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Automated simultaneous triple dissolution profiles of two drugs, sulphamethoxazole–trimethoprim and hydrochlorothiazide–captopril in solid oral dosage forms by a multicommutation flow-assembly and derivative spectrophotometry

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Abstract

This article deals with the simultaneous determination of three dissolution profiles with the aid of the new and emerging continuous-flow methodology known as multicommutation. This methodology is based on a flow network of a set of solenoid valves controlled by the computer and acting as independent multicommutators to allow the easy and automated control of flowing solutions. The obtained three dissolution profiles from one dosage form are the whole formulation profile or "global profile" recommended by pharmacopoeias, and, at same time, are recorded two "individual" profiles from two drugs present in the formulation. This is the second attempt to obtain simultaneously three dissolution profiles with a single spectrophotometric detector and the first with the multicommutation methodology. The selected pharmaceutical formulations contained a couple of active principles with overlapped spectra, namely sulphamethoxazole and trimethoprim or hydrochlorothiazide and captopril. The obtained empirical plots profiles fitted with the Higuchi equation also known as the three-parameter equation.

Keywords: Pharmaceuticals; Dissolution profiles; In vitro availability; Solenoid valves; Multicommutation; Sulphamethoxazole; Trimethoprim; Hydrochlorothiazide; Captopril

1. Introduction

Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution of the drug under physiological conditions and the permeability across the gastrointestinal tract. Because of the critical nature of the first two steps, in vitro dissolution test may be relevant to the prediction of in vivo performance. These "in vitro" dissolution tests are also useful to assess the lot-to-lot quality of a drug product, as a guide development of new formulations, to ensure continuing product quality, and performance after certain changes in the formulation, the manufacturing process, the site of manufacture and the scale/up of manufacturing process. More recently, it has been proposed also as a test for generic formulations by comparing the dissolution profile with a reference formulation and through the calculation of numerical factors defined by European Agency for Drug Evaluation and the Federal Food and Drug Administration [1,2].

The dissolution profile of a pharmaceutical formulation or the in vitro availability is an established mandatory test in international pharmacopoeias [3–5]. Formerly recommended

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for oral formulations, now procedures are published for tablets, sugar-coated pills, capsules, patches and even for suspensions.

This dissolution testing of a pharmaceutical solid dosage form is time consuming and labour intensive, since it usually involves a number of manual operations; due to that, automated procedures are of interest for labour saving and improving analytical performance. One of them is the flow injection analysis (FIA) [6–8]. According to its high sampling frequency, low sample consumption and good reproducibility, FIA has proved to be an effective means for interfacing spectrophotometric detectors with the conventional drug dissolution equipment, involving the automation of such operations [9–11]. Some published articles deal also with dissolution profiles by means of FIA manifold provided with analytical detector other than the UV–vis spectrophotometer [12,13].

The work presented in this article is focused to obtaining three simultaneous dissolution profiles, namely the "standard" (global) profile and two individual profiles corresponding to two present drugs in the formulation. For first time, this is based on the new and emerging multicommutation methodology. This work can be considered as a new step on improving the automation of dissolution profiles as established in a former work from this laboratory dealing for first time on three simultaneous dissolution profiles with the aid of a FIA manifold provided with a single spectrophotometric detector [14].

This emerging multicommutation methodology is based on the use of solenoid valves (SV) forming a flow network, as differential elements and replaces the insertion volumes of FIA with insertion times, thereby expanding the scope of time-based sampling method. With electronic timing devices, the associated error is minimal.

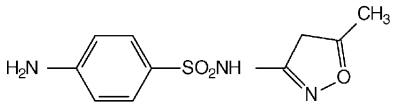
Multicommutation provides some valuable advantages versus "classical" FIA, like the miniaturization of flow assemblies, a reduced sample and reagent consumption, increased reproducibility, facilitates the development of fully automatic analytical methods and improves economy and simplicity, and in addition, the resulting assemblies are highly flexible and easy to alter [15–17].

For the present work, two binary mixtures of pharmaceuticals, all of them with overlapped spectra, were selected. The proposed mathematical method was the derivative spectrophotometry with the aid of the mathematical procedure "zero crossing". The officially recommended procedures in pharmacopoeias result in a dissolution profile of the whole formulation at fixed wavelength. The efforts focused to obtain the individual profile of one active principle in the formulation are interesting and at present are not included in pharmacopoeias.

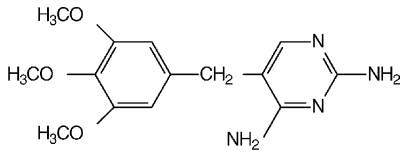
On the other hand, the simultaneous determination of two compounds with overlapped spectra has been solved by different mathematical approaches; one of them is the derivative spectrophotometry. This is an analytical technique of great utility for extracting both qualitative and quantitative information from spectra composed of unresolved bands and has demonstrable advantages for the resolution of specific analytical problems. Derivative spectrophotometry is an effective way for analysing mixtures, particularly with the quick recording of the diode array spectrophotometers; thus, the continuous flow assembly-diode array spectrophotometers seem a useful couple for solving such mixtures as those found in pharmaceutical formulations.

