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Effect of pharmacotechnical design on the in vitro interaction of ketoconazole tablets with non-systemic antacids

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Abstract

In certain polytherapy programs, ketoconazole can be administered with some antacids that could modify its dissolution rate and reduce its absorption leading to therapeutic failures. The aim of this work was to evaluate the influence of some excipients on this interaction in vitro. In this way, six formulations of directly compressible ketoconazole tablets were developed. The results confirmed that the dissolution rate of ketoconazole tablets was significantly reduced in the presence of antacids. Nevertheless this interaction was remarkably avoided in some of the formulations checked and in some conditions. In this way, the inclusion of a disintegrant (sodium starch glycolate) not only increased the dissolution rate of ketoconazole in the tablets, as expected, but it also modified the degree in which the dissolution rate was decreased in the presence of antacids. It was proved that a suitable selection of the excipients and therefore the modification in the rate in which the drug was released, could play an important role to modify a pharmacokinetic interaction based on a reduction of the solubility of the drug as a function of the pH value of the medium.

Keywords: Ketoconazole; Direct compression; Tablet; Disintegrant; Antacids; Interaction

1. Introduction

A prerequisite for drug absorption and clinical success for all drugs given orally in a solid dosage form is its dissolution within the gastrointestinal tract which in many cases, can be the rate-limiting step in the in vivo overall absorption process (Remon et al., 1983).

Chemically, ketoconazole is (α)*cis*-1-acetyl-4-[*p*-[[2-(2,4dichlorophenyl)-2-imidazol-1-ylmethyl) 1,3-dioxolan-4-yl]methoxy]phenyl] piperazine (Fig. 1). About its physical properties it is a white or almost white powder practically insoluble in water, freely soluble in methylene chloride, soluble in methanol and sparingly soluble in alcohol (European Pharmacopoeia 3rd Ed., 1997).

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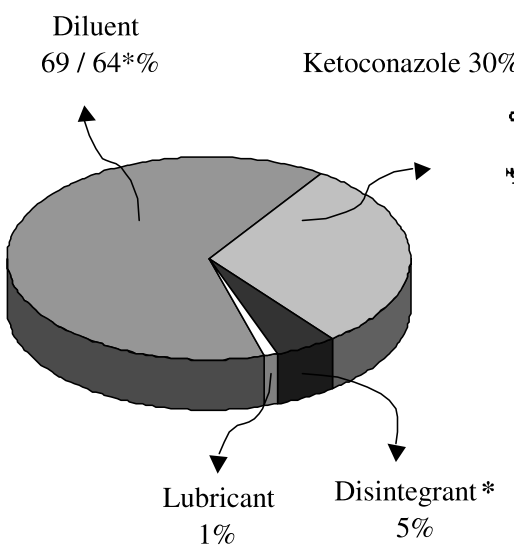
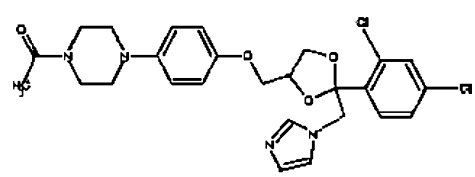
From a pharmacological point of view, ketoconazole is an imidazole antifungal synthetic agent, which must be administered either topically or by mouth. Its effects are based on the interference of the ergosterol synthesis, what leads to the alteration of the permeability of the cell membrane for those sensitive fungi. Ketoconazole has displayed significant activity against a broad range of superficial and systemic infections caused by pathogenic yeasts, dermatophytes and filamentous fungi (Minagawa et al., 1983), and it is often used in the treatment of opportunistic fungal infections in patients suffering from immuno-deficiencies. Since ketoconazole is a weak base with pK_a values of 2.94 and 6.51 (Carlson et al., 1983), an acid medium is required to transform the drug into the soluble hydrochloride salt. In this way, a lot of factors that could reduce the solubility of ketoconazole and therefore, provoke therapeutic failures have been described by many authors. Among those factors, the most important are the concomitant use of certain drugs like antacids, H_2-blockers, etc. the kinds of diet, some physiological situations like the massive presence of saliva in the stomach, the reflux from the duodenum, the day to day variability of gastric secretion in the same individual and between individuals, the age (it is known that there is a higher incidence of achlorhydria/hypochlorhydria in geriatric and paediatric population), some illnesses like AIDS, etc. (Brass et al., 1982; Daneshmend and Warnock, 1988; Lake-Bakaar et al., 1988; Lelawongs et al., 1988; Piscitelli et al., 1991; Carver et al., 1994; Chin et al., 1995; Lindahl et al., 1997).

