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RESEARCH PAPER

# Influence of Pharmacotechnical Design on the Interaction and Availability of Norfloxacin in Directly Compressed Tablets with Certain Antacids

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**ABSTRACT**

*Norfloxacin is a fluorquinolone that can interfere with antacids that contain aluminum and magnesium salts by complexation and modification of its solubility, which reduces its absorption and may lead to therapeutic failures. The purpose of this work was to evaluate the effect of the pharmaceutical design on this interaction and to develop a formulation of norfloxacin tablets in which this process could be avoided. Norfloxacin tablets were designed in 28 formulations. The interaction was studied in terms of in vitro dissolution behavior (USP 23, apparatus 2) in simulated gastric fluid with different doses of four commercially available antacid preparations. It was observed that dissolution rates were markedly reduced in the presence of all antacids studied. This phenomenon was practically avoided with some formulations of norfloxacin tablets in which a disintegrant (sodium starch glycolate or crospovidone) was included. These results indicated that the chelation among metal ions and norfloxacin could be affected by the delivering ability of the drug in the tablet. It was demonstrated that the pharmacotechnical design could modify an interaction process. Some formulations of tablets, in which the reduced dissolution rates in the presence of nonsystemic antacids in vitro was practically avoided, were developed by direct compression.*

***Key Words:*** *Antacid; Chelates; Disintegrant; Dissolution; Interaction; Norfloxacin.*

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## INTRODUCTION

Norfloxacin is an orally administered quinolone derivative chemically related to nalidixic acid. It has demonstrated a broad spectrum of antibacterial activity against gram-positive and gram-negative aerobic bacteria. This drug is bactericidal and works by inhibition of DNA-gyrase; thus, this antimicrobial agent is indicated for treating both complicated and uncomplicated urinary tract infections in patients who are candidates for oral therapy (1, 2). Chemically, this fluorquinolone is 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline–carboxylic acid. There is a large body of information in the literature on the interaction of quinolones with antacids; in this way, the oral absorption of fluorquinolones in general, and norfloxacin in particular, has been shown to be less when they are ingested with certain antacid preparations containing aluminum and magnesium salts (3–5). Two possible mechanisms responsible for this interaction have been suggested. The solubility of norfloxacin and other quinolones appears to be influenced by pH due to the fact that such compounds in aqueous solution exist mainly in their zwitterionic form [$I^{+-}$] owing to the acid/base interaction between the basic nitrogen at the position 4′ of the piperazine and the 3-carboxylic acid group (6), as can be seen in Fig. 1B. On the other hand, chelation between metal ions contained in some antacid preparations and the 3-carboxyl and 4-oxo substituents on the quinolone nucleus results in a complex that is more polar and unable to be absorbed (7–9). This interaction has also been observed in the presence of different metal ions, such as $Ca^{2+}$, $Cu^{2+}$, $Fe^{3+}$, and $Zn^{2+}$ (7,10–12) and can be detected in vitro by spectrofluorimetry (13). Moreover, the formation of chelates between norfloxacin and the antacid preparations used in the present study has been reported previously (13).

In the present paper, 28 formulations of directly compressible norfloxacin tablets were developed to study the influence of the pharmacotechnical design on the in vitro dissolution behavior and on the mentioned interaction with antacids. The effect of fillers, lubricants, and superdisintegrants on the release of norfloxacin tablets in the presence of different antacid preparations was investigated.

## MATERIALS AND METHODS

### Drug Assay

The amount of norfloxacin released was spectrophotometrically assayed at 276 nm using a previously validated analytical method (13) for norfloxacin in simulated gastric fluid, prepared as described in USP 23 (14), and 0.1 N hydrochloric acid as solvents with a pH of about 1.2. A Beckman DU-6 spectrophotometer was used in the range of concentrations between 0 and 10 μg/ml. All the samples from dissolution studies were previously filtered using a 0.45-μm cellulose acetate filter. The influence of the eluent, the excipients, and the antacids used in this study were evaluated previously, and no significant interferences were found.

