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ORIGINAL ARTICLE

Determination of Isoniazid Gained Fluorescent with 9-Anthraldehyde by HPLC-FL Method in Dosage Forms

Fatma Demirkaya Miloglu[1] · **Burak Bayrak**[1] · **Yucel Kadioglu**[1]

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Abstract

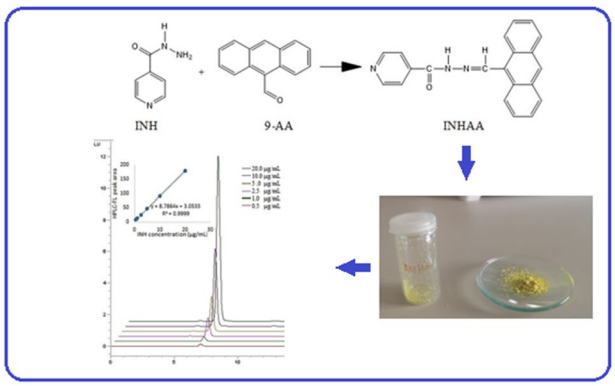
Purpose Tuberculosis is a chronic necrotizing bacterial infection caused by *Mycobacterium tuberculosis*, which has not lost its prevalence in the society from the past to the present. Isoniazid (INH) is an important drug used in the treatment of tuberculosis and is used for all forms of tuberculosis caused by *Mycobacterium tuberculosis*, unless there is resistance. This study is aimed to develop and validate a new HPLC with fluorescence detector (HPLC-FL) based on the formation of a coloured product (9-anthraldehyde isonicotinoyl hydrazone, INHAA) resulting from the condensation reaction of INH with 9-anthraldehyde(9-AA) for the determination of INH in dosage forms.

Methods Optimum INHAA formation was obtained at 68 °C and 1.97 mL 0.05 M 9-AA for 3 h using a chemometric tool which is one of the green analytical chemistry strategies. INHAA was separated on a C18 reversed-phase column in conjunction with an isocratic elution of a mobile phase composed of methanol-Milli-Q grade water and detected by fluorescence detection (FL) at excitation (390 nm) and emission (489 nm) wavelengths.

Results The method was linear over concentration range that varies between 0.5 and 20 µg/mL INH. The limit of detection (LOD) and limit of quantitation (LOQ) were estimated based on three and ten times the baseline noise and were found to be 0.11 µg/mL and 0.33 µg/mL INH, respectively. The optimized HPLC-FL parameters were applied to the analysis of drug dosage forms INH containing for quality control purposes.

Conclusion A new HPLC-FL method was developed for the analysis of INH in drug dosage forms, which saves time, effort and chemicals in the experimental design.