The pharmacotechnical design has been found to be very important to improve or avoid some kinds of pharmacokinetic interactions (Córdoba Díaz et al., 2000b). In the present paper, six formulations of previously designed and evaluated directly-compressible ketoconazole tablets (Córdoba Díaz et al., 2000a), have been studied in order to elucidate the influence of the galenical design on the in vitro interaction between ketoconazole and antacids, due to the fact that such drugs are usually administered concomitantly in polytherapy programs. This interaction makes up nowadays one of the biggest problems that often makes more difficult the clinical use of ketoconazole. The effect of fillers and superdisintegrants on this process was evaluated.





FORMULATIONS

Diluent	Disintegrant	
	(-)	(+) *
L	1-A	1-B
M	2-A	2-B
P	3-A	3-B

Fig. 1. General composition of ketoconazole tablets (* formulations B only). Mean weights of 275 mg and hardnesses of 70–80N were used as a reference.

A rapid, sensitive and reproducible analytical method by UV spectrophotometry was developed for the assay of ketoconazole samples resulting from the dissolution experiments. The reliability of such method was also proved in the presence of the antacids and the excipients used in the present paper by means of a validation study.

2. Materials and methods

2.1. Pharmacotechnical design of ketoconazole tablets

Six formulations of directly compressible ketoconazole tablets were designed as described in Fig. 1. All tablets were obtained in an eccentric press using 10 mm-punches from several diluents: a commercially available mixture of α-lactose monohydrate and amorphous lactose–Pharmatose®DCL 11 (L) (DMV, Quimidroga SA, Spain), a directly compressible mannitol–Pearlitol®500 DC (M) (Roquette-Laisa, Spain) and a dibasic calcium phosphate anhydrous-A-TAB® (P) (Rhône-Poulenc, USA). Hydrogenated vegetable oil-Lubritab® (O) (Edward Mendell Co. Inc., Juliá/Parrera SA, Spain) as a direct-compression lubricant and sodium starch glycolate-Explotab® (D) (Edward Mendell Co. Inc., Juliá/Parrera SA, Spain) as a superdisintegrant agent (only in batches B) were added to complete the design of the final tablets. All the formulations were pharmacotechnically evaluated in a previous paper (Córdoba Díaz et al., 2000a) using as a reference the requirements specified by the U.S. Pharmacopoeia, 24th revision (USP 24/NF 19) (2000).

2.2. In vitro dissolution assay

Dissolution studies were conducted at 37.0 ± 0.1 °C in 300 ml of 0.1N hydrochloric acid using a USP 24-paddle dissolution tester at 50 ± 1 r.p.m. This medium has been reported to be one of the most commonly used in these studies to imitate the physiological gastric fluid (Lindahl et al., 1997). A volume of only 300 ml were used in order to obtain a pH value more similar to those obtained in vivo with the addition of antacids. Solubility studies were previously carried out to ensure sink conditions through all the dissolution experiments. Solubility values were at least 10 times greater that the theoretical maximum concentration in all media (with or without antacids).

All dissolution studies were conducted using six replicates. The profiles obtained in absence of antacids were considered to be the reference dissolution curve for each formulation.

Four commercially available non-systemic antacids were selected: Almax® (Almirall Prodesfarma), Maalox® (Rhône Pharma), Bemolan® (Roche) and Aligest Plus® (Shering-Plough). An accurately weighed amount of each antacid was added to 300 ml of 0.1N HCl and maintained under magnetic stirring during 30 min at 1100 r.p.m. to simulate two dose fractions of each antacid preparation: half a dose and a full dose. The medium was suitably filtered and kept at 37 °C in order to obtain a stable pH. All pH values were determined with a previously calibrated Mettler AT 200 pH-meter. Bemolan®, whose active substance is a complex salt (magaldrate), provided the lowest pH results. Since the solubility of ketoconazole is closely dependent of the acidity of the medium, this was the antacid which was chosen to perform the proposed interaction studies, because it was the best candidate to establish a therapeutic plan using concomitantly ketoconazole tablets and an antacid.