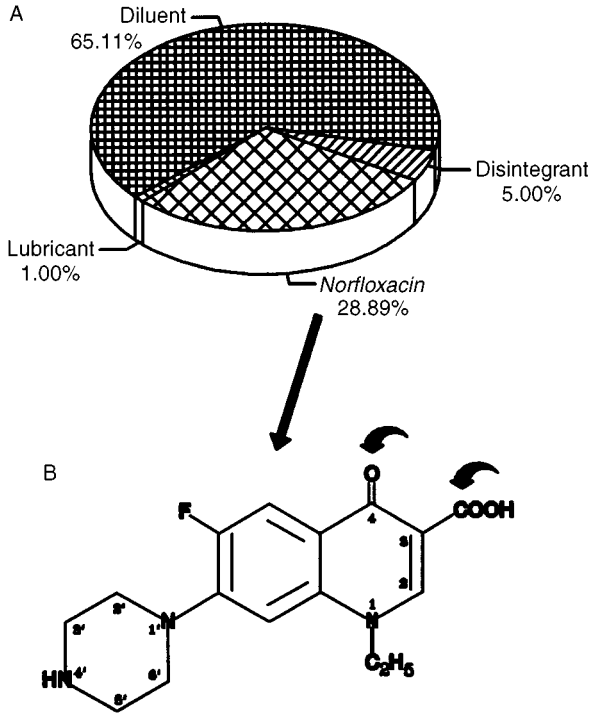


**Figure 1.** A. General composition of the norfloxacin tablets used in the present study. B. Numbered structural formula of norfloxacin showing the substituents that would play an important role in the formation of chelates in the presence of metal ions.

### Formulation of Norfloxacin Tablets

Norfloxacin tablets in 28 formulations were developed by direct compression, using different kinds of diluents, lubricants, and superdisintegrants, as described in Fig. 1A and Table 1. All series of tablets were punched in an eccentric press using a mean weight of 450 mg and a hardness value of 70–80 N as a reference. Tablet diameter was 12.0 mm in all cases. The physical properties (angle of repose, compressibility, Hausner ratio, etc.) of powder mixtures corresponding to the 28 formulations

***Table 1***

*General Composition of the Different Formulations of Norfloxacin Tablets*

| Formulation | Diluent | A | B | C | D |
|---|---|---|---|---|---|
| I | Tablettose | M | L | P + M | E + M |
| II | Ludipress | M | L | P + L | E + L |
| III | Cellactose | M | L | P + M | E + M |
| IV | Avicel PH200 | M | L | P + L | E + L |
| V | Emcocel 90M | M | L | P + L | E + L |
| VI | Compril | M | L | P + L | E + L |
| VII | Pearlitol | M | L | P + L | E + L |

M = formulations including 1% of magnesium stearate as a lubricant; L = Lubritab; P = formulations including 5% of polyplasdone-XL as a disintegrant; E = Explotab.

were evaluated previously, as was the technological characterization of tablets (15,16) on the basis of friability, uniformity of dosage units (using 130 mg as the mean amount of norfloxacin in the tablet), disintegration, and in vitro dissolution using the requirements specified for the U.S. Pharmacopeia (14).

Formulations I and II were made from two lactose derivatives as diluents: α-lactose monohydrate (Tablettose®; Meggle Milchindustrie GMBH and Co. KG, Madrid, Spain) and a coprocessed lactose-povidone-crospovidone (Ludipress®; BASF Wyandotte Corp., Barcelona, Spain), respectively. In tablet III formulations, a cellulose-lactose coprocessed excipient (Cellactose®; Meggle Milchindustrie) was used. Series IV and V were formulated from two commercially available microcrystalline celluloses (MCCs) as direct compression fillers: Avicel® PH200 (FMC Corp., Madrid, Spain) and Emcocel® 90M (Edward Mendell Co., Inc., Madrid, Spain), and tablets VI and VII were formulated using saccharidic derivatives different from lactose: Compril® (Glyco Ibérica SA, Madrid, Spain), composed of a lipopolysaccharide, and a directly compressible mannitol (Pearlitol®; Roquette-Laisa, Barcelona, Spain). These products are widely used as direct compression excipients in the pharmaceutical design of tablets (17–22).

