

In vitro evaluation of sustained released matrix tablet formulations of clarithromycin

Lütfi Genç*, A. Muhittin Kıran

Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical
Technology, 26470, Eskişehir, TURKEY

Abstract

Sustained release matrix tablets of clarithromycin were prepared using different polymers as Hydroxypropyl methylcellulose (HPMC), Carbopol 934 and Eudragit RL/PO by direct compression technique. For the quality control of these formulations, weight deviation, hardness, friability, diameter-height ratio, content uniformity of the active substance and in vitro dissolution technique were performed. HPLC was used for the assay of clarithromycin and the assay method was validated. Dissolution profiles of the tablets were plotted and evaluated kinetically. The effects on drug release of polymer type and concentrations were investigated by 2^3 factorial design. The tablets containing HPMC, Carbopol 934 and Eudragit RL/PO were found suitably to sustain drug release.

Keywords

Sustained release, Matrix tablet, Clarithromycin, 2^3 factorial design, Validation

Introduction

When designing an oral sustained release formulation, the hydrophilic matrices present an alternative to other monolithic or multi particulate pharmaceutical dosage forms. Hydrophilic matrices became extremely popular in controlling the release of drugs [1, 2, 3].

Acrylic acid and cellulose derivatives may be used for hydrophilic matrices for controlled release oral delivery [4, 5, 6, 7, 8, 9]. The drug volume fraction profiles of a colored and very soluble drug, buflomedil pyridoxal

phosphate, in the gel layer of initially glassy HPMC matrices were studied by Colombo et al [10]. It was demonstrated that drug release kinetics does not only depend on drug diffusion and matrix erosion, but also on drug dissolution in the gel and on polymer relaxation. Çelebi and Ünlü [11] evaluated hydrophilic matrix tablets of diltiazem using three grades of HPMC according to 2^3 factorial design. They reported the effect of the polymer ratio on diltiazem release from matrix tablets. Pérez-Marcos et al [12] evaluated the possible use of three types of Carbomer, with different molecular weights, in the formulation of hydrophilic furosemide matrices. Their results showed that variables associated with the type and proportion of carbomer, with insignificant effects on porosity, play an important role in the release characteristics of the active principle. The acrylic polymers Eudragit RL, RS and NE were developed for pH-independent, delayed release of active ingredients by diffusion from oral dosage forms (swellable, permeable coating and matrix structures) [13]. Metha et al [14] investigated release performance of a poorly soluble drug from a novel, Eudragit-based multi-unit erosion matrix. Matrix erosion and drug release followed zero order kinetics.

Clarithromycin is a semi-synthetic macrolide antibiotic. It is used in the treatment of leprosy, upper tunistic mycobacterial infections, respiratory–tract, skin and soft-tissue infections. It is given 250 mg twice daily by mouth, increased to 500 mg twice daily if required [15,16,17]. High-performance liquid chromatography (HPLC) is routinely used for the selective and accurate determination of clarithromycin in pharmaceutical matrices [18, 19, 20].

The aim of the work was to evaluate the influence of polymer type and concentration on dissolution rate of matrix tablets. Matrix tablets of clarithromycin were prepared by direct compression technique. The objective of this work is to outline 2^3 factorial design and to study the effect of three factors; HPMC, Carbopol 934 and Eudragit RL/PO on the dissolution rate of

clarithromycin in matrix tablets [11,21]. The ideal matrix tablet formulation was found by evaluating of these findings and evaluated kinetically. For the quality control of tablets, physical control and in vitro dissolution techniques were performed. HPLC was used for the assay of clarithromycin and the assay method was validated. Dissolution profiles of each tablet were plotted.

Results and Discussion

Application of factorial design experiments to pharmaceutical problems has appeared to be extremely useful. The effects of several factors (**A**, **B** and **C**) and their interactions (**ab**, **bc**, **ac** and **abc**) can be determined simultaneously by factorial design experiments [11,21,22]. Calculation of total effects for 2^3 factorial design and the effects of A, B and C and their interactions on the T values are shown in Table 1. The differences of importance between T values have also been examined and for the factors polymer type and concentration F values have been calculated. F8 has been found as the most appropriate formulation. This model was applied to the evaluation of the dissolution rate of matrix tablets.