The resolution of binary mixtures of compounds with overlapping spectra by derivative spectrophotometry is frequently made on the basis of zero-crossing measurements [11,18–20] which are based on the measurement of the absolute value of the derivative spectrum of the mixture at an abscissa value (wavelength) where the intensity of one of the components of the mixture goes to zero. At this wavelength, the intensity is directly proportional to the other component. This means to find the best pH for the aqueous mixture to find the suitable zero crossing points.

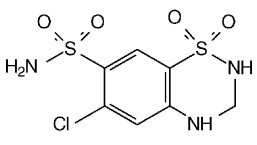
The studied active ingredients in this article were two couples, sulphamethoxazole and trimethoprim [4,5,21,22], and hydrochlorothiazide and captopril [4,5,23]. See molecular formulas.



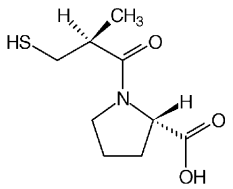
Sulfamethoxazole



Trimethoprim



Hydrochlorothiazide



Captopril

2. Experimental

2.1. Apparatus and reagents

2.1.1. Apparatus

pH-meter Crison 2001 (Crinson Instruments, S.A., Barcelona, Spain). As detector, it was used. Agilent UV–vis photo-diode array spectrophotometer (Model HP8453) provided with a 1 cm light path flow cell Hellma 6Q (Hellma GmbH & co Mülheim, Germany) of 18 μl of inner volume.

Multicommutation manifolds comprised PTFE coil (internal diameter of 0.8 mm) and pump tubing of tygon both from Omnifit. Model 161T031 solenoid valve (NResearch, Nortboro, MA)—its actuation was programmed by using a home-made software running on Pentium-type computer in Microsoft Windows 98. Peristaltic pumps were Gilson model Minipuls-2.

The dissolution apparatus was from Turu Grau, S.A., Spain, equipped with six dissolution vessels immersed in the thermostated bath at 37 °C and a speed regulating device that allows the shaft rotation speed to be selected and maintained at the rate specified in the individual monograph (according to USPXXII).

2.1.2. Reagents

All reagents were analytical pure grade unless stated otherwise and prepared in deionised water (18 MΩ cm) using system Sybron/Barnsted Nanopure II, provided with filter 0.2 μm.

Acetic and hydrochloride acids (J.T. Baker), sodium acetate, disodium hydrogen phosphate and potassium hydroxide (Probus), potassium chloride and sodium chloride (Panreac), glycine (Scharlau): pharmaceutical active ingredients (sulphamethoxazole, trimethoprim, hydrochlorothiazide and captopril) were all from Guinama.

For calibrations, all the sample stock solutions were freshly prepared everyday. The studied commercially available formulations were: EDUPRIM® tablets (Lab. F5 Profas, Madrid, Spain): sulphamethoxazole 400 mg, trimethoprim 80 mg. SEPTRIN tablets (Celltech Pharma, Madrid, Spain): sulphamethoxazole 400 mg, trimethoprim 80 mg. BRONQUI MUCIL capsules (J. Uriach & Cía, Barcelona, Spain): sulphamethoxazole 400 mg, trimethoprim 80 mg. MOMENTOL capsules (Squibb Industria Farmacéutica, Barcelona, Spain): sulphamethoxazole 400 mg, trimethoprim 80 mg. ECADIU tablets (Elan Farma, Barcelona, Spain): captopril 50 mg, hydrochlorothiazide 25 mg. CAPTOPRIL-HIDROCLOROTIAZIDA NORMON 50/25 EFG tablets (Lab. Normon S.A., Madrid, Spain): captopril 50 mg, hydrochlorothiazide 25 mg.

2.2. Procedures

Preliminary experiments in batch were performed to establish or to confirm the best medium for the simultaneous determination of the two active pharmaceutical ingredients. Once finished these assays, the suitable multicommutation assembly was designed to "translate" the batch method to the continuous-flow and to perform the simultaneous dissolution tests. Once selected the most appropriate assembly, all chemical and hydro-dynamical parameters were optimised by the univariate or the MSM multivariate method [24,25]. The residence time should be carefully tested to obtain measurements (including whole spectra) only in the maximum of the transient output. Finally, the dissolution profiles were performed and the obtained results were adjusted by regression analysis using the Statistica software [26].