The influence of disintegrants on the release behavior of many drugs from solid dosage forms is well documented (23–25). To evaluate the effect of the presence of a superdisintegrant on the interaction mechanisms, two widely used disintegrants agents, like a crospovidone (Polyplasdone®-XL; ISP Chemicals Corp., Barcelona, Spain) and a sodium starch glycolate (Explotab®; Edward Mendell Co., Inc., Juliá Parrera, Spain) were incorporated in formulations C and D, respectively (see Table 1). The influence of lubricants was also studied using magnesium stearate (Panreac-Montplet and Esteban, Barcelona, Spain) or a polyhydrogenated vegetable oil (Lubritab®; Edward Mendell Co., Inc.).

## Interaction Studies

All formulations of norfloxacin tablets were studied in terms of dissolution behavior in the presence of the antacid preparations described in Table 2. All the in vitro dissolution studies were performed at 37.0°C ± 0.1°C using the USP 23 paddle (apparatus 2) at a revolution speed of 50 ± 1 rpm and simulated gastric fluid (300 ml), alone or including the antacid, as the dissolution medium. Only 300 ml were used in each dissolution experiment to obtain a pH value more similar to those obtained in vivo with the addition of the antacids. To ensure sink conditions, the solubility of the drug was studied previously under all the work conditions, and it turned out to be about 100 times greater than the concentrations obtained in the dissolution medium.

Two dose fractions of each antacid preparation were assayed with each formulation: ½ and 1, using as unitary value the average weight obtained for 20 tablets (see Table 2). For each dissolution test, 10 tablets corresponding to an antacid preparation were powdered, and a sieve fraction below a 100-μm screen was used. The corresponding amount of antacid powder was accurately weighed and added to the gastric fluid. The mixture was stirred in a magnetic stirrer using a rotation speed of 1100 rpm for 20 min to neutralize the hydrochloric acid of the gastric fluid. The final pH value was measured for each assay. The resulting mixture was filtered and heated in the dissolution apparatus to reach the work temperature. Samples were collected at different times depending on the dissolution behavior of each formulation of norfloxacin tablet and diluted to fit the concentrations to be mea-

***Table 2***

*Detailed Compositions of the Antacid Tablet Preparations*

| Trade Name | Code | Composition of Each Tablet | | Average Weight |
|---|---|---|---|---|
| Almax® (Almirall) | A | Almagate (INN)[a] | 0.500 g | 1.218 g |
| | | Saccharin calcium | 0.003 g | |
| | | Other excipients | | |
| Maalox® (Rhône Poulenc-Rorer) | M | $Al(OH)_3$ | 0.600 g | 1.781 g |
| | | $Mg(OH)_2$ | 0.300 g | |
| | | Saccharose | 0.050 g | |
| | | Other excipients | | |
| Bemolan® (Boehringer Mannheim) | B | Magaldrate (INN)[b] | 0.400 g | 1.103 g |
| | | Other excipients | | |
| Aligest Plus® (Schering-Plough) | L | $Al(OH)_3$ | 0.298 g | 1.623 g |
| | | $Mg(OH)_2$ | 0.328 g | |
| | | $CaCO_3$ | 0.410 g | |
| | | Simethicone | 0.025 g | |
| | | Saccharin sodium | 0.005 g | |
| | | Aspartame | 0.010 g | |
| | | Other excipients | | |

[a] Almagate (INN): $[Al_2Mg_6(OH)_{14}(CO_3)_2 \cdot 4H_2O]$.
[b] Magaldrate (INN): $[Al_5Mg_{10}(OH)_{31}(SO_4)_2 \cdot x\ H_2O]$.

sured, as previously described. All the dissolution studies were performed in triplicate.