The physical characteristics of the matrix tablets are given in Table 2. The tablet must be sufficiently strong and resistant to shock and abrasion to withstand handling during manufacture, packaging, shipping, and use. This property is measured by two tests, the hardness and friability tests. Tablet hardness effects in vitro dissolution of a dye from sustained release tablets made of different types of polymers. Differences in density and porosity could influence the dissolution rate of drug from the tablet by affecting the initial rate of penetration of dissolution medium at the tablet surface and subsequent disintegration and dissolution. Our tablets provided good weight uniformity and friability ($F < 1.0\%$). These results were in accordance with the pharmacopoeia limits [USP 26]. Regression equation is $y = 1139.67 x - 5.73$ and regression coefficient (r) is $= 0.9999$. (y = Concentration ($\mu\text{g/mL}$), x = Absorbance)

Source of Variation	T values			D.F.	Sum of Square	Mean Square	F
	Exp.1	Exp.2	Exp.3				
(1)	239.242	241.534	236.973	-	-	-	-
a	153.547	150.444	154.091	1	5703.4884	5703.4884	700.9489
b	513.357	504.333	511.684	1	107797.38	107797.38	13248.1132
ab	423.048	427.563	424.116	1	9890.4848	9890.4848	1215.5236
c	223.359	226.415	224.079	1	112913.41	112913.41	13876.8645
ac	168.558	166.951	169.418	1	17856.943	17856.943	2194.5876
bc	139.268	140.258	143.327	1	113723.54	113723.54	13976
abc	240.838	249.763	243.514	1	9328.664	9328.664	1146.4769
Residual				16	130.189	8.13681	
Total				23	377474.29		

Tab. 1. Analysis of variance for 2³ factorial experiment for the time at which 63.2 % of the active ingredient dissolved (T).

Tablet specifications	Tablet Code No							
	F1	F2	F3	F4	F5	F6	F7	F8
Clarithromycin amount(mg)	464.77	469.48	474.77	485.81	477.41	461.16	488.55	475.21
Hardness (kg)	4±2.6	10±1.5	5±0.0	4±0.2	4±1.06	6±0.0	6±0.01	4±0.98
Friability (%)	0.6	0.3	0.7	0.7	0.8	0.5	0.6	0.9
Diameter-height ratio	3.43±0.1	3.38±0.7	3.41±0.2	3.47±0.44	3.5±0.2	3.43±0.28	3.44±0.26	3.45±0.46
Tablet weight (mg)	525.8 ±5.87	527.61 ±1.4	524.58 ±0.5	523.56 ±0.92	523.04 ±0.4	522.25 ±1.39	527.55 ±0.63	521.3 ±1.4

Tab. 2. Tablet specifications (n=10).

In the validation parameters, the RSD for the sample preparation step might be approximately 1% [23,24]. As shown in Table 3, these results are suitable for method validation. Reproducibility refers to the use of HPLC assay method for

clarithromycin in different laboratories, as in a collaborative study. An important step in the validation of any analytical method is the establishment of the relationship between released % (y) and the concentration of the analyte (x) and the method may be calibrated. When correlation coefficient is above 0.9990, the assay method was acceptable. The satisfying recoveries confirm the suitability of the proposed method for the routine analysis of clarithromycin in pharmaceuticals (Table 4) [23,25,26]. According to the results, the proposed method is able to access the analyte in the presence of common excipients and hence, it can be considered specific. Results in Table 5 indicate that clarithromycin showed good detection limit.

Concentration ($\mu\text{g/mL}$)	Medium: 0.1M Sodium acetate buffer
Repeatability (day = 3, n=6)	
0.0498	1.608
0.498	3.260
4.98	1.369
Precision (day = 3, n=6)	
0.0498	1.609
0.498	3.260
4.98	1.760

Tab. 3. Repeatability and precision of HPLC (clarithromycin peak response) (RSD %)

The effects of polymer type and concentration on in vitro release of clarithromycin has also been investigated. Drug release profiles are given in Figure 1 and 2 (n=6). The drug release from matrix tablets depended upon the concentration and type of polymers. Approximately 85 % clarithromycin was released in the first five hours from F1 (without polymer). The release of clarithromycin from matrix tablets was different than that of control tablets (F1).