Graphical abstract



Keywords Isoniazid · HPLC-FL · Central composite design · Derivatization · Drugs

✉ Fatma Demirkaya Miloglu
fdkaya@atauni.edu.tr; fdemirkayamiloglu@gmail.com

Extended author information available on the last page of the article

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1 Introduction

Tuberculosis (TB) is a chronic necrotizing bacterial infection caused by *Mycobacterium tuberculosis*, which varies in transmission patterns and public health practices [1]. It is the most common and oldest infection leading cause of human morbidity and mortality worldwide [2, 3]. According to the World Health Organization (WHO), an estimated 10.6 million people worldwide infected with TB in 2021, People who are infected but have not (yet) developed the disease cannot pass it on, there is a 5–10% lifetime risk of developing TB in people infected with TB bacteria. At the same time, tuberculosis is the second deadliest infectious disease in the world after Covid-19 [3]. In fact, the COVID-19 pandemic has increased, not decreased, the global burden of TB [4]. Although women are more likely to develop tuberculosis than men, the rate varies according to regional differences. Factors such as HIV infection, other chronic diseases, diabetes mellitus, malnutrition, smoking and air pollution cause TB [5]. Tuberculosis occurs when a person inhales droplets and is transmitted from person to person through the air with respiratory movements such as speaking, coughing and sneezing of the sick person, droplets with a diameter of 1–5 microns loaded with 1–3 bacilli [1]. Drugs are the most important factor in the treatment of TB. The purpose of the using drugs in the treatment of TB is to save the patient's tissues, shorten the treatment period, and return the patients to their homes and productive lives by eliminating their contagiousness… The drugs used in the treatment can be divided into two groups. Isoniazid (INH), rifampicin, pyrazinamide, ethambutol and streptomycin are the first group of drugs. They are known for their easy availability and high treatment success when used regularly [6]. INH is the hydrazide of isonicotinic acid. INH is the most potent of the currently available anti-TB drugs. It has a bacteriostatic effect on dormant bacilli and a bactericidal effect on fast-growing bacilli at concentrations found in clinical doses [7]. In addition, the drug's ability to penetrate macrophages and caseous lesions, good absorption, ease of administration and low cost make it the most important anti-TB drug. In addition, INH produces advanced morphological changes in mycobacteria [8, 9]. The acid-resistance of the bacteria is lost. INH has no antibacterial effect on bacteria other than *Mycobacterium tuberculosis*. Therefore, it is a very narrow-spectrum drug, but its mechanism of action is not well understood [10].

Several papers have described for HPLC–UV methods for the determination of INH in pharmaceuticals. These methods include single or in combination with two or more other anti-tuberculosis drugs [11–15] and precolumn derivatization with phenethyl isocyanate [16, 17] 6-methyl-2-pyridinecarboxaldehyde [18] and 5-methylfuran-2-carboxaldehyde [19] and in solid lipid nanoparticles [20]. INH has also been determined by HPLC–MS/MS method [21, 22]. In addition, there are colourimetric methods in which the determination of INH is based on the formation of gold nanoparticles [23]. An HPLC-FL method is available for the determination of INH. In this study, INH was determined by a post-column photochemical reaction using an HPLC-FL [24]. No study based on the formation of a coloured fluorescent product (9-anthraldehyde isonicotinoylhydrazine, INHAA) as a result of the reaction of INH with 9-anthraldehyde (9-AA) using HPLC-FL in pharmaceutical preparations has been reported.

In addition, both Ma et al. [25] and Zhao et al. [26] developed spectrofluorometric methods by providing fluorescence in INH with a method based on the reduction of MnO_2 layers to Mn^{2+} with INH. A spectrofluorometric method was developed by Lapa et al. [27] based on the fluorometric monitoring of cerium (III) formed during the oxidation of INH by cerium (IV) in pharmaceutical preparations. In the study by Azizi et al. [28], they developed a calorimetric and fluorometric sensor for INH using coooh nano leaves and measurements with exchange of INH. In these studies, optimization was studied with a single factor, which could not determine interactions between experimental factors. These methods require a lot of experimental work to determine the optimal level of each factor. Green Analytical Chemistry is one of the current topics of analytical chemistry, providing an increase in environmentally friendly studies in parallel with an improvement in the quality of analytical results [29]. Recently, chemometric techniques involving experimental design, methods that provide the principles of green analytical chemistry (allowing to filter out interferences of the analyzed substance and using less chemicals and time, with acceptable accuracy and precision) have been applied to determine experimental conditions in chemistry.

In this context, it was aimed to optimize a formation reaction of coloured fluorescent product (INHAA) of INH by applying a response surface methodology; to develop, and validate a new HPLC-FL method based on the colored fluorescent product (INHAA) to determine INH in dosage form in the study.

2 Material and Methods

2.1 Chemicals and Reagents

INH, 9-AA and HPLC-reagent grade methanol were purchased from Sigma-Aldrich (Germany). Analytical-reagent grade methanol and ethanol were purchased from Riedel-de Haen, (Germany). All other solvents and chemicals used

in this study were of analytical grade. Milli-Q grade water was obtained using the Milli-Q system; EASY pure RF. The commercial pharmaceuticals containing INH (I.N.H.® (300 mg) and Isovit® (100 mg)) were purchased from a pharmacy in Erzurum/Turkey.