### Treatment of Dissolution Data

The results obtained from dissolution studies in terms of concentration and percentage of norfloxacin released were analyzed mathematically using the function proposed by Weibull and Langenbucher (26,27). Specifically, the percentage of drug released $C$ can be related to the dissolution time $t$ by the following equation:

$$\log[-\ln(100 - C)] = \beta\log(t - t_0) - \beta\log t_{63.2} \quad (1)$$

where $\beta$ is the Weibull shape parameter, $t_0$ is the lag time, and $t_{63.2}$ is a constant corresponding to the time needed to release 63.2% of the total amount of the norfloxacin in the tablet. A linear relation should be obtained when $\log[-\ln(100 - C)]$ is plotted as a function of $\log(t - t_0)$. The extrapolated $y$-axis intercept is $-\beta \log t_{63.2}$, and the slope is $\beta$.

To obtain a parameter for the comparative study of dissolution rates of each formula in the presence of antacids without using a kinetic model, the dissolution efficiency at the time 40 min $DE_{40}$ was also calculated from the area under the curve corresponding to the dissolution profile (28,29) using the following expression:

$$DE_t(\%) = \frac{\int_0^t y dt}{y_{100}} 100 \quad (2)$$

In this way, such a treatment of the dissolution data would permit a calculation of $t_{63.2}$ and $DE_{40}$ for each formula in the presence of the above-mentioned antacids (½ and 1 dose fraction) and provide a basis for comparisons of the interaction process.

## RESULTS AND DISCUSSION

Formulation I-B was not investigated in terms of interaction with antacids due to the bad quality of the resulting norfloxacin tablets, as described in a previous paper (16). Apart from this, it was observed in some formulations that the dissolution rate of norfloxacin in the tablets was affected markedly by the presence of the antacid preparations in the dissolution medium. Figure 2 illustrates this, as can be seen from the dissolution profiles resulting for formula VII-A under the above-mentioned conditions. The profile was different for each antacid. In this way, the most dramatic decrease of the dissolution rate was obtained with antacid L. A larger decrease was also found with a 1 dose fraction in comparison to a ½ dose fraction. In sharp contrast, totally different results in terms of in-

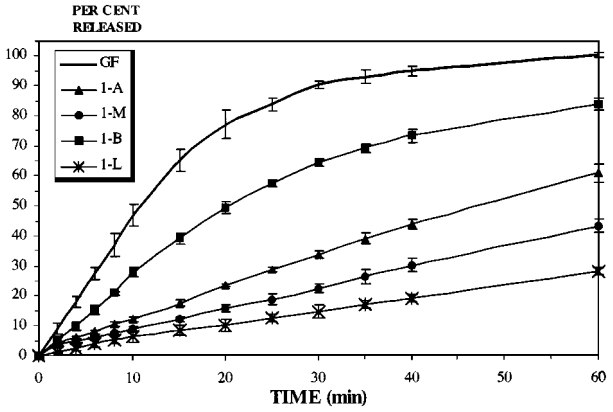


**Figure 2.** Dissolution profiles of norfloxacin tablets VII-A in the presence of 1 dose fraction of each antacid in comparison to the profile obtained in gastric fluid (GF) alone (mean ± SD). The profiles corresponding to one-half dose fraction were not plotted for clarity.

teraction were obtained for tablets VII-D (including 5% sodium starch glycolate), as can be seen in Fig. 3.

