysed antacids, which posses ability to chelate fluoroquinolones, potential simultaneous application of these types of drugs (antacids and fluoroquinolones) has appreciable influence on dissolution rate of ciprofloxacin and moxifloxacin tablets.
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