Regression equation	Regression coefficient	Recovery values
$y = 1139.633 x - 5.555$ (1.day)	0.9999	$99.38 \pm 0.35\%$ (for $0.0498 \mu\text{g/mL}$)
$y = 1137.623 x - 3.873$ (2.day)	0,9999	$99.05 \pm 0.21 \%$ (for $0.498 \mu\text{g/mL}$)
$y = 1137.402 x - 5.444$ (3.day)	0,9999	$100.05 \pm 0.12 \%$ (for $4.98 \mu\text{g/mL}$)

y = Concentration ($\mu\text{g/mL}$), x = Absorbance

Tab. 4. Accuracy results (n=6)

Parameters	Results
Linear range ($\mu\text{g/mL}$)	0.05 – 5.00
LOD ($\mu\text{g/mL}$)	8.26×10^{-4}
LOQ ($\mu\text{g/mL}$)	2.72×10^{-3}

Tab. 5. Detection limit (LOD) and Quantitation limit (LOQ) results (n=6)

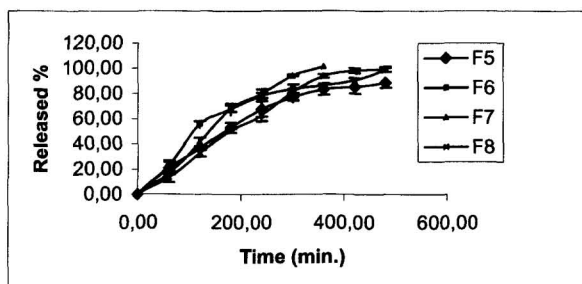


Fig.1. Dissolution profiles of F1, F2, F3 and F4

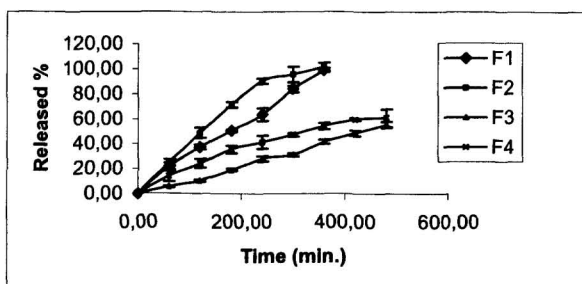


Fig. 2. Dissolution profiles of F5, F6, F7 and F8

On the other hand, as observed in F2-8 formulated tablets, polymer type and concentration have an important effect on the release rate of the drug. All of clarithromycin was released from F2(10% HPMC) and F7(5% Eudragit + 5% Carbopol) in the first 6 hours. But, 55.4 % drug from F3 (10% Carbopol) in 7.5 hours, 66.91 % drug from F4 (5% HPMC + 5% Carbopol) in 7.5 hours, 83.5 % drug from F5 (%10 Eudragit) in 7.5 hours, 101.88 % drug from F6 (5% HPMC + 5% Eudragit) in 8.0 hours and 99.45% drug from F8 (3.33% HPMC + 3.33% Eudragit + 3.33% Carbopol) in 8 hours were released. An increase in polymer content resulted with a slow release rate of drug as was expected. According to dissolution results, F6 and F8 were found to be the most suitable formulations for clarithromycin. These results decisively show that variables associated with type and proportion of polymer, play an important role in the drug release characteristics. Amount and origin of the polymer are key parameters for the control of drug release. Therefore, the ratio of drug to polymer is an important factor in the release of drug [11,14]. Mechanisms for drug release from matrices of polymer imply water penetration in the matrix (with drug dissolution on the surface, causing its immediate release), hydration and swelling of these polymers, diffusion of the dissolved drug, and the erosion of gelatinous polymer layer. When the hydrophilic matrix tablet is conducted in an aqueous environment, firstly clarithromycin is released from the surface of the matrix tablet and then water penetrates into the matrix. The polymer swells to form a gel layer and the matrix increases, drug is released through the gel barrier and this process continues until the tablet is completely eroded. Today, compressed hydrophilic matrices have become most popular as modified release dosage forms for oral administration. Among the swellable polymers used to prolong drug release, cellulose derivatives, in particular HPMC, provoked considerable interest because most display good compression characteristics, including when directly compressed, and have adequate swelling properties that allow rapid