Ketoconazole in the samples from dissolution studies was spectrophotometrically assayed at a wavelength of 269.0 nm using 0.1N hydrochloric acid (HCl) as solvent. A Beckman DU-7 spectrophotometer was used in the range of concentration between 0 and 500 μg/ml. All the samples were previously filtered through a 0.45 μm cellulose acetate filter. This analytical method was validated and the influence of solvents, excipients or antacids was evaluated.

The results obtained in terms of concentration and percentage of ketoconazole released were mathematically analysed using the function proposed by Weibull and Langenbucher (Gibassier et al., 1982). The percentage of drug released (C) can be related to the dissolution time (t) by the Eq. (1):

$$\log[-\ln(100-C)] = \beta \log(t-t_0) - \beta \log T_d, \quad (1)$$

where β is the Weibull shape parameter, t the time, t_0 is the lag time and T_d is a constant corresponding to the $t_{63.2}$ or time needed to release the 63.2% of the total amount of drug in the tablet. A lineal regression analysis when $\log[-\ln(100-C)]$ is plotted vs. $\log(t-t_0)$, provides directly the β and $t_{63.2}$ values.

Besides, dissolution efficiency (DE) and mean dissolution time (MDT) were calculated using Eq. (2) and Eq. (3). Such amodelistic parameters are very useful to compare different profiles types because the evaluation of dissolution characteristics of the different formulations is not conditioned by the goodness of the fitting to a theoretical model of our data.

$$DE_t(\%) = \frac{\int_0^t C \, dt}{t}, \quad (2)$$

$$MDT = \frac{ADC}{M_\infty}. \quad (3)$$

In that equations, y is the percentage of drug dissolved, t the time, ADC is the area upper dissolution curve and M_∞ is the cumulative amount of drug dissolved at the maximum time considered (Hernández et al., 1994).

3. Results and discussion

3.1. Validation of the analytical method

A maximum absorbance wavelength of 269.0 nm was selected. Increasing concentrations of ketoconazole provided responses that showed good linearity in the range of concentrations of 10–500 μg/ml ($r^2 = 0.99989$).

Table 1 shows the main resulting validation parameters including the R.S.D. in all cases. These results proved that the developed UV-spectrophotometric technique was precise, sensitive and accurate for the analysis of ketoconazole in samples obtained from dissolution studies. It was also evidenced that the presence of antacids and excipients in the medium had not a significant influence on the assay of the drug. The sensibility was found to be good enough for the analysis of dissolution samples.

3.2. In vitro interaction studies

Fig. 2 show the average dissolution profiles resulting for the different ketoconazole tablets formulations in 0.1N HCl without antacid, in the presence of 1/2 dose of Bemolan® ($pH = 3.5 \pm 0.1$) and a full dose ($pH = 4.3 \pm 0.2$). In general lines and according to the standard deviations obtained, a high extent of homogeneity was observed for the six formulations.

Table 2 shows the resulting mean values of t_{50}, $t_{63.2}$, t_{70} and t_{80} obtained from the fitting of a Weibull kinetic model to our data. To avoid the possible error obtained inherent to the fitting is also very important to take into account the results of the amodelistic parameters DE and MDT showed in Table 3.

The profiles obtained in 0.1N HCl revealed that tablets 1A, formulated from a lactose derived, provided a more rapid release of ketoconazole than tablets 2A and 3A, whose fillers were a mannitol derived and a calcium phosphate derived, respectively. As expected, the inclusion of the disintegrant agent (D) in the mixtures (formulations B) resulted in a significant increase in the dissolution profile in all the batches in comparison to those tablets prepared without this excipient (formulations A). The strong improvement of the dissolution rate of ketoconazole by addition of 5% of D, can be explained by an increment in the 'wetted' surface of the tablets which promotes the dispersability of the system and also the solubility of the drug. In contrast, previous results (Córdoba Díaz et al., 2000a) evidenced that tablets 2 exhibited slower disintegration rates than tablets 1 and 3.