Procedure for capsules, uncoated tablets and plain-coated tablets: place the stated volume of the dissolution medium in the vessel of the apparatus, assemble the apparatus, equilibrate the dissolution medium to 37 ± 0.5 °C, and remove the thermometer. Place one unit (tablet or capsule) in the apparatus, taking care to exclude air bubbles from the surface of the dosage unit, and immediately operate the apparatus at the rate specified in the individual monograph. Within the time interval specified, or at each time stated, withdraw a specimen (by aspiration from the peristaltic pump to the flow-assembly) from a zone midway between the surface of the dissolution medium and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. Perform the analysis as directed in the individual monograph. Repeat the test with additional dosage units.

The conditions for realization of the dissolution test were taken from U.S. Pharmacopoeia; medium: 900 ml of 0.1 mol l^{-1} HCl; rotation speed: 75 rpm for SMT and TRP, respectively, 50 rpm for HCT and CTP; temperature: 37 °C; and apparatus: as described in USP, using paddle for tablet dissolution and basket for capsules dissolution. A filter unit was added to the tip of the tubing to avoid the insoluble material.

Fig. 1a and b depicts the proposed flow assemblies which were connected to the vessel where the dissolution profile was performed. The couple sulphamethoxazole–trimethoprim was monitored at the same medium, pH, as that required for dissolving the formulation which means a flow-assembly as simple as possible. A solenoid valve allowed the sequential insertion (aspiration at a flow-rate of 3.3 ml min^{-1}) of three segments of solution from the vessel and carrier solution (the same medium of dissolution). The reactor length (L) was as short as possible to connect with the flow-cell (34.1 cm) and a complete cycle lasted 80 s. The absorption monitoring was based on the first derivative at 247 and 257 nm for trimethoprim and sulphamethoxazole, respectively. The global profile was obtained at 254 nm.

The pair hydrochlorothiazide–captopril was solved at a different pH than that required for monitoring. To change the pH required a flow manifold provided with two solenoid valves. A SV selected the flow from two streams, 0.4 mol l^{-1} NaOH and pure water (carrier solution). Then, a second SV allowed the sequential insertion of 11 segments of the solution from the vessel (aspiration during 0.3 s) and the NaOH solution (aspiration during 0.2 s). Flow rate was 2.7 ml min^{-1} and the reactor length (L) 40.0 cm. The solution profiles were

