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Screening of conditions controlling spectrophotometric sequential injection analysis

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Abstract

Background: Despite its potential benefits over univariate, chemometrics is rarely utilized for optimizing sequential injection analysis (SIA) methods. Specifically, in previous vis-spectrophotometric SIA methods, chemometrically optimized conditions were confined within flow rate and reagent concentrations while other conditions were ignored.

Results: The current manuscript reports, for the first time, a comprehensive screening of conditions controlling vis-spectrophotometric SIA. A new diclofenac assay method was adopted. The method was based on oxidizing diclofenac by permanganate (a major reagent) with sulfuric acid (a minor reagent). The reaction produced a spectrophotometrically detectable diclofenac form. The 2^6 full-factorial design was utilized to study the effect of volumes of reagents and sample, in addition to flow rate and concentrations of reagents. The main effects and all interaction order effects on method performance, i.e. namely sensitivity, rapidity and reagent consumption, were determined. The method was validated and applied to pharmaceutical formulations (tablets, injection and gel).

Conclusions: Despite 64 experiments those conducted in the current study were cumbersome, the results obtained would reduce effort and time when developing similar SIA methods in the future. It is recommended to critically optimize effective and interacting conditions using other such optimization tools as fractional-factorial design, response surface and simplex, rather than full-factorial design that used at an initial optimization stage. In vis-spectrophotometric SIA methods those involve developing reactions with two reagents (major and minor), conditions affecting method performance are in the following order: sample volume > flow rate ≈ major reagent concentration >> major reagent volume ≈ minor reagent concentration >> minor reagent volume.

Background

Sequential injection analysis (SIA) is the second generation of an extended family called flow injection (FI) techniques [1]. SIA gathers valuable advantages, including automation, miniaturization, versatility and cost-effectiveness, over other generations and versions of FI techniques. Recent articles reviewing the principles, developments and applications of FI techniques are available elsewhere [2,3].

On the other hand, optimizing experimental conditions is a prior in developing analytical methods. A literature survey was carried out by the Scopus® database using the phrase "sequential injection analysis". Since the introduction of SIA technique in 1990 [1], the survey has enumerated 639 articles. Within the extracted results, a further literature survey, using the keywords "chemometrics" or "multivariate", was carried out. In the latter survey, thirty-nine articles were found, i.e. the rest of articles reported developing SIA methods using the univariate approach.

The univariate approach optimizes conditions one-by-one by varying levels of one condition while levels of other conditions are held at constant levels. This procedure makes the univariate approach time- and reagent-consuming. Moreover, the univariate approach is unable to consider interaction effect between conditions and hence the maximum efficiency of analytical methods might not be obtained.

On the other hand, chemometrices, as a group of multivariate approaches, is more powerful than the univariate approach. The strategy of chemometrics is that to obtain the highest efficiency of analytical methods in the shortest way. Hence, chemometrices reduces consumption of

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reagents and sample, besides it saves time and minimizes effort. Chemometrics gains its strategy throughout the following ways: (i) examining the effect of conditions and their interactions on the efficiency of analytical methods, (ii) optimizing conditions with considering their interactions, (iii) developing more than one analytical aspect at the same time, (iv) reducing a large amount of data that can be easily interpreted and (v) testing the ruggedness [4-6].

Among the most common effective chemometric optimization approaches are the experimental design-based methods. The remarkable applications of experimental design include factor screening, response surface examination, system optimization and system robustness. Factorial design, which is the dominant factor screening method, allows to select which factors are significant and at what levels [4-6].

On the other side, for its selectivity, simplicity and familiarity, spectrophotometric detection is frequently used with SIA [7-10]. In SIA with UV detection, multivariate curve resolution with alternating least squares (MCR-ALS), as a chemometric tool, was successfully utilized to treat second-order data in order to optimize resolution using UV detection [11-15]. However, the most applied spectrophotometric detection that used with SIA methods is in the vis range, which is more selective. In those methods, chromogenic reactions, which most probably are redox, complexation, ion pairing and charge transfer, are usually applied. Most of those reactions involved two reagents or more [16-26]. In those methods, the chemometrically optimized conditions limited within flow rate and concentrations of reagents while other such effective conditions as volumes of reagents and sample were neglected.