For the sake of clarity, all the resulting dissolution profiles for each formula are not shown in this paper. Only the final mean values of the $t_{63.2}$ constant and the dissolution efficiency at 40 min calculated from Eqs. 1 and 2, respectively, are exposed. The resulting $t_{63.2}$ values corresponding to the tablets formulated from lactose derivatives as direct compression excipients (tablets I and II) are provided in Table 3. The mean pH value obtained with each dose fraction of each antacid is also shown in the same table. In all cases, the $r$ values (correlation

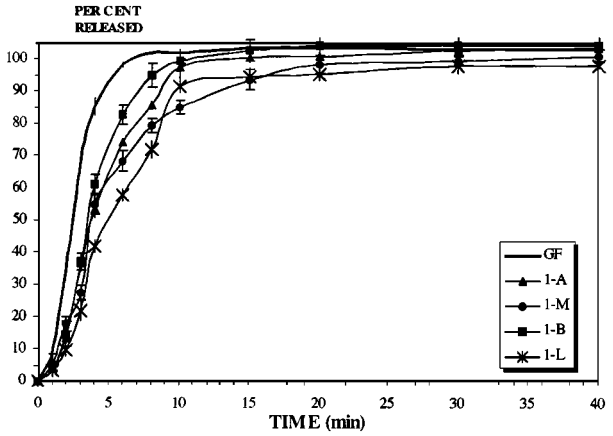


**Figure 3.** Dissolution profiles for formulation VII-D in gastric fluid alone and in the presence of different antacids (1 dose fraction).

coefficient resulting from fitting the dissolution profiles to a Weibull kinetic model) were higher than 0.99, and the standard deviation (SD) for each set of data did not reveal significant variability for each profile. The standard deviations are not shown in the tables for clarity. In all cases, a modification of the dissolution times was found with the addition of the antacids. A totally different behavior was observed among formulations I and II in terms of interaction. A dramatic increase in the $t_{63.2}$ values was obtained for formulation I-A when the antacids were added in the medium, whereas in tablets I-C and I-D, this interaction was practically avoided, also in the presence of antacid L, the most powerful neutralizing agent of the four preparations studied. In contrast, the use of a disintegrant did not provoke a modification of the interaction in formulations II.

The mean $t_{63.2}$ values corresponding to formulations III are shown in Table 4. As can be seen, a dramatic increase in the dissolution times was obtained in the presence of antacids, with the exception of tablets III-D, in which the interaction is practically avoided in vitro. The final values for tablets IV and V, formulated from two MCC derivatives, are given in Table 5. It was found in all cases that a dramatic increase in the dissolution times was obtained in the presence of antacids. The effect of this interaction was decreased using crospovidone as a disintegrant and was practically avoided with sodium starch glycolate. In general lines, higher dissolution times were obtained with tablets V compared to tablets IV; these results indicated that the dissolution behavior was different when using one MCC or another.

Table 6 shows the resulting mean values of $t_{63.2}$ for tablets formulated from saccharidic excipients different from lactose (formulations VI and VII). In tablets VI, the interaction with antacids was practically avoided, especially with sodium starch glycolate. Nevertheless, the mean $t_{63.2}$ could not be taken into account in terms of comparison due to the high variability obtained in the different dissolution experiments, which could be caused by the lack of uniformity in terms of pharmacotechnical properties of the four batches mentioned: VI-A, VI-B, VI-C, and VI-D. Problems in the initial mixing could be responsible for this variability. In formulations VII, with a low variability, a decrease of the interaction with antacids was obtained by including a superdisintegrant, especially when using sodium starch glycolate (tablets VII-D).

To avoid the possible error obtained inherent to the fitting of a certain kinetic model to the dissolution data, the comparative interaction among the different formulations was studied using a parameter such as dissolution efficiency, obtained from Eq. 2. Figures 4–6 show the