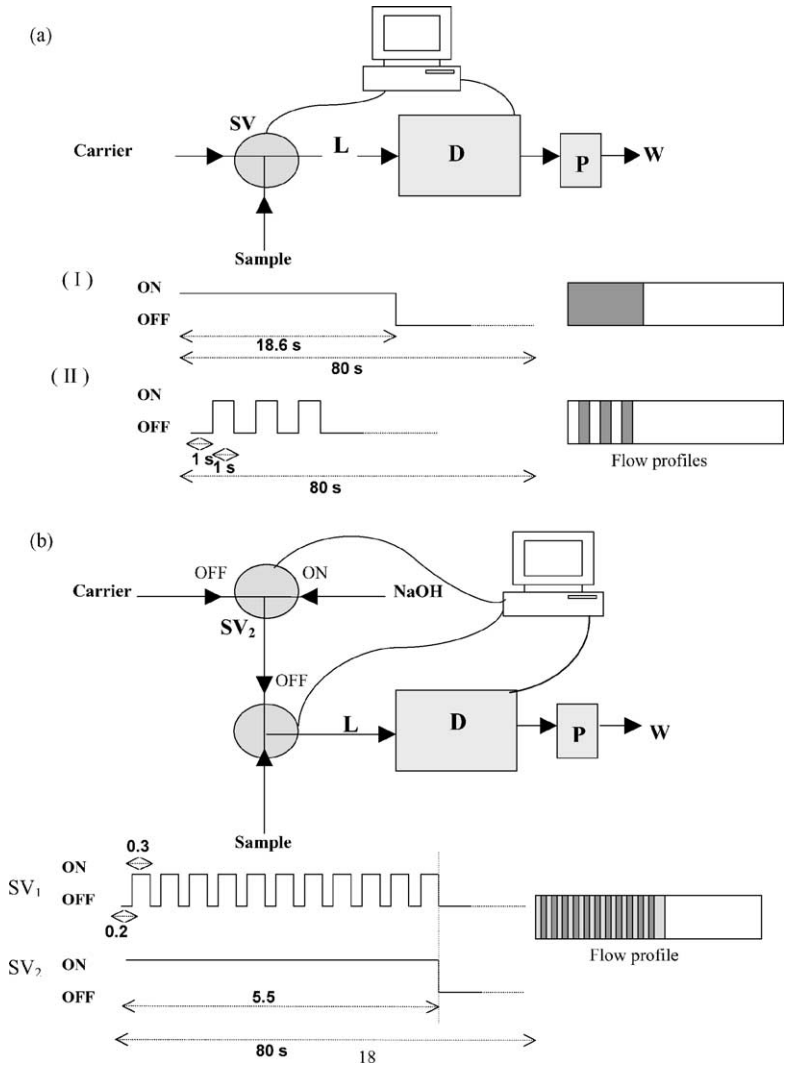


Fig. 1. Flow-assemblies proposed for the dissolution profile. (a) Flow-assembly for mixtures when changes in pH (dissolution vessel and spectrophotometric measurements) are not required; mixture sulphamethoxazole–trimethoprim. Flow rate, 3.3 ml min^{-1}; *L*, 34.1 cm; carrier, HCl 0.1 mol l^{-1}. Determination in the first derivative spectra at 247 and 257 nm for trimethoprim and sulphamethoxazole, respectively. Global profile absorbance at 254 nm. (I) Insertion sample for the most sensitive determination: 18.6 s (ON position) (only one segment). (II) Insertion sample for the dissolution test: sample insertion (ON position), 1 s; carrier insertion (OFF position), 1 s; number of segments, 3. The cycle starts again every 80 s. (b) Flow-assembly proposed for changing the pH from dissolution vessel to the spectrophotometric flow-cell; mixture hydrochlorothiazide–captopril. Flow rate, 2.7 ml min^{-1}; *L*, 40.0 cm; carrier, water; NaOH solution, 0.4 mol l^{-1}. Determination in the first derivative spectra at 250 for captopril and at 273 nm in the absorbance spectra for hydrochlorothiazide. Global profile absorbance at 240 nm. SV_1: insertion sample (ON position), 0.3 s; insertion NaOH (OFF position), 0.2 s; number of segments, 11. SV_2: insertion of NaOH (ON position), 5.5 s (only one segment). The cycle starts again every 80 s. SV, solenoid valve; *L*, length to the detector; D, UV–vis detector; P, peristaltic pump; W, waste. Sample in HCl 0.1 M.

recorded by using the first derivative spectra for both active principles, namely at 250 nm for captopril and at 273 for hydrochlorothiazide. Global profile absorbance was recorded at 240 nm.

3. Results and discussion

3.1. Preliminary assays

Preliminary experiments were performed in batch to establish and confirm the procedure for determination of different couples of drugs that occurs in the same pharmaceutical preparation. UV–vis spectra were recorded at different pH values and then, different derivative orders (from zero, first, etc.) were obtained. The goal was to obtain zero crossings in which the signal from one drug was not interfered by the other with the minimum sensitivity losses.

Different aqueous solutions were freshly prepared from all tested drugs with concentrations of 30 or 20 mg l^{-1}. Aliquots of the stock solutions were taken and the pH potentiometrically adjusted over the range 1–12 by dropping 0.1 mol l^{-1} HCl or NaOH. Spectra were recorded from 190 to 350 nm; first- and second-order derivative spectra were obtained to

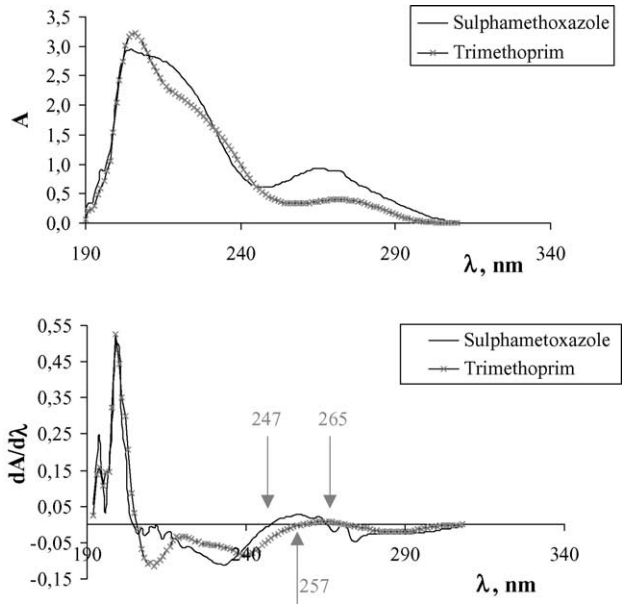


Fig. 2. Top, UV absorption spectra of trimethoprim (50 mg l^{-1}) and sulphamethoxazole (20 mg l^{-1}) in 0.1 mol l^{-1} HCl. Bottom, first derivative spectra of both drugs.

find the suitable zero crossings. Shorter pH range (8.0, 8.3, 8.6, 8.9, 9.2, 9.6, 9.9) was required for the set of pharmaceuticals sulphamethoxazole and trimethoprim.

3.1.1. Sulphamethoxazole and trimethoprim

As reported, spectra for dissolutions of separated drugs were tested over the range 1.0–12.0. The best sensitivity for determination of the couple sulphamethoxazole–trimethoprim was found at pH 1.

Observed results give no differences of the spectra over the pH range 1.0–4.3; as the former is the recommended for the dissolution of the formulation, it can result in a simple flow manifold; then, pH 1 was selected for further work. Fig. 2 shows the absorbance spectra and the first derivative spectra for sulphamethoxazole and trimethoprim in HCl 0.1 mol l^{-1}.