Therefore, it has been proposed, for the first time, to screen conditions controlling vis-spectrophotometric SIA methodologies. An issue that would reduce effort and time when developing new methods in the future. As an example, a new vis-spectrophotometric SIA method for the assay of diclofenac was adopted.

Diclofenac is chemically named 2-[(2,6-dichlorophenyl)aminophenyl]-acetic acid (Figure 1). It is a potent analgesic and anti-inflammatory agent. Due to its use for many treatments, diclofenac is prepared in a wide range of formulations including tablets, capsules, drops, injections, suppositories, gels and ointments. The extensive worldwide use of diclofenac has aroused researchers to develop many assay methods using various analytical techniques. In this issue, it has been found that, within the last five years, more than fifteen methods were reported. Gravimetry [27], spectrophotometry [28,29], fluorometry [30], Raman Spectroscopy [31,32], diffuse reflectance photometry [33], potentiometry [34,35], multisyringe flow injection analysis with amperometry [36], liquid chromatography [37,38], high performance liquid chromatography [39-41], thin layer chromatography [42], high performance thin chromatography [43] and gas chromatography-mass spectrometry [44] were utilized.

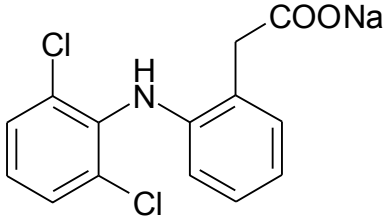

Figure 1 Chemical structure of sodium diclofenac.

Results and Discussion

Preliminary study

Recently, permanganate, as the superior oxidizing agent with its high absorptivity, has been found selective in controlled conditions for the assay of some medicines in their formulations [17,19,26,45,46]. In the current work, it has been found that diclofenac can be oxidized by permanganate in sulphuric acid media. The oxidized form of diclofenac is spectrophotometrically detectable at 450 nm.

Before undertaking any screening study, it is important to delineate clearly the boundaries of conditions controlling SIA. The minimum and maximum applied levels of conditions are introduced in Table 1.

Regarding levels of flow rate for spectrophotometric measurement, following the practice of SIA [17-19,21,23,24,26,45,46], 15-30 μL/s is the most suitable range. Flow rate lower than 15 μL/s decreases sample frequency while flow rate higher than 30 μL/s decreases repeatability.

The range of 1.0 - 5.0 mmol/L was adopted for permanganate concentration. Higher diclofenac concentration might not be completely oxidized by permanganate concentration lower than the adopted range. On the other hand, at permanganate concentration above the

Table 1 Levels of experimental condition applied for the 2^6 full-factorial design optimization

Experimental condition	Minimum level	Maximum level
Flow rate (μL/s)	15	30
Permanganate concentration (mmol/L)	1.0	5.0
Sulphuric acid concentration (mmol/L)	10	100
Permanganate volume (μL)	50	100
Sulphuric acid volume (μL)	30	60
Diclofenac volume (μL)	30	60

adopted range, significant absorbance of diclofenac was not obtained.

For sulfuric acid concentration, a level higher than 100 mmol/L distorted the base line of a SIA-gram and produced poor repeatability as in previous procedures [17-19,21,23,24,26,45,46]. On the contrary, acid concentrations bellow 10 mmol/L did not record significant absorbance.

The volume ranges of reagents and sample were adopted based upon the criteria of that to obtain significant absorbance and acceptable repeatability. It has been found that, generally, high volume produced non-repeatable results while low volumes decreased absorbance.

Screening of conditions using factorial design

Unless otherwise described the term "response" refers here to the absorbance of an oxidized form of diclofenac. As mentioned before, the 2^6 full-factorial design was adopted. The base 2 stands for the minimum and the maximum levels of experimental conditions. The power 6 is the number of experimental conditions those would be optimized, which include flow rate, permanganate concentration, sulfuric acid concentration, permanganate volume, sulfuric acid volume and sample volume. A total of 64 experiments using 100 μg/mL diclofenac, as the result of the 2^6 full-factorial design, were conducted. For validation purpose, each experiment was repeated three times, which is practicable when using such a fully-automated technique as SIA.