The antacid preparation added to the dissolution medium provoked a remarkable decrease in the percentage of ketoconazole dissolved vs. time. A more dramatic decrease was found with one dose fraction in comparison to 1/2 fraction. It was observed a decrease in the DE_{30} values of about 96–99% for tablets A in the presence of one dose of the antacid, taking as a reference the value

Table 1
Main parameters resulting from the validation study of the UV-spectrophotometric method (MR, mean recoveries in percentage)

Test	Value	RSD (%)	Confidence limits	t_{exp}
Linearity				
Slope	0.00253	1.420	0.00255 ↔ 0.00252	298.1
Intercept	0.00308	0.335	0.01382 ↔ 0.00766	0.639
Accuracy				
Three replicates	Concentration 200 μg/ml	0.817		
Repeatability				
Concentration 50 μg/ml	2.71			
Concentration 250 μg/ml	1.30			
Concentration 450 μg/ml	0.78			
Reproducibility				
4 days and two spectrophotometers	1.7			
Roughness: influence of the presence of antacids in the medium				
With antacid	MR = 101.15	2.619		
Without antacid	MR = 100.04	1.007		
Specificity: influence of the presence of excipients in the medium				
With excipients	MR = 99.07	0.862		
Without excipients	MR = 99.62	1.103		
Sensitivity				
Quantification limit	Concentration 5.73 μg/ml			
Detection limit	Concentration 1.72 μg/ml			

calculated from the resulting profiles in 0.1N HCl. In contrast, the decrease found for formulations B ranged from 35 to 64%. Besides, it was found that the different dissolution times obtained were significantly lower for tablets B in the presence of antacids in comparison to those values resulting for tablets A.

The interaction was avoided in the presence of half a dose of antacid in formulation 1B and notably optimised when there was a full dose in the dissolution medium. In this way, batch 1B could be selected as an interesting design to be studied in vivo and to be adapted to an industrial production. Those findings are more important if we take into account that nowadays it is suggested to space out the administration of antacids and ketoconazole for at least 2 h, what is a serious problem in some pathologies. It is also advisable that in these kinds of patients, only half a dose of a low powerful antacid agent should be prescribed if it would be possible.

4. Conclusions

The divergences found between disintegration and dissolution results for all the ketoconazole formulations in tablets indicated that, although it is true that disintegration studies should be considered to be as a very important data to evaluate new formulations, the preformulation and control studies should always include also properly designed dissolution experiments. This fact is of prime importance in ketoconazole tablets in

which the U.S. Pharmacopoeia, 24th revision (USP 24/NF 19) (2000) does not require to carry out such dissolution studies.

In the light of the above previously reported results, it can be concluded that there exist a dramatic interaction process between ketoconazole and magaldrate provoked by the modification of the pH value of the media, as previously described by many authors. This interaction was remarkably optimised in formulations B with the inclusion in the original design of a disintegrant agent. Not only did the disintegrant modify the dissolution characteristics, but it also showed a clear influence on the interaction described in the present study. This can be due to the fact that the pH is not the only factor responsible for such interaction, and any kind of interaction between the molecules of ketoconazole and the antacids could take place in the dissolution medium. In this way, a modification of the release of the drug could affect the rate in which that reaction is normally conducted. Nevertheless, this fact should be prospectively studied with other techniques and confirmed in vivo.