Two series of drug solutions were prepared in 0.1 mol l^{-1} HCl to mimic the conditions during the dissolution tests with continuously increasing of concentrations. Prepared concentrations were in the range 20–150 mg l^{-1} for sulphamethoxazole and 20–80 mg l^{-1} for trimethoprim. No variations were observed in the zero crossings at any tested concentration. Two zero crossings for trimethoprim, 257 and 272 nm, and four for sulphamethoxazole, 247, 265, 270 and 272 nm, were found. The highest sensitivity zero crossings were set at 247 and 257 for the determination of trimethoprim and sulphamethoxazole, respectively. See Fig. 3.

The assembled flow manifold was the simplest possible due to the required pH measurement was the same of dissolving solution. It consisted of a single solenoid valve allowing the sequential insertion of sample (ON position) and carrier segments (OFF position) (Fig. 1a). The peristaltic pump placed after the detector aspirated the stream to the detector flow-cell. The hydrodynamic parameters to be optimised were insertion time of sample (or sample volume) aliquots, number of segments, length of the reactor and flow-rate. After a previous univariate optimisation to stabilise the best limits, the multivariate optimisation was performed.

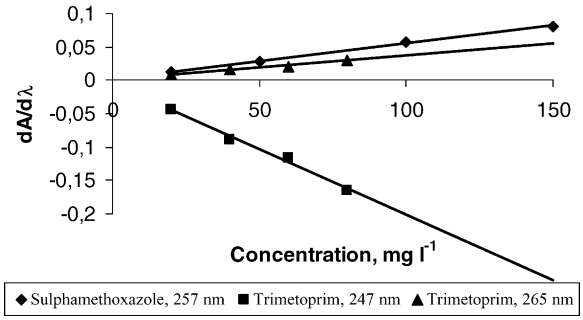


Fig. 3. Calibration graphs for sulphamethoxazole and trimethoprim in 0.1 mol l^{-1} HCl at different wavelengths and obtained from the first derivative.

The results of the preliminary optimisation of the influence of the insertion time of sample on the analytical signal, that is, the time when solenoid valve is open to allow an aliquot of sample to be inserted into the system, are depicted in Fig. 4. The output increase with the sample volume was faster up to an insertion time of 12 s, and after it, smaller increases were observed. By keeping the global insertion time in 12 s, the next assay was to study the set (number) of small sample segments to be inserted into the system, due to solenoid valves allowing the sequential insertion segments of two different solutions (sample and carrier). As expected, maximum signals were obtained with small number of segments and high ratios sample timing/carrier timing, due to the minor sample dispersion.

The multivariate optimisation resulted in 16 vertices, after it was considered the system did not merit further research. All peak heights were searched at 257 nm (zero-crossing of trimethoprim), bearing in mind the optimisation program only allowed a single value. The three vertices with the highest values were pre-selected and series of 20 measurements

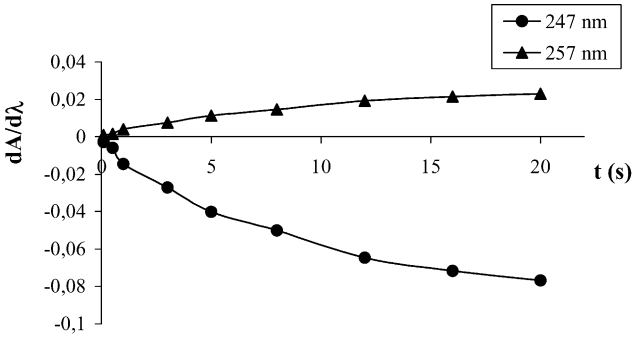


Fig. 4. Influence of insertion time or influence of the inserted sample volume. The inserted sample was 0.1 mol l^{-1} HCl containing 50 mg l^{-1} of sulphamethoxazole and 40 mg l^{-1} of trimethoprim.

were run again at 247 and 257 nm to select the best compromise sensitivity—reproducibility—consumption of sample. After it, the selected values for further work were: flow-rate 3.3 ml min^{-1}, sample insertion time, 18.6 s, and length of the reactor (*L*), 34.1 cm. This set of conditions resulted in a R.S.D. (%) of 1.5 and 1.6 at 247 and 257 nm and with 50 and 40 mg l^{-1} of sulphamethoxazole and trimethoprim, respectively. The sample consumption was of 1.0 ml per insertion.

The calibration graphs were further obtained by preparing solution over the range of concentrations 5–60 mg l^{-1} all in 0.1 mol l^{-1} HCl. The fitting equations were: $dA/d\lambda = 0.00045C + 0.00021$ (r^2 0.9997) and $dA/d\lambda = -0.00157C - 0.00117$ (r^2 0.9990) for sulphamethoxazole and trimethoprim, respectively.