***Table 3***

*Resulting Mean Values of $t_{63.2}$ (min) for Each Formulation Containing a Lactose Derivative as a Main Direct Compression Excipient*

| Conditions | pH | I-A | I-C | I-D | II-A | II-B | II-C | II-D |
|---|---|---|---|---|---|---|---|---|
| GF | 1.10 | 13.68 | 13.96 | 9.97 | 10.02 | 7.49 | 6.70 | 3.55 |
| +½ A | 1.95 | 22.04 | 7.54 | 2.23 | 18.35 | 22.86 | 11.98 | 11.46 |
| +1 A | 4.32 | 89.09 | 19.74 | 3.12 | 73.91 | 77.91 | 53.21 | 64.99 |
| +½ M | 2.49 | 43.03 | 7.55 | 2.16 | 22.61 | 16.00 | 16.98 | 17.31 |
| +1 M | 6.45 | 194.5 | 16.04 | 7.04 | 262.6 | 238.7 | 157.8 | 141.4 |
| +½ B | 1.44 | 16.07 | 7.93 | 1.82 | 14.48 | 11.31 | 9.67 | 8.21 |
| +1 B | 3.75 | 40.17 | 7.75 | 2.01 | 37.59 | 28.41 | 23.33 | 24.37 |
| +½ L | 5.10 | 152.0 | 13.98 | 4.12 | 181.9 | 284.8 | 206.8 | 135.3 |
| +1 L | 7.88 | 1590 | 15.73 | 11.23 | 1620 | 1777 | 1186 | 1117 |

***Table 4***

*Mean $t_{63.2}$ Values (min) for Formulations III*

| Conditions | III-A | III-B | III-C | III-D |
|---|---|---|---|---|
| GF | 42.71 | 25.36 | 38.38 | 27.37 |
| +½ A | 95.43 | 83.10 | 49.77 | 6.12 |
| +1 A | 188.2 | 152.7 | 73.92 | 14.05 |
| +½ M | 120.5 | 115.2 | 52.02 | 8.15 |
| +1 M | 210.0 | 166.5 | 64.54 | 19.88 |
| +½ B | 67.15 | 62.55 | 43.99 | 28.25 |
| +1 B | 129.4 | 105.2 | 48.07 | 6.55 |
| +½ L | 339.5 | 298.0 | 91.97 | 23.26 |
| +1 L | 1262 | 1031 | 101.6 | 30.38 |

evolution of $DE_{40}$ for some formulations alone and in the presence of the different antacids (½ and 1 dose fraction). For the sake of clarity, only the most important points from the calculations were plotted. In this way, a large reduction of the interaction was obtained in formulations I with sodium starch glycolate (I-D), as can be seen in Fig. 4. Some formulations, such as tablets II, did not appeared to be influenced by whether or not disintegrant was present in the composition of the tablet in terms of interaction with antacid. This phenomenon is illustrated in Fig. 5. In contrast, many other formulations, such as tablets III, IV, V, and VII, make up an example of cases in which, modifying the formulation by the inclusion of 5% disintegrant, totally different results were obtained in terms of interaction. Figure 6, which represents the evolution of $DE_{40}$ for formulation VII-A in comparison to tablets VII-D, shows an example of this.

A clear relationship between pH of the medium and extent of interaction could not be calculated due to the fact that, as previously mentioned, the modification of the pH value and the solubility of the drug were not the only mechanisms responsible for the interaction. The chelation between norfloxacin and the antacids in the frame of dissolution studies was previously evidenced (13), and the stability of each complex was also studied by fluorescence (30). In this work, totally different extents of interaction were found using very similar pH values, but changing the kind of antacid in the dissolution medium. From this study, it can be concluded that the nature of the antacid plays an important role in the mechanism of such interaction.

## CONCLUSIONS

The results obtained in the present study confirmed that the interaction between norfloxacin and the antacids takes place during the release of the quinolone in the tablets during the dissolution process. That is the reason why a properly designed in vitro dissolution test can be used to study this kind of pharmaceutical interaction. It was observed that tablets formulated without a disintegrant exhibited dissolution times significantly longer in the presence of the studied antacids. In some formulations, like II and VI, the use of a disintegrant in the tablet did not yield a significant modification in terms of interaction.