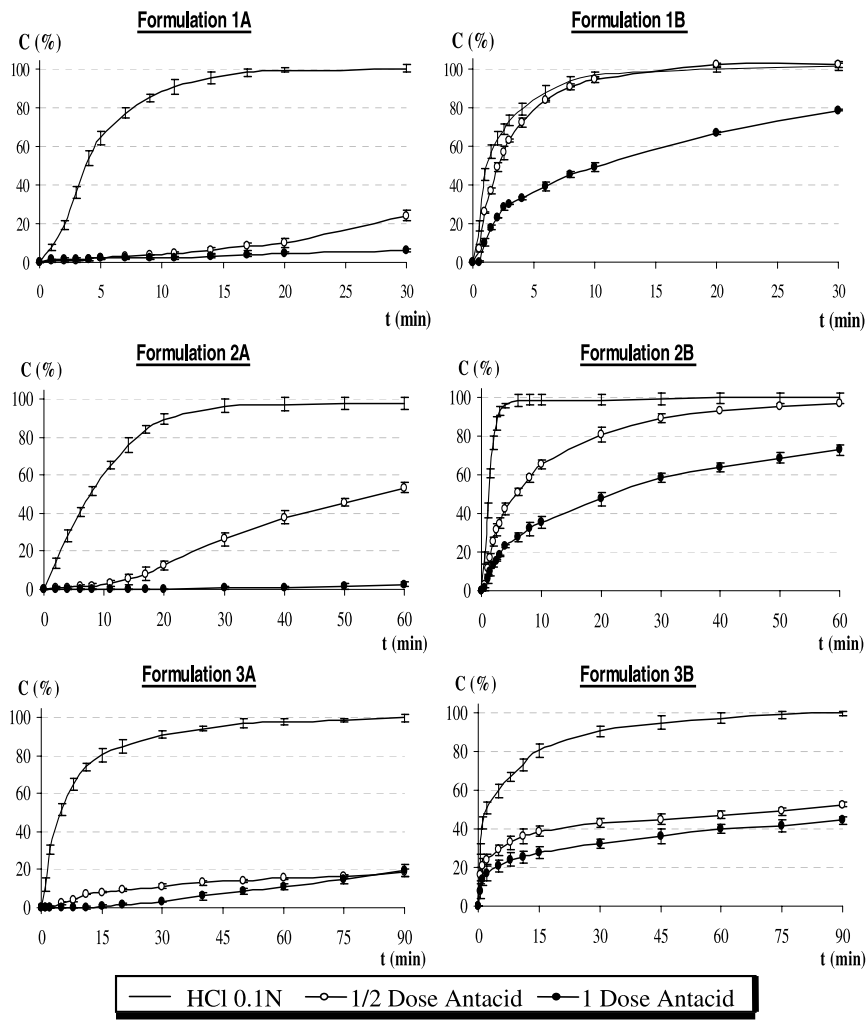


Fig. 2. Resulting dissolution profiles for all the formulations studied (mean ± SD).

Table 2
Resulting values for the determination coefficients (r^2) and t_x (time necessary to release an X percent of ketoconazole) using a Weibull function by linear regression analysis

Parameter	Condition	1−A	1−B	2−A	2−B	3−A	3−B
r^2	0.1N HCl	0.99165	0.97310	0.99952	0.99956	0.99642	0.98585
	+1/2 antacid	0.99113	0.99531	0.99094	0.99900	0.99859	0.99379
	+1 antacid	0.98216	0.98886	0.98712	0.99674	0.99644	0.99727
t_{50} (min)	0.1N HCl	4.3	1.5	7.5	1.2	4.2	4.0
	+1/2 antacid	114.8	2.2	51.3	5.7	1.1 e3	69.9
	+1 antacid	3.6 E6	9.4	234.8	21.1	163.2	166.0
$t_{63.2}$ (min)	0.1N HCl	5.6	2.3	10.3	1.5	7.5	7.1
	+1/2 antacid	158.8	2.9	62.0	9.5	2.2 E3	285.9
	+1 antacid	1.3 E7	17.1	273.9	38.5	200.3	537.4
t_{70} (min)	0.1N HCl	6.4	2.8	12.1	1.7	10.0	9.5
	+1/2 antacid	154.1	3.3	68.3	12.4	3.2 E3	583.3
	+1 antacid	2.7 E7	23.1	296.1	52.1	222.1	974.5
t_{80} (min)	0.1N HCl	7.9	4.1	15.5	2.1	15.6	14.9
	+1/2 antacid	283.9	4.2	79.3	18.6	5.8 E3	1.8 E3
	+1 antacid	8.2 E7	36.9	334.6	84.0	261.2	2.5 E3

Table 3
Amodelistic parameters calculated from Eq. (2) and Eq. (3) where DE_{30} is the dissolution efficiency at 30 min and MDT_{30} is the medium dissolution time at the same time

Parameter	Condition	1−A	1−B	2−A	2−B	3−A	3−B
DE_{30}	0.1N HCl	83.343	91.329	67.917	94.489	71.247	74.497
	+1/2 antacid	8.674	89.479	9.022	66.854	6.794	35.870
	+1 antacid	3.526	54.458	0.220	39.062	0.790	26.077
MDT_{30}	0.1N HCl	4.997	2.601	9.625	1.653	8.626	7.651
	+1/2 antacid	27.398	3.156	27.293	9.944	27.962	19.239
	+1 antacid	28.942	13.663	29.934	18.281	29.763	22.177

References

Brass, C., Galgiani, J.N., Blaschke, T.F., Defelice, R., O'Reilly, R.A., Stevens, D.A., 1982. Disposition of ketoconazole, an oral antifungal, in humans. Antimicrob. Ag. Chemother. 21, 151–158.