formation of an external gel layer controlling drug release. Eudragit RL and RS, also referred to as ammoniomethacrylate copolymers in the USP monograph, are copolymers synthesized from acrylic acid and methacrylic acid esters with Eudragit RL having functional quaternary ammonium groups. The ammonium groups are present as salt and give rise to pH-independent permeability of the polymers [4, 23, 27]. These knowledges support our formulation.

Clarithromycin modified-release (MR) tablets (500 mg once daily) was found to be as effective as standard clarithromycin immediate release (IR) tablets (250 mg twice daily). The principal advantage of clarithromycin MR over the standard IR formulations is the ease of once-daily dosing. It has been suggested that a patient's ability to fit a drug-dosing schedule into his or her normal daily routine is significantly associated with compliance [28, 29]. These studies support the use of clarithromycin MR formulation in a once-daily dosing regime. For this reason, we decided to prepare matrix tablet formulations of clarithromycin.

F6 and F8 showed the best fit to Higuchi kinetic according to the Akaike's Information Criteria ($AIC = -6.08, -14.20$), Weighted Sum of Squared Deviations ($WSSD = 0.0106, 0.2917$) and r square ($r^2 = 0.9769, 0.9931$) results, respectively [30]. As for the kinetic evaluations the highest determination coefficient and the best linear relation were observed for matrix tablets (F6 and F8) by Higuchi equation [31]. Graphically Higuchi distribution gave a straight line (Fig 3).

In the present investigation, controlled release tablet forms containing different types of polymers were developed. Using different types and concentrations of polymers, controlled drug release was looked at. The effects of different polymer and concentrations, respectively, on the drug release were investigated.

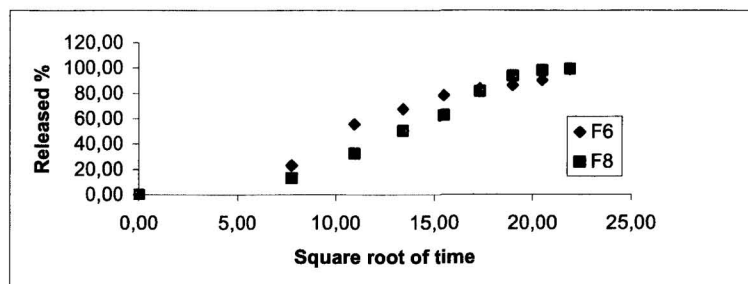


Fig. 3. The release of clarithromycin from F6 and F8 according to Higuchi equation.

The combination of diffusion and erosion release mechanisms in matrix systems comprising an insoluble hydrophobic and a hydrophilic gel-forming part depends greatly on the wettability of the added drug. Furthermore, with wettable and water soluble drugs, the matrices swelled and releases were mainly achieved by diffusion and erosion due to dissolution of the gel formed. However, with less wettable drugs, the matrix erodes, due to deaggregation caused by the inability of the matrix to accommodate the swelling of gel forming hydrophilic part.

Experimental

Materials

Clarithromycin (Ambfar, The Netherlands), HPMC E 15(100 000 mPa s, Fluca), Carbopol 934 (Goodrich), Eudragit RL/PO (Röhm Pharma), Potassium dihydrogen phosphate (Carlo Erba), Phosphoric acid (Merck), Methanol (Merck). All chemicals were of analytical grade.

Apparatus

HPLC (Hewlett Packard HP 1100), Tablet machine (Korsch AR 400, Erweka), pH-meter (Orion, Shimadzu), Dissolution test apparatus (Aymes, Turkey), Friabilator (Roche), Hardness apparatus (Monsanto).