In formulations I, II, IV, V, and VII, it was found that the interaction with antacids could be modified completely by the inclusion of a disintegrant. It was also observed that this effect was achieved more successfully with the most powerful disintegrant of the two studied: sodium starch glycolate. Besides, the presence of the antacid in the dissolution medium provoked an increase in the dissolution rate of the norfloxacin tablet. This phenomenon appeared to be especially important in a pH range of 1.4–2.5, in which the disintegrant is more efficient.

***Table 5***

*Mean $t_{63.2}$ Values (min) for Formulations IV and V*

| Conditions | IV-A | IV-B | IV-C | IV-D | V-A | V-B | V-C | V-D |
|---|---|---|---|---|---|---|---|---|
| GF | 32.90 | 22.27 | 16.27 | 1.37 | 37.74 | 30.65 | 21.77 | 2.73 |
| +½ A | 29.95 | 31.72 | 15.59 | 2.13 | 42.62 | 34.24 | 26.88 | 3.00 |
| +1 A | 80.47 | 43.20 | 16.88 | 3.38 | 49.05 | 67.30 | 29.85 | 4.60 |
| +½ M | 49.85 | 35.73 | 15.91 | 2.51 | 45.48 | 43.81 | 27.50 | 3.95 |
| +1 M | 78.78 | 50.09 | 27.33 | 4.97 | 174.5 | 151.6 | 32.40 | 5.22 |
| +½ B | 35.87 | 29.67 | 27.66 | 1.93 | 50.89 | 52.05 | 22.75 | 3.08 |
| +1 B | 45.60 | 41.97 | 31.22 | 2.54 | 81.21 | 73.04 | 18.31 | 3.92 |
| +½ L | 136.8 | 71.69 | 28.68 | 9.95 | 276.5 | 230.7 | 59.04 | 8.43 |
| +1 L | 113.7 | 93.88 | 35.81 | 9.06 | 339.6 | 297.4 | 40.39 | 10.02 |

***Table 6***

*Mean $t_{63.2}$ Values (min) for Tablets VI and VII*

| Conditions | VI-A | VI-B | VI-C | VI-D | VII-A | VII-B | VII-C | VII-D |
|---|---|---|---|---|---|---|---|---|
| GF | 12.21 | 7.72 | 19.93 | 13.65 | 15.21 | 15.42 | 6.47 | 2.96 |
| +½ A | 22.46 | 16.43 | 20.75 | 16.95 | 23.31 | 27.36 | 8.34 | 4.49 |
| +1 A | 26.36 | 19.90 | 30.89 | 16.95 | 77.59 | 142.4 | 17.40 | 5.08 |
| +½ M | 19.45 | 14.26 | 20.12 | 15.43 | 26.60 | 31.13 | 12.97 | 5.95 |
| +1 M | 42.91 | 20.30 | 25.03 | 14.21 | 177.5 | 132.5 | 28.38 | 6.34 |
| +½ B | 14.73 | 3.43 | 19.25 | 12.45 | 21.52 | 24.35 | 7.44 | 3.60 |
| +1 B | 21.14 | 16.62 | 22.06 | 15.77 | 30.54 | 40.41 | 11.02 | 4.53 |
| +½ L | 34.57 | 12.75 | 24.67 | 14.44 | 91.48 | 262.2 | 44.20 | 5.18 |
| +1 L | 51.25 | 22.18 | 27.91 | 14.46 | 200.2 | 252.1 | 62.13 | 6.39 |