New calibration graphs were performed by preparing mixtures of both drugs; one of them was varied and the other was kept in a constant concentration; it was repeated during three days with freshly prepared solutions. The average of the calibration curves were: $dA/d\lambda = (0.00046 \pm 0.00009)C - (0.0008 \pm 0.0008)$ (r^2 0.997) and $dA/d\lambda = -(0.00160 \pm 0.00012)C - (0.007 \pm 0.004)$ (r^2 0.995) for sulphamethoxazole and trimethoprim, respectively. No differences were found between the slopes obtained in presence of the other drug, which is a clear evidence of no matrix effects.

Those calibration graphs were also obtained for high concentrations of sulphamethoxazole bearing in mind in the dissolution assays this drug varied over the range 0–450 mg l^{-1} and trimethoprim up to 90 mg l^{-1}. The study of so high concentrations resulted in very high absorbance values, and due to that, new optimisation of hydrodynamic parameters was required.

However, when we tried to optimise the assembly and perform new calibration graphs at high sulphamethoxazole concentrations, no linearity was found over concentrations about 200 mg l^{-1} of sulphamethoxazole, probably due to non-complete solubility of the drug just as a clean opalescence was always observed. New assays at 37 °C and in different media (even at 0.2 mol l^{-1} of NaOH) always resulted in a non-linear behaviour and some opalescence appearance. These problems were not observed with trimethoprim at concentrations up to 90 mg l^{-1}.

To avoid this problem, several preliminary assays were carried out with tablets of Eduprim. Dissolution tests were performed employing different conditions for time insertion of sample and carrier, looking for lower absorbance values (<1.5) and good reproducibility of the peaks when the dissolution test was completed and the maximum concentration was reached.

The selected conditions were: sample insertion time, 1 s; carrier (HCl 0.1 mol l^{-1}) insertion time, 1 s; and number of insertions (sample and carrier), 3. (See Fig. 1a.II.)

3.1.2. Hydrochlorothiazide and captopril

The influence of pH on the spectra over the range 1.0–12.0 resulted in no variations of the hydrochlorothiazide spectra on the whole studied range; however, captopril showed relevant changes. At pH lower to 11–12, the captopril only presented one absorbance band around 200 nm. At highest pH, a second band appears around 230 nm (see Fig. 5). In the acidic medium, the determination of captopril only would be possible at 226 nm in the first-order derivative spectrum. However, at pH 11, the determination with the first-order derivative spectrum should be possible at 250 nm.

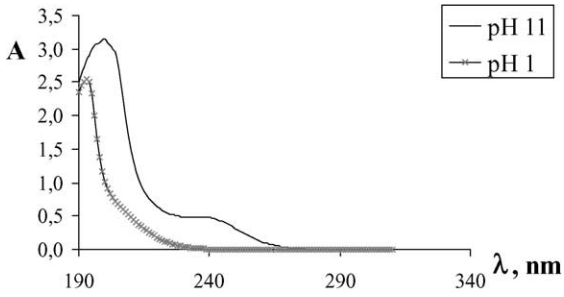


Fig. 5. UV absorption spectra of captopril (20 mg l^{-1}) in acid and basic medium.

A larger study on the influence of pH was performed to establish the use of buffer solutions to obtain the zero crossings at basic pH. Prepared buffer solutions and pH were the following: borax buffer at pH values: 10.0 and 10.5; glycine buffer at 10.0, 10.5, 11.0, 11.5 and 12.0; phosphate buffer at pH 11.0 and 12.0; NaOH/KCl buffer at pH 12.0. The pH was potentiometrically adjusted in all assayed solutions. Also, NaOH and KOH, both 0.1 mol l^{-1}, were compared. The use of NaOH medium was shown to be suitable.

To select the medium for the determination, some calibration graphs were performed with the aid of the manifold depicted in Fig. 1.a.I. Calibration graphs of hydrochlorothiazide and captopril, prepared in 0.1 mol l^{-1} HCl or 0.1 mol l^{-1} NaOH, were obtained. The comparison of the relative errors in the determination of samples prepared in the lab showed the best results (smaller errors) for the captopril determination can be obtained in basic medium at 250 nm with the first derivative spectrum. Fig. 6 shows the absorbance spectra and the first derivative spectra for captopril and hydrochlorothiazide at pH 11.

As the dissolution test must be performed in 0.1 M HCl, the flow-assembly was modified by adding a second solenoid valve (see Fig. 1b). Before starting the measurements, only the carrier (water) was leaded to the detector flow-cell. Next, the valve 1 and 2 switches to ON position alternatively, to insert the sample (prepared in the HCL solution) and the NaOH solution to obtain the required pH.

To obtain the most suitable conditions, two simplex assays were performed and a univariate re-optimisation was carried out. The conditions selected were as follows: length of reactor (*L*), 40 cm; flow-rate, 2.7 ml min^{-1}; concentration of NaOH, 0.4 mol l^{-1}; SV_1: ON position (insertion time of sample), 0.3 s; OFF position (insertion time of NaOH), 0.2 s; and number of insertions (sample and NaOH), 11; SV_2: ON position (flow NaOH) during 5.5 s.