Factorial Design

The effect of HPMC (**A**), Carbopol 934 (**B**) and Eudragit RL/PO (**C**) was studied in separate 2^3 factorial experiments. The levels and variation intervals for the eight treatment combination are the calculation matrix for a 2^3 factorial design, with the following combinations of factors **A**, **B** and **C** at two levels (3.33-10 %): **(1)**, **a**, **b**, **ab**, **c**, **ac**, **bc**, and **abc**. We used 3 factors, each at only two levels in Table 6. These levels are polymer concentrations, the “high” and “low” levels of a factors, or presence and absence of a factors [21,22].

Factors	Level	
	Low (-)	High (+)
A , HPMC	%3.33	%10
B , Carbopol 934	%3.33	%10
C , Eudragit RL/PO	%3.33	%10

Tab. 6. Factorial design parameters and experimental conditions

Preparation of matrix tablets

Eight formulations were prepared on an instrumented single-punch tablet machine by direct compression technique. Magnesium stearate was used as the lubricant (1.0 %) and HPMC, Carbopol 934 and Eudragit RL/PO were the polymers in different concentrations (3.33-10 %). Contents of matrix tablet formulations are given in Table 7. Each formulation was prepared separately. All ingredients of each formulation were mixed in cubic mixer. The position of the bottom punch face in the bore determines the volume of the die-cavity and hence the tablet weight. Tablet hardness was adjusted using hardness control nut.

The following tests were applied to the tablets; amount of clarithromycin, crushing strength, diameter-height ratio and friability. Tablet weight uniformity

was calculated according to USP 26 and tablet thickness was determined using a micrometer. Tablet hardness tests were carried out using a Monsanto hardness tester. For friability tests, twenty tablets were weighed (W_1) and rotated at one hundred revolutions for 4 min in a Roche friabilator. The tablets were then reweighed (W_2) and the percentage friability (%F) was calculated.

Tablet Code No								
Contents (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Clarithromycin	470	470	470	470	470	470	470	470
HPMC	-	47	-	23.5	-	23.5	-	15.67
Carbopol 934	-	-	47	23.5	-	-	23.5	15.67
Eudragit RL/PO	-	-	-	-	47	23.5	23.5	15.67
Mg Stearat	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7

Tab. 7. Content of matrix tablet formulations of clarithromycin

Assay method and its validation

HPLC method with a 210 nm DAD detector, 250x4.6 mm Ultracarb C20 column was used for clarithromycin assay [18, 19, 20]. Flow rate is about 1.0 mL per minute and injection volume is 20 μ L. Methanol and 0.067 M monobasic potassium phosphate (650:350) were used as mobile phase (adjusted with phosphoric acid to a pH of 4). 49.8 mg clarithromycin was weighed accurately and dissolved in 10 mL mobile phase (4.98 μ g/mL stock solution). Six samples of 0.1-5.0 mL were taken from this stock solution and diluted to 10 mL with mobile phase (0.0498-4.98 μ g/mL solutions). Clarithromycin peak responses of these samples were determined. Regression equation and regression coefficients were calculated to be $y=1139.67x-5.73$ and $r = 0.9999$.

Validation of an analytical method is the process by which it is established, by laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical applications. The validation of the

types of methods are Accuracy, Precision, Specificity, Detection limit, Quantitation limit, Linearity and Range [20, 23, 24, 25].

Precision: The precision of an analytical method is the degree of agreement among individual test results when the method is applied repeatedly to multiple sampling of a homogenous sample. 0.0498, 0.498 and 4.98 $\mu\text{g/mL}$ solutions were prepared using stock solution of clarithromycin. The peak responses of these samples were measured. The standard deviation or relative standard deviation (coefficient of variation) of a series of measurements were calculated. Same procedure was made on different days.

Accuracy: The accuracy of an analytical method is the closeness of the test results obtained by that method to the true value. 0.0498-4.98 $\mu\text{g/mL}$ solutions were prepared using stock solution of clarithromycin. The peak responses of these samples were measured. Regression equation and regression coefficients were then calculated. Accuracy is calculated as the percentage of recovery by the assay of the known added amount of analyte (three concentrations: 0.0498, 0.498, 4.98 $\mu\text{g/mL}$) in the sample using regression equation ($n=6$).