It was found that the experiment that included the conditions of low flow rate (15 μL/s), high permanganate concentration (5.0 mmol/L), high acid concentration (100 mmol/L), low permanganate volume (50 μL), high acid volume (60 μL) and high sample volume (60 μL) recorded the highest response, which was 1.87. Another experiment also recorded almost the same response, namely 1.77. The conditions of the latter experiment are the same of the frontal experiment with the exception of the use of low acid volume (30 μL).

The main effects "E", n = 6, and all interaction order effects, n = 57, on absorbance were calculated using equation 1 [4-6]. "y(+1)" and "y(-1)" are the absorbance values at the minimum and the maximum levels of an examined factor, respectively. "n" is the number of experiments at one level. "n" in the current design = 32.

$$E = \frac{\sum y(+1)}{n} - \frac{\sum y(-1)}{n} \quad (1)$$

A wide range of grades, ranging from 0.005 to 0.450, was obtained. To simplify that range, effect factors > 0.1 were considered significant. It has been found that for effect factor of < 0.1 the difference in responses at minimum and maximum levels of a condition, e.g. acid volume, with other fixed conditions was almost less than 0.1. From the viewpoint of spectrophotometry, the difference in absorbance of < 0.1 is insignificant. Figure 2 shows factors of > 0.1, which is considered, as relatively effective factors. It has been found that the most effective factor is sample volume that positively effect on response. High diclofenac volume increases the number of moles of diclofenac and hence increases absorbance. In the second order of effect is the positive effect of permanganate concentration and negative effect of flow rate (Figure 2). Negative effect of the latter condition indicates slow oxidation reaction of diclofenac. Increasing permanganate concentration with increasing response emphasizes that the oxidation of diclofenac by acidified permanganate is slow. Regarding other main factors, permanganate volume and acid concentration recorded relatively lower effect than other main factors while acid volume did not record significant effect. On the other side, although the effect of both permanganate concentration and flow rate are in the same order, the most significant interaction effect was recorded for sample volume with permanganate concentration.

In order to set up the optimum conditions, it has to compromise between results obtained from factorial design and those obtained from the calculation of effect factors. Primarily, there was no significant difference between the responses obtained from experiments those recorded the responses of 1.87 and 1.77, which differed in acid volume. The results obtained from the calculations of the main and interaction effect factors show that acid volume has the lowest effect (Figure 2). Therefore, the maximum efficiency, in terms of sensitivity, rapidity and reagent consumption, of the proposed SIA method can be extracted from conditions of experiment that recorded the response of 1.77. Consequently, the optimum adopted conditions were minimum flow rate (15 μL/s), maximum permanganate concentration (5.0 mmol/L), minimum acid concentration (10 mmol/L), minimum permanganate volume (50 μL), minimum acid volume (30 μL) and maximum diclofenac volume (60 μL).

Method validation

To examine the linear range and the weighed regression of calibration equation, a long series of diclofenac standard solutions were applied to the proposed SIA procedure under the optimum conditions. The method was found to be linear, with a correlation coefficient of 0.9998, in the range of 10 - 150 μg/mL. The weighed regression of calibration is described in equation 2. "A" is the absorbance of the oxidized form of diclofenac. "C" is the concentration of diclofenac. Figure 3 shows a SIA-gram obtained by a one-shot run of four standard