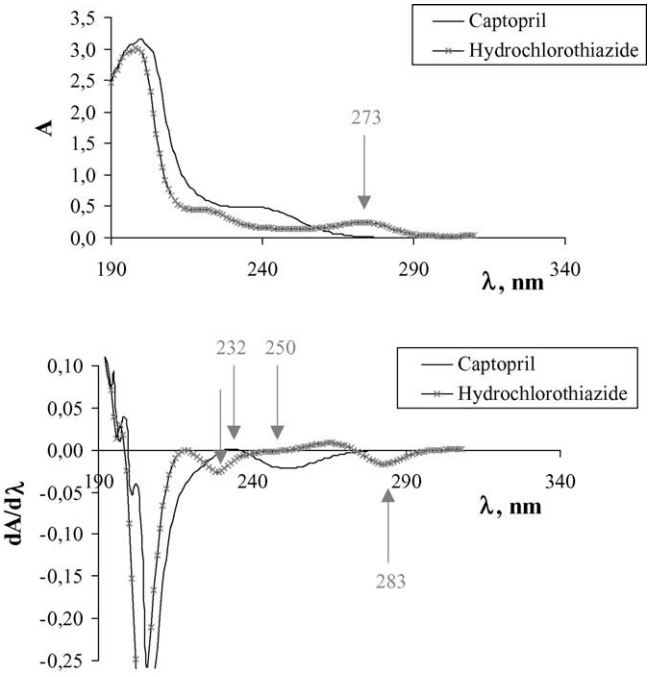


Fig. 6. Top, UV absorption spectra of captopril (20 mg l^{-1}) and hydrochlorothiazide (5 mg l^{-1}) at pH 11. Bottom, first derivative spectra of both drugs.

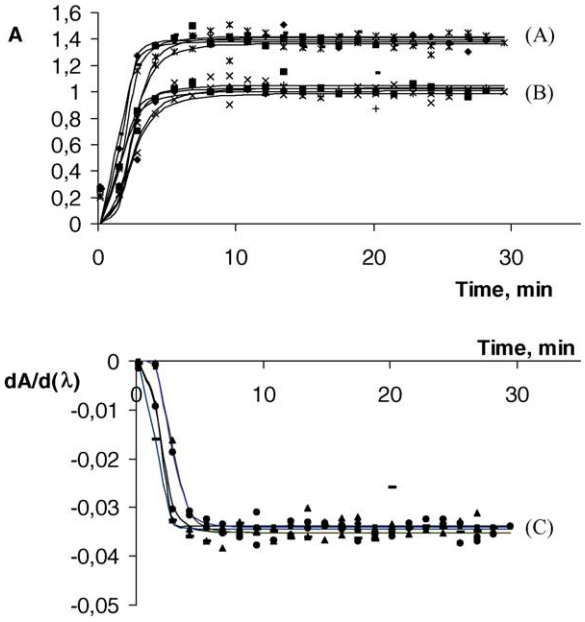


Fig. 7. Dissolution profile of tablets containing hydrochlorothiazide and captopril (captopril–hydrochlorothiazide Normon 50/25 EFG; Lab. Normon S.A., Spain); five replicates: (A) global profile; (B) hydrochlorothiazide; and (C) captopril.

To select the most suitable wavelengths for the determination of hydrochlorothiazide and captopril, calibration graphs with the optimised system were obtained in the first derivative spectra at 231 and 283 nm for hydrochlorothiazide, and at 249 and 250 nm in the first derivative spectra for captopril determination. Three samples containing both drugs were studied by the above reported wavelengths. As result and by considering the conditions where the errors were smaller, the determination of hydrochlorothiazide at 273 nm in the absorbance spectra and of captopril at 250 nm in the first derivative spectra were selected for the dissolution test.

The average calibration graphs from three independents assays were: $dA/d\lambda = -(0.00059 \pm 0.00005)C + (0.0001 \pm 0.0009)$ (r^2 0.992) and $A = (0.0228 \pm 0.0015)C + (0.29 \pm 0.02)$ (r^2 0.994) for captopril at 250 nm (concentration over the range 10–50 mg l^{-1}) and for hydrochlorothiazide at 273 nm (concentration over the range 5–25 mg l^{-1}), respectively. The errors obtained in the determination of the samples, in general, were smaller than 10% excepting when the concentration of CTP was very small, about 10 mg l^{-1}.

3.1.3. Regression analysis of the solution profile plots

To check the reproducibility of the resulting profiles, the regression analysis of the curves was studied with the aid of so called three-parameter equation or Higuchi equation.

$$V_2 = \frac{a}{1 + (b/V_1)^c}$$

The depicted parameter meanings are: *a*—signal figure (first absorbance derivative) when the total solution is finished; *b*—half-maximum signal or the signal at half-time of the required interval of total dissolution; *c*—the exponent related with the slope of the climbing interval of the profile; and V_1 was the time of the dissolution test in minutes and V_2 the signal at the wavelength selected. The suitability of the Higuchi equation was discussed elsewhere [7].