Specificity: The specificity of an analytical method is its ability to measure accurately and specifically the analyte in the presence of components that may be expected to be present in the sample matrix. Specificity may often be expressed as the degree of bias of test results obtained by analysis of samples containing added impurities, degradation products, related chemical compounds, or placebo ingredients when compared to test results from samples without added substances. This bias may be expressed as the difference in assay results between the two groups of samples.

Detection and quantitation limits: The limits of detection is a parameter of limit tests. It is the lowest concentration of analyte in a sample that can be detected. Limit of quantitation is a parameter of quantitative assays for the low levels of

compounds in sample matrices, such as impurities in bulk drug substances and degradation products in finished pharmaceuticals.

In vitro dissolution studies and evaluation of release kinetics

Dissolution tests were performed according to the paddle method described in USP 26, Apparatus II. The rotating speed was 50 rpm and the temperature was $37 \pm 0.5^\circ\text{C}$. Dissolution studies were carried out in 900 mL 0.1 M Sodium acetate buffer. 1 mL of samples were taken from the dissolution media at appropriate time intervals with the aid of an injector fitted with a Schleicher-Schuell filter paper having a porosity of 0.5 μm or finer, and use the filtrate as the assay preparation. The peak responses of the samples were recorded. The amounts of clarithromycin released were evaluated by using the standard calibration curve equation ($n = 6$).

The results thus obtained were evaluated kinetically by zero, first - order, Hixson Crowell, RRSBW, Q Square Root of Time, Higuchi equation, Spherical, Cylindrical and Slab Erosion (the rate constant k' , k'' and k''' were obtained according to Hopfenberg). The release rate constants (k), correlation coefficients (r) and determination coefficients (r^2) were calculated by means of a computer program [30].

The in vitro release profiles (percentage of drug released versus time) obtained from the clarithromycin matrix tablet formulations were fitted to the main models which have been proposed to describe drug release kinetics from tablets and other polymer matrices.

References

- [1] Vazquez M J, Perez-Marcos B, Gomez-Amoza J L, Martino-Pacheco R, Souto C.
Concherio, A. Influence of technological variables on release of drugs from hydrophilic matrixes.
Drug Dev. Ind. Pharm. 1992,18 (11-12),1355-75.
- [2] Hashim A, Wanpola L A.
Improving the release characteristics of water-soluble drugs from hydrophilic sustained release matrices by in situ gas generation.
Int. J. Pharm. 1987, 35, 201-209.
- [3] Remington's Pharmaceutical Sciences 1990, 18, p. 1676.
- [4] Handbook of Pharmaceutical Excipients 2000, p.195, 240.
- [5] The Extra Pharmacopoeia-Martindale 1999, p. 1472.
- [6] Espinoza-Ramos R, Villafuerte-Robles L.
Influence of admixed lactose on pelanserin hydrochloride release from HPMC matrix tablets.
Pharm. Acta Helv. 1999, 74, 65-71.
- [7] Nokhodchi A, Rubinstein M H.
An overview of the effects of material and process variables on the compaction and compression properties of HPMC and EC.
S.T.P. Pharm. Sci. 2001, 11(3),195-202.
- [8] İkinçi G, Çapan Y, Şenel S, Dalkara T, Hıncal A A.
Formulation and *in vitro/in vivo* investigation of carbamazepine controlled release matrix tablets.
Pharmazie 1999, 54 (2), 139-141.
- [9] Heng P W S, Chan L W, Easterbork M G, Li X.
Investigation of the influence of mean HPMC particle size and number of polymer particles on the release of aspirin from swellable hydrophilic matrix tablets.
J.Control. Release 2001,Vol.76(1-2), 39-49.
- [10] Colombo P, Bettini R, Catellani P L, Santi P, Peppas N.
A Drug volume fraction profile in the gel phase and drug release kinetics in HPMC matrices containing a soluble drug.
European J. Pharm. Sci. 1999, 9(1), 33-40.
- [11] Çelebi N, Ünlü G.
Formulation and evaluation of hydrophilic matrix tablets of diltiazem using factorial design based studies.
Pharmazie 1999, 54 (12), 910-914.