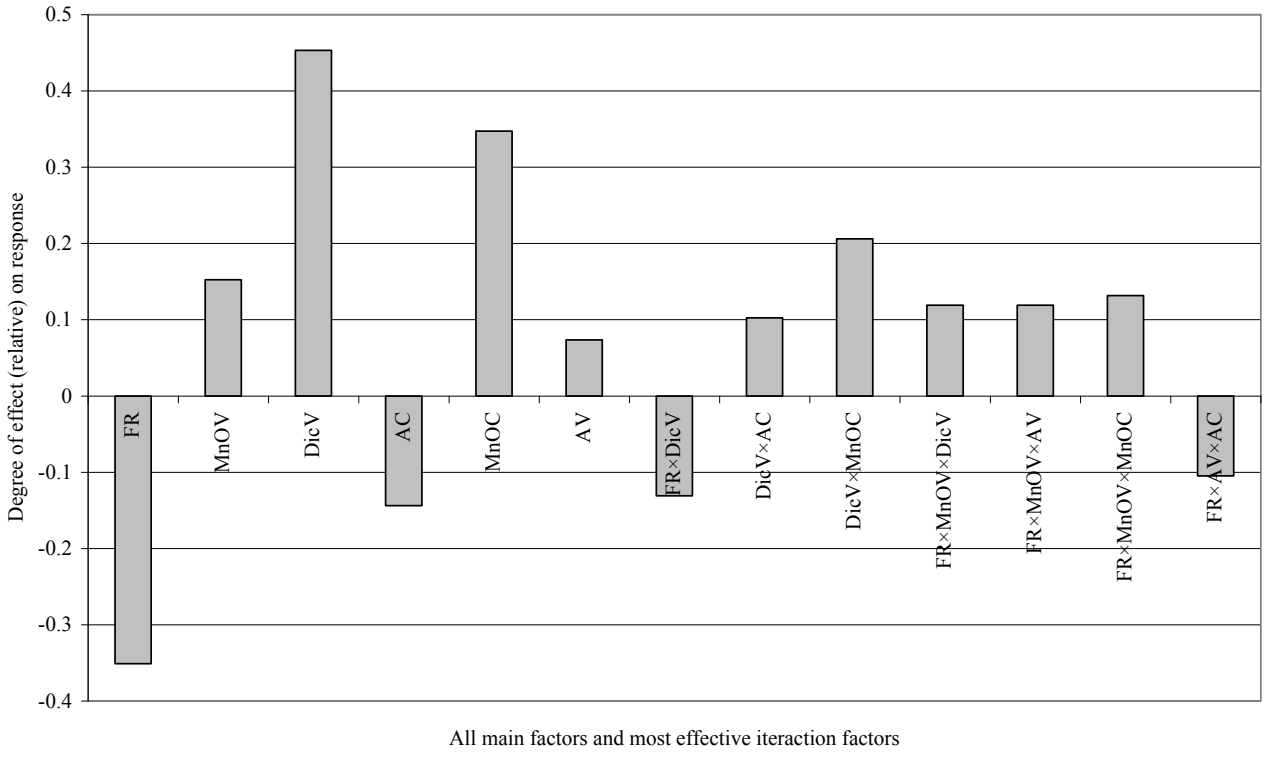

Figure 2 Most effective main and interacting conditions on the response of the SIA method. FR: flow rate (μL/s), MnOV: permanganate volume (μL), DicV: diclofenac volume (μL), AV: acid volume (μL), AC: acid concentration (mmol/L), MnOC: permanganate concentration (mmol/L).