2.2 Instruments and Chromatographic Conditions

The HPLC system was a 1200 series from Agilent Technologies (Germany) coupled to a 1260 Infinity II spectrofluorometric detector. Chromatographic separation was performed by using a mobile phase consisting of methanol-Milli-Q grade water (40:60 v/v) at a flow rate of 1 mL/min through a Brisa LC^2 C_{18} column stationary phase (250×3 mm, 5 µm; Technokroma, USA). The mobile phase was filtered through a 0.47 µm nylon membrane filter and degassed ultrasonically before use. The injection volume was 20 µL. The fluorescence intensity of INHAA for INH determination was measured at an emission wavelength of 489 nm with the excitation wavelength set at 390 nm. The retention time of INHAA was determined to be 7.4 min and the total run time of the method was selected to be 13 min.

2.3 Proposed Methods and Experimental Design

The method is based on the conversion of 9-AA and INH compounds to the fluorescent INHAA compound as a result of the condensation reaction. For this purpose, 9-AA (0.05 M) was added to the standard solutions of INH (0.5 g/mL) and then it was stirred at 68 °C for 3 h with constant stirring and the reaction was terminated at 25 °C under reflux for 15 min. The residue was crystallized with boiling ethanol. A yellow fluorescent INHAA product was obtained (Fig. 1). The central composite design method, which is one of the chemometric design methods, was applied in order to determine the appropriate values of 9-AA concentration (A) and temperature (B), which are effective in realizing the indicated condensation reactions. The maximum and minimum values of each parameter were determined and these values were set as 0.5–2 mL for 0.05 M 9-AA and 40–70 °C for temperature. These values were determined as a set of 13 experiments according to the 2-factor central composite design. Statistical analysis and experimental design for the method were performed by using Microsoft Excel 2017 and Design-Expert8.0 software (Stat-Ease Inc., Minneapolis, MN, USA), respectively.

2.4 Preparation of Standard Solution and Controls

The pure INHAA (1 mg/mL) was used as the standard solution for analytical purposes. This stock solution was further diluted with methanol to obtain a final concentration of INH in the range of 0.5–20 µg/mL for the calibration curve and quality control (QC) samples containing 1, 5 and 15 µg/mL of INH.

2.5 Tablet Procedure

Ten tablets of each of two commercial pharmaceutical preparations (Isovit® (100 mg) and I.N.H.® (300 mg)) in tablet form containing INH were taken and their average weights calculated. After the tablets were crushed into powder, approximately 0.5 g of each was taken and stock solutions were prepared with methanol, sonicated for 15 min and cooled to room temperature. After filtering the resulting solution, INH was converted to INHAA by using condensation reaction with 9-AA as described above. Dilutions were made to obtain the desired concentrations of INH.

3 Results and Discussion

3.1 Initial Experiments and Central Composite Design on the Fluorescence Intensity

The INHAA compound was formed by entering the condensation reaction of 9-AA and INH in the most suitable solvent medium. The structural analysis of the resulting compound (INHAA) was carried out using H-NMR spectroscopy. The use of DMSO-d6 allows the observation of the labile