- [12] Perez-Marcos B, Gutierrez C, Gomez-Amoza J L, Martinez-Pacheco R, Souto C, Concheiro A.
Usefulness of certain varieties of carbomer in the formulation of hydrophilic furosemide matrices.
Int. J. Pharm. 1991, 67, 113-121.
- [13] Florence A T, Attwood, D.
Physicochemical Principle of Pharmacy, Second edition, 1988, p.320.
- [14] Mehta K A, Kışlalioğlu M S, Phuapradit W, Malick A W, Shah N H.
Release performance of a poorly soluble drug from a novel, Eudragit®-based multi-unit erosion matrix.
Int. J. Pharm. 2001, 213(1-2), 7-12.
- [15] Barradell L B, Plosker G L, Mctavish D.
Clarithromycin: A review of its pharmacological properties and therapeutic use in *Mycobacterium avium-intracellulare* complex infection in patients with Acquired Immune Deficiency Syndrome.
Drugs 1993, 46 (2), 289-312.
- [16] Conte J E, Golden J A, Duncan S, Mckenna E, Zurlinden E.
Intra-pulmonar pharmacokinetics of clarithromycin and of erythromycin.
Antimicrobial Agent and Chemotherapy 1995, 39(2), 334-338.
- [17] Drug Facts and Comparisons.
St. Louis, A Wolters Kluwer Company 1997, p.2189.
- [18] Morgan D K, Brown D M, Rotsch T D, Plaszc A C.
A reversed-phase HPLC method for the determination and identification of clarithromycin as the drug substance and in various dosage forms.
J. Pharmaceutical and Biomedical Analysis 1991, 9(3), 261-269.
- [19] Chu S-Y, Sennello L T, Sonders R C.
Simultaneous determination of clarithromycin and 14[®]- hydroxy-clarithromycin in plasma and urine using HPLC with electronical detection.
J. Chromatography 1991, 571, 199-208.
- [20] Rotsch T D, Spanton M, Cugier P, Plaszc A C.
Determination of clarithromycin as a conta-minant on surfaces by HPLC using electronical detection.
Pharm. Res. 1991, 8(8), 989-991.
- [21] Cohran W G, Cox G M.
"Experimental Designs" John Wiley and Sons, New York, 1957.
- [22] Montgomery D C.
Design and analyses of experiments, Copyright, by John & Sons, Inc., 1997, Capter 7, p.290.
- [23] USP 26-NF 21 2003, 3th Edition, 2439-2445.
- [24] Beuving G.
Validation of Analytical Methods,
Validation Seminar, İstanbul, 31 May- 01 June 2001.

- [25] Pav B, Misztal G, Hopkala H, Drozd J.
Development and validation of a HPLC method for the determination of cetirizine in pharmaceutical dosage forms.
Pharmazie 2002, 57, 313-315.
- [26] Reiley C M, Fell F.
Development and validation of analytical methods. Progress in Pharmaceutical and Biomedical Analysis, 1996, Vol. 3, 20-22.
- [27] Wise D L.
Handbook of Pharmaceutical controlled release Technology, Marcel Dekker, Inc., New York, p.1-30, 2000.
- [28] Adam D, Glaser-Caldow E, Wachter J, Brueckner O-J, Hein J, Kroemer B, Hirsch J.
Comparative efficacy of clarithromycin modified release and immediate release formulations in the treatment of lower respiratory tract infection.
Clinical Therapeutics, 2001, Vol.23(4), 585-595.
- [29] Weiss K, Vajaka A.
An open label, randomized, multicenter, comparative study of the efficacy and safety of 7 days of treatment with clarithromycin extended release tablets versus clarithromycin immediate release tablets for the treatment of patients with acute bacterial exacerbation of chronic Bronchitis.
Clinical Therapeutics, 2002, Vol.24(12), 2105-2122.
- [30] Ağabeyoğlu T İ.
Dissol.: A basic computer program for the kinetic assessment of dissolution data, Presented at National Pharmaceutical Congress, İstanbul, 1984.
- [31] Higuchi T.
Mechanism of Sustained-Action Medication.
J. Pharm.Sci. 1963, 52(12), 1145-1149.

Received February 20th, 2004

Accepted December 1st, 2005