Carlson, J.A., Mann, H.J., Canafax, D.M., 1983. Effect of pH on disintegration and dissolution of ketoconazole tablets. Am. J. Hosp. Pharm. 40, 1334–1336.

Carver, P.L., Berardi, R.R., Knapp, M.J., Rider, J.M., Kauffman, C.A., Bradley, S.F., Atassi, M., 1994. In vivo interaction of ketoconazole and sucralfate in healthy volunteers. Antimicrob. Ag. Chemother. 38, 326–329.

Chin, T.W.F., Loeb, M., Fong, I.W., 1995. Effects of an acidic beverage (Coca Cola) on absorption of ketoconazole. Antimicrob. Ag. Chemother. 39 (8), 1671–1675.

Córdoba Díaz, D., Córdoba Díaz, M., Córdoba Borrego, M., Moreno Cerezo, J.M., 2000a. Nuevos diseños de preformulación en comprimidos de ketoconazol por compresión directa. Industria Farmacéutica 4, 93–98.

Córdoba Díaz, M., Córdoba Borrego, M., Córdoba Díaz, D., 2000b. Influence of pharmacotechnical desing on the interaction and availability of norfloxacin in directly compressed tablets with certain antacids. Drug Dev. Ind. Pharm. 26 (2), 159–166.

Daneshmend, T.K., Warnock, D.W., 1988. Clinical pharmacokinetics of ketoconazole. Clin. Pharmacokinet. 14, 13–34.

European Pharmacopoeia 3rd Ed., 1997. European Department for the Quality of Medicines Council of Europe. Strasbourg, France, pp. 1072–1073.

Gibassier, D., Sado, P., LeVerge, R., Devissaguet, J.P., 1982. Tests de dissolution et fonction de Weibull. Labo. Pharma. Prob. Techn. 30, 250–255.

Hernández, R.M., Rodriguez, A., Calvo, B., Pedraz, J.L., Bonferoni, C., Sangalli, M.E., Caramella, C., Conte, E., Dominguez-Gil, A., 1994. Evaluación biofarmacéutica de comprimidos de sulfato de salbutamol elaborados con hidroxipropilmetilcelulosa. Industria Farmacéutica 2, 39–45.

Lake-Bakaar, G., Tom, W., Lake-Bakaar, D., Gupta, N., Beidas, S., Elsakr, M., Straus, E., 1988. Gastropathy and ketoconazole malabsorption in the acquired immuno deficiency syndrome (AIDS). Ann. Intern. Med. 109, 471–473.

Lelawongs, P., Barone, J.A., Colaizzi, J.L., Hsuan, A.T.M., Mechlinski, W., Legendre, R., Guarnieri, J., 1988. Effect of food and gastric acidity on absorption of orally administered ketoconazole. Clin. Pharm. 7, 228–235.

Lindahl, A., Ungell, A.L., Kunston, L., Lennernäs, H., 1997. Characterization of fluids from stomach and proximal jejunum in men and women. Pharm. Res. 14 (4), 497–502.

Minagawa, H., Kitaura, K., Nakamizo, N., 1983. Effects of pH on the activity of ketoconazole against *Candida albicans*. Antimicrob. Ag. Chemother 23 (1), 105–107.

Piscitelli, S.C., Goss, T.F., Wilton, J.H., D'Andrea, A.T., Goldstein, H., Schentag, J.J., 1991. Effects of ranitidine and sucralfate on ketoconazole bioavailability. Antimicrob. Ag. Chemother. 35, 1765–1771.

Remon, J.P., Belpaire, F., Van Severen, R., Braeckman, P., 1983. Interaction of antacids with antiarrhythmics. Arzneim.-Forsch. 33 (I), 117–120.

U.S. Pharmacopoeia, 24th revision (USP 24/NF 19), 2000. 12601 Twinbrock Parkway, Rockville, MD 20852, USA, pp. 864–865.