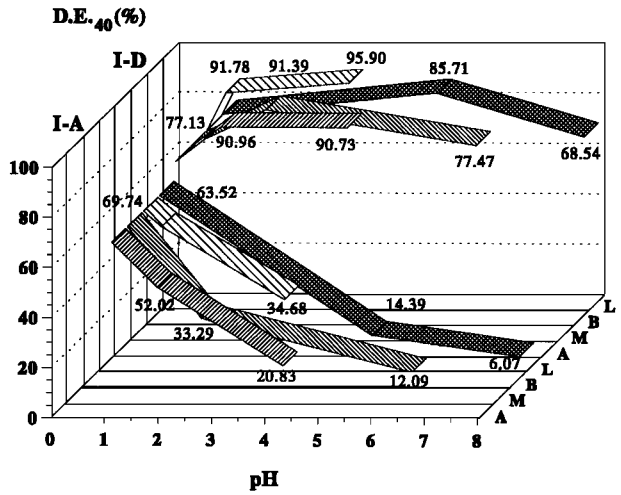


**Figure 4.** Mean dissolution efficiency *DE* at 40 min obtained for tablets I-A and I-D alone and in the presence of different antacids.

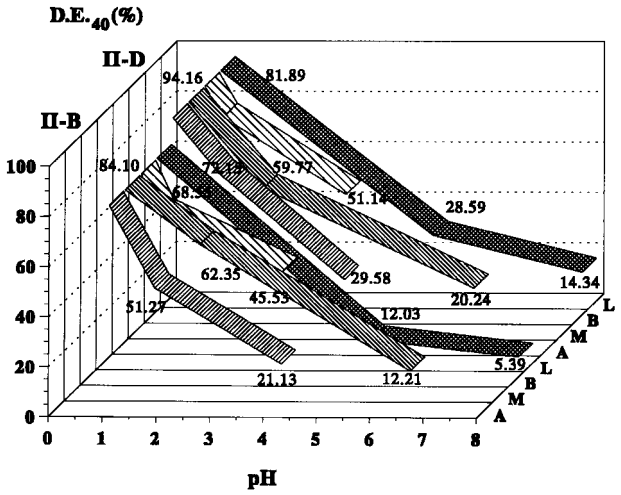


**Figure 5.** Mean $DE_{40}$ values for formulations II-B and II-D.

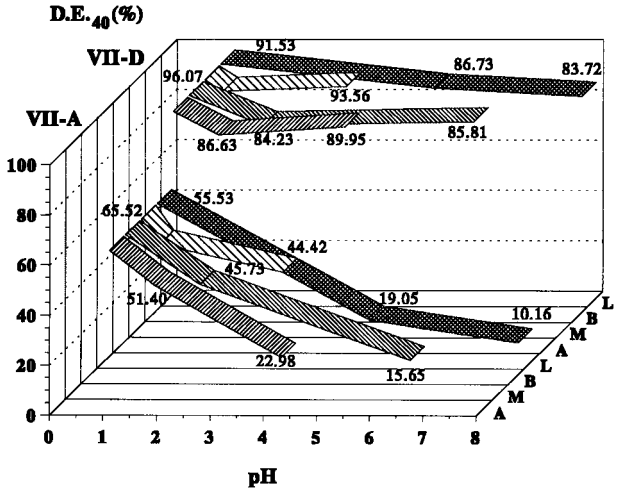


**Figure 6.** Mean $DE_{40}$ values for the formulations VII-A and VII-D.

There is a large body of information on the interaction of quinolones and antacids that could lead to a decrease in the oral absorption of the drug and thus to therapeutic failure, but the influence of the pharmacotechnical design of the tablet on this interaction and the possibility of modifying this process by improving the formulation (and thus the dissolution behavior of the quinolone) has not yet been studied extensively. In the present work, a number of formulations, like I-C, I-D, III-D, IV-D, V-D, and VII-D, in which the interaction with antacids has been practically avoided, have been developed. From the comparative data of in vitro availability, we are able to conclude that tablets IV-D and VII-D can be chosen as possible candidates for development, by direct compression, of an industrial formulation with a low degree of interaction with antacids. Although these results should be confirmed prospectively in vivo, the in vitro method discussed here can be very useful in a preformulation screening to elucidate the more convenient formula of a solid dosage form in the frame of the studies of this kind of pharmacokinetic interaction.

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