Computerised calculations were performed with the aid of the program "Statistica" working in windows (©Statsoft Inc., 1993). Examples from this work are depicted in Fig. 7.

The Higuchi equation allows an easy comparison of the parameters and the curves and it fits better than polynomial equations; all this was discussed elsewhere [27].

3.1.4. Dissolution profiles on commercially available pharmaceutical formulations

Dissolution tests were performed by connecting the officially recommended dissolution assembly to the proposed flow manifold. The dissolution profiles were obtained with three commercially available formulations of sulphamethoxazole and trimethoprim, namely Septrim (tablets), Bronquimucil (capsules) and Momentol (tablets), and two commercially available formulations of captopril and hydrochlorothiazide, namely Ecadiu and captopril–hydrochlorothiazide Normon (both tablets). For the first couple, the determinations were performed at 247 and 257 nm in the first derivative spectra for trimethoprim and sulphamethoxazole, respectively, and at 254 nm directly in the absorbance spectra for the global profile. With the second couple, captopril was determined in the first derivative spectra at 250 nm, hydrochlorothiazide at

Table 1
Three-parameter Higuchi equation for the dissolution profile from a commercial preparation containing sulphamethoxazole and trimethoprim

	Sulfametoxazole				Trimetoprim				Global profile			
	a (R.S.D.,%)	*b* (R.S.D.,%)	*c* (R.S.D.,%)	r^2	*a* (R.S.D.,%)	*b* (R.S.D.,%)	*c* (R.S.D.,%)	r^2	*a* (R.S.D.,%)	*b* (R.S.D.,%)	*c* (R.S.D.,%)	r^2
Septrim	0.029 (16.9)	4.5 (23.4)	2.6 (28.1)	0.990	−0.045 (15.7)	1.9 (23.5)	4.5 (22.0)	0.94	1.94 (6.0)	4.4 (12.7)	2.21 (5.1)	0.995
Bronqui-Mucil	0.030 (7.3)	4.1 (5.9)	3.2 (21.3)	0.96	−0.044 (12.4)	2.9 (10.7)	6.1 (27.6)	0.93	2.30 (5.3)	5.1 (6.0)	2.0 (17.8)	0.993
Momentol	0.021 (18.1)	2.1 (26.0)	4.05 (1.7)	0.90	−0.032 (11.7)	2.2 (25.1)	5.3 (26.4)	0.95	1.75 (6.4)	2.9 (14.2)	4.2 (7.8)	0.990

Each depicted figure is the average from five dissolution profile assays.

Table 2
Three-parameter Higuchi equation for the obtained dissolution profile from a commercial preparation containing captopril and hydrochlorothiazide

	Hydrochlorothiazide				Captopril				Global profile			
	a (R.S.D.,%)	*b* (R.S.D.,%)	*c* (R.S.D.,%)	r^2	*a* (R.S.D.,%)	*b* (R.S.D.,%)	*c* (R.S.D.,%)	r^2	*a* (R.S.D.,%)	*b* (R.S.D.,%)	*c* (R.S.D.,%)	r^2
Ecadiu	1.20 (15.4)	3.0 (17.1)	0.95 (8.6)	0.97	−0.0334 (5.0)	1.72 (10.6)	4.1 (20.0)	0.93	1.38 (2.3)	1.7 (15.7)	2.1 (37.5)	0.96
Normon	1.02 (2.3)	2.1 (20.0)	3.1 (20.7)	0.96	−0.0346 (1.9)	2.2 (27.7)	5.3 (19.6)	0.98	1.39 (1.6)	2.0 (24.1)	3.8 (10.6)	0.97

Each parameter is the average of five dissolution profile tests.

273 nm and global profile at 240 nm both directly in the absorbance spectra.

The regression analysis of the obtained plots with the three-parameter equation is reported in Tables 1 and 2, in which depicted figures are the average of five independent assays. It can be seen from the results that the three-parameter equation offers a suitable approach to describe the dissolution test curve of preparation containing both pairs. Also the four-parameter equation was tested, but it described worse the results.

4. Conclusions

This article proposes for first time the simultaneous determination of three dissolution profiles in one formulation with the aid of the new and emergent methodology known as multicommutation. The global profile of the formulation (as the recommended procedure in pharmacopoeias) is obtained along with two "individual" profiles of two drugs present in the formulation.

The use of multicommutation assembly resulted in a new step toward a quick, automated procedure for dissolution profiles by using a versatile methodology versus other "classical" flow methodologies.

The method should be optimised for each couple, and it was applied to two pairs of pharmaceuticals (sulphametoxazole–trimethoprim and captopril–hydrochlorothiazide) with overlapped spectra.

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