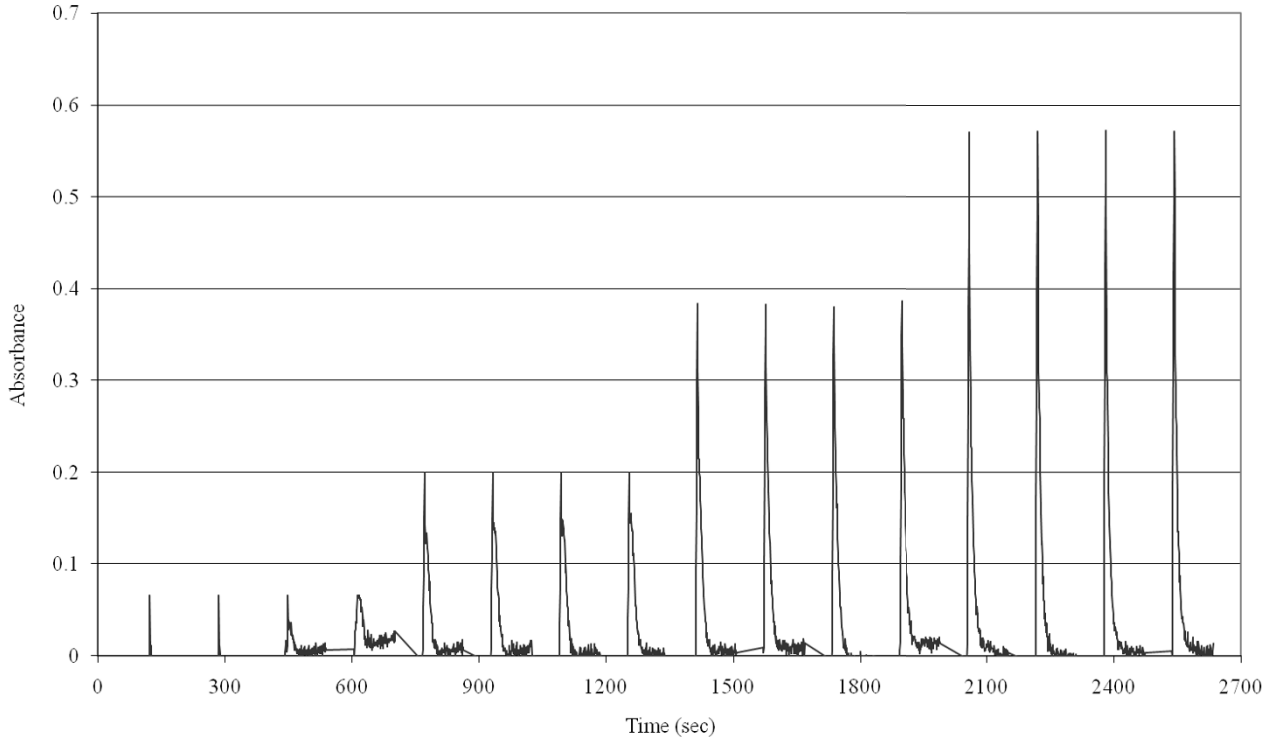

Figure 3 Spectrophotometric SIA-gram of four diclofenac standard solutions (10, 50, 100 and 150 μg/mL). Each solution was measured four times.

solutions (10, 50, 100 and 150 μg/mL) of diclofenac; each standard solution was measured four times.

$$A = 0.003C + 0.024 \quad (2)$$

To examine the repeatability and the intermediate-precision, a standard solution of 50 μg/mL diclofenac was applied to the SIA method seven times in a day and five times over a week, respectively. The relative standard deviation (RSD) for repeatability study was 1.34% while the RSD for inter-mediate precision was 2.75%. The automation of SIA rendered the proposed method precise.

The limits of detection (LOD) and quantification (LOQ) were also examined. LOD was obtained as the concentration of a solute resulting in a peak height three times the baseline noise level. LOQ was obtained as the concentration of solute resulting in a peak height ten times the baseline noise level. The LOD and LOQ were found to be 1.37 and 4.57 μg/mL, respectively. Satisfactorily detectability of the SIA method was obtained by successful optimization.

Method application

The method was applied to bulk and pharmaceutical samples, namely tablets, injection and gel. Bulk, tablets and injection samples were also applied to the British Pharmacopoeia (BP) methods [47]. The BP recommends a classical potentiometric method for diclofenac assay in raw materials while a LC method is recommended for tablet and gel formulations [47]. For diclofenac assay in injection formulation, a previous validated HPLC method was applied [48]. Each sample was analyzed seven times. The recovery, RSD and t-test values were calculated. The obtained results are introduced in Table 2. The experimental t-test values were lower than those tabulated values, which prove the reliability of the current SIA method.

Experimental

Instrumentation

The assembly constructed for the current work included a SIA system, miniaturized fiber optic spectrometric devices and pumped-tubes (Figure 4).

Table 2 Results obtained by the SIA method and realized by the British Pharmacopoeia method for diclofenac assay in raw materials and pharmaceutical formulations

Trade name	Formulation	Diclofenac content	Mean recovery ± RSD(%)[1]	t[2]
Samf®	Bulk	-	99.3 ± 1.45	2.14
OlfenTM-25	Tablets	25 mg	98.5 ± 2.14	2.06
OlfenTM-50	Tablets	50 mg	98.1 ± 2.81	2.11
Olfen®-75 I.M.	Injection	75 mg in 2 ml	99.1 ± 2.26	1.87
Voltaren®	Gel	1% (w/w)	103.4 ± 3.49	2.23
Diclogesic®	Gel	1% (w/w)	102.7 ± 3.18	2.70

1: RSD: relative standard deviation for 7 replicates; 2: t-test value.

The SIA system is a FIALab® 3500 (Medina, WA USA). It is composed of a syringe pump (SP), multi-position valve (MPV), holding coil (HC), Z-flow cell (Z), pump tubing and personal computer (PC). The SP includes 24,000 increments with high-resolution stepper motor, which drives the piston at rates from 1.5 seconds to 10.0 min per stroke with > 99% accuracy at full stroke. The syringe has a volume of 2.5 mL. The MPV is chemically inert and has eight ports with a standard pressure of 250 psi (gas)/600 psi (liquid); zero dead volume. The Z is a 10 mm path-length Plexiglass compatible with fiber optic connectors. Pump tubing was used to connect sequential injection analyzer devices and to make HC with a long of 200 cm. Pumped tubes of "0.03 inch" ID Teflon type was supplied from Upchurch Scientific, Inc. (Oak Harbor, WA, USA).

The optical manifold included a radiation source, spectrometer and fiber optic connectors. All optical devices were fabricated by Ocean Optics (Dunedin Florida, USA). The radiation source is an LS-1 Tungsten Halogen Lamb optimized for VIS-NIR (360 nm - 2 μm wavelength range). The detector is a USB2000 Spectrometer adapted to 200 - 1100 nm wavelength range. The fiber optic connectors are 200 micron Sub-Miniature version A®.

FIALab® for Windows version 5.0 supplied from FIAlab (Medina, WA, USA) was used for programming and controlling the whole assembly.

Chemicals and reagents

All chemicals and reagents, which were used in this study, were of analytical reagent grade. The quality of water was distilled deionized. Diclofenac sodium was supplied from Sigma (Taufkirchen, Germany). Potassium permanganate and sulphuric acid were supplied from Fluka (Buchs, Switzerland). Diclofenac sodium in the bulk form as well as inactive ingredients those possibly found in pharmaceutical formulations were a generous gift from Samf® Medicinal Factory (Khartoum North, Sudan). Inactive ingredients included sodium citrate, microcrystalline cellulose, magnesium stearate, maize starch, carnauba wax, povidone and talc.

Pharmaceutical samples

Olefn™-25 tablets (25 mg diclofenac sodium), Olefn™-50 tablets (50 mg diclofenac sodium), Olefn®-75 I.M. (75 mg diclofenac sodium) ampoules, which were prepared by Mepha Ltd. Aesch-Basel, Switzerland, were examined in the current study. Voltaren® gel (1% (w/w) diclofenac sodium), which was prepared by Novartis, Aesch-Basel, Switzerland, was also examined. Diclogesic® gel (1% (w/w) diclofenac sodium) that was prepared by Dar Al-Dawa, Naur, Jordan was examined as well.

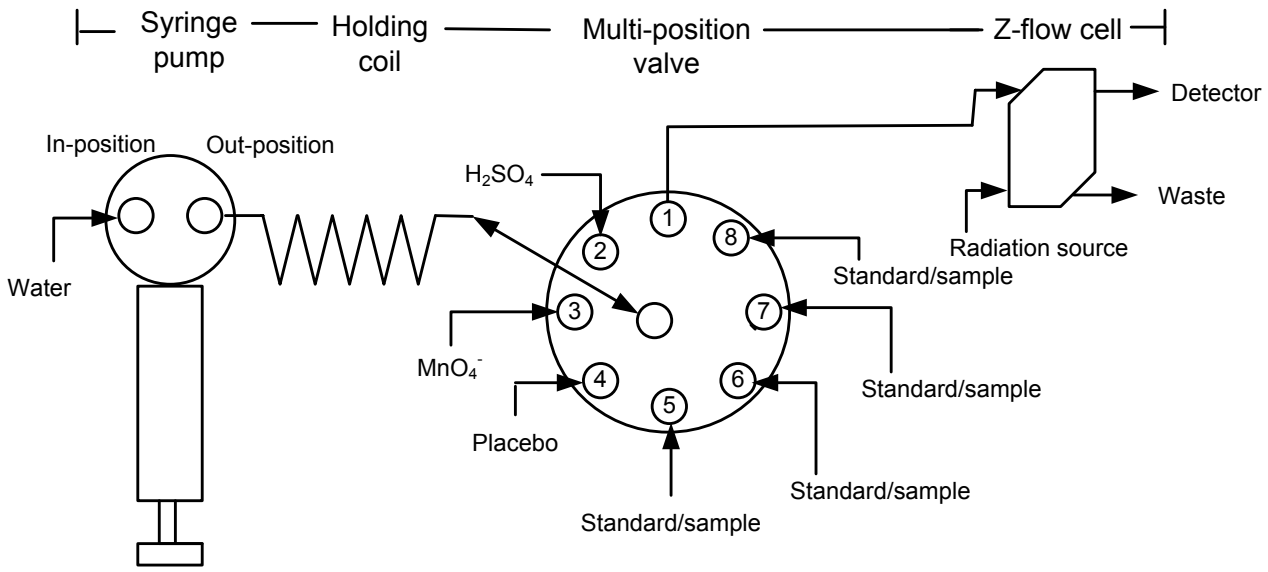

Figure 4 Schematic diagram of a SIA manifold constructed for diclofenac assay in pharmaceutical formulations.

Preparation of reagents and standard solutions

A standard stock solution of 20 mmol/L potassium permanganate was prepared and standardized weekly in an appropriate way. An appropriate amount of diclofenac was dissolved in water to prepare 1000 μg/mL as stock standard solution. Working standard solutions of diclofenac, potassium permanganate and sulfuric were daily prepared by dilution.

Preparation of pharmaceutical samples

Twenty tablets were triturated and homogenized. An appropriate quantity, which is equivalent to 50 μg/mL diclofenac, was weighed and dissolved in 10 mL of water. Then, the obtained solution was heated in water-bath at 85°C for 5 min and centrifuged for 5 min. The supernatant was filtered directly into a volumetric flask with an appropriate volume. The remaining material in the tube was treated two times again with hot water according to a previous procedure [47]. Finally, after cooling at room temperature, water was added to the solution to complete the volume of the volumetric flask.

For injection preparation, ten ampoules were discharged and mixed. An adequate volume was diluted to obtain 50 μg/mL diclofenac.

For gel preparation, five tubes were released. An accurately weighed portion of gel was treated as the tablet preparation procedure [47].

Sequential injection analysis procedure

As shown in Figure 4, a single-channel SIA manifold was constructed to perform on-line developing reaction and spectrophotometric measurement. The Z was attached to port-1 in the MPV. The radiation source and the spectrometer were connected with the Z by fiber optic connecters. Water, as a propelling solution, was linked with the in-position mode. Sulphuric acid, permanganate and placebo solutions were linked with port-2 to 4, respectively, in the MPV. Four standard/sample solutions were attached to port-5 to -8. As briefly described below, a rapid protocol controlling the proposed SIA procedure was programmed.

i. Following the practice of SIA, each solution was loaded into their relative tubes by aspiration using the SP. Then, excess volumes were dispensed to the waste.
ii. To propel solutions, the syringe was filled with 1500 μL of water.
iii. For blank measurement, acid and permanganate solutions were sequentially aspirated into the HC.
iv. The solutions were mixed using three times reverse-flow of 10 μL volume at a flow rate of 10 μL/s.
v. A placebo solution was injected into the HC and mixed with acidified permanganate as in step iv.
vi. The mixture was dispensed through Z at the required flow rate. The peak height (PA) of absorbance was recorded.
vii. For standard/sample measurement, steps iv-vi were repeated with replacing a standard/sample solutions instead of a placebo solution.

Conclusions

The current work deals with the screening of conditions controlling spectrophotometric SIA and developing a

new assay method for diclofenac. From the obtained results, the following conclusions can be made.

i. Full-factorial design is a powerful tool for the screening of conditions controlling SIA. It is also powerful for optimizing conditions at initial stage. However, other such chemometric approaches as fractional-factorial design, response surface and simplex could be more powerful for further optimization stages.

ii. In developing vis-spectrophotometric SIA methods those involve a developing reaction with two reagents (major and minor), it has been found that the main factors with their effect types, i.e. positive or negative, were ordered as follows: (+ sample volume) > (- flow rate) ≈ (+ major reagent concentration) >> (+ major reagent volume) ≈ (- minor reagent concentration) >> (+ minor reagent volume).

iii. It has been also found that there was a significant interaction effect between sample volume and major reagent concentration.

iv. Generally, in SIA that involves a developing reaction, it is recommended to utilize a chemometric tool for optimizing effective conditions (i.e. sample volume, flow rate and major reagent concentration) while less effective conditions could be fixed at suitable levels.

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Competing interests
The author declares that they have no competing interests.

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