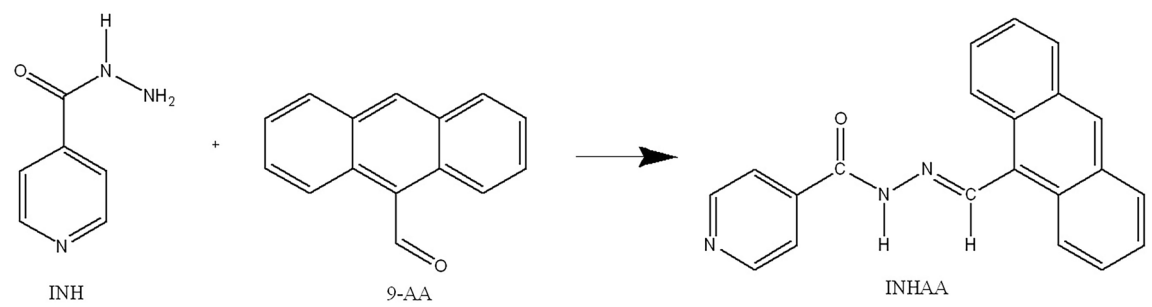


Fig. 1 Formation reaction of INHAA

hydroxylic protons at room temperature with δ / ppm, usually, below 300 Hz. The results obtained are consistent with the structure of the compound [30].

INH does not show fluorescent properties (Fig. 2A) 9-AA, which has fluorescent properties (Fig. 2B), was used to gain fluorescent properties of INH (retention time:11.7 min). When INH is converted to the yellow coloured INHAA compound, its absorbance shifts to the visible region and it gains fluorescent properties. The retention time of the formed INHAA was 7.4 min. (Fig. 3). Examination of the chromatograms showed that there were no interferences at the retention time indicated (Figs. 2 and 3).

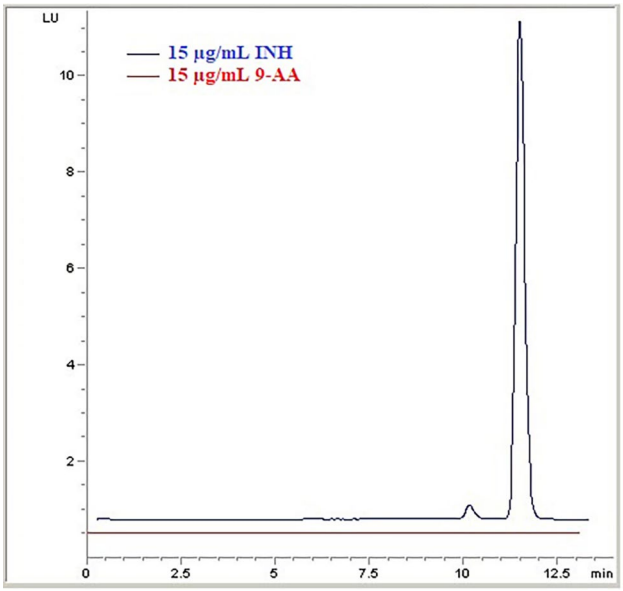


Fig. 2 HPLC-FL chromatograms of 15 µg/mL INH (A) and 15 µg/mL 9-AA (B). The chromatographic conditions were: methanol-Milli-Q grade water (40:60 v/v) mobile phase, 1 mL/min flow rate, λex:390 nm and λem:489 nm

The central composite design was used for to determine the optimum reaction conditions which are effective 9-AA concentration (A) and temperature (B). According to the factors required for the specified chemometric design and the specified intervals, 13 experiments were performed and chromatograms were taken for each experiment. Low and high values of the variables were selected based on stoichiometry and initial experiments, ranging from 0.5 to 2 mL for (0.05 M) 9-AA (A) and from 30 to 70 °C for temperature (B). In the study, all experiments were performed in random order. In this way, the effects of uncontrolled variables that could bias the measurements were minimized. The central points were repeated 6 times to determine the experimental error. The aim of the design of these experiments was to obtain the highest peak area in the chromatogram for INHAA in the shortest possible run time. By using the peak area values, the following equation was obtained:

$$Y = 12.34 + 4.57 \times A + 3.29 \times B + 1.80 \times AB - 1.34 \times A^2 - 2.66 \times B^2$$

where Y is the peak area, A and B represent the factors 9-AA concentration (A) and temperature respectively. This equation was solved by the iteration method using design-expert 8 software in numerical analysis and the three-dimensional plot of the surface response curve is shown in Fig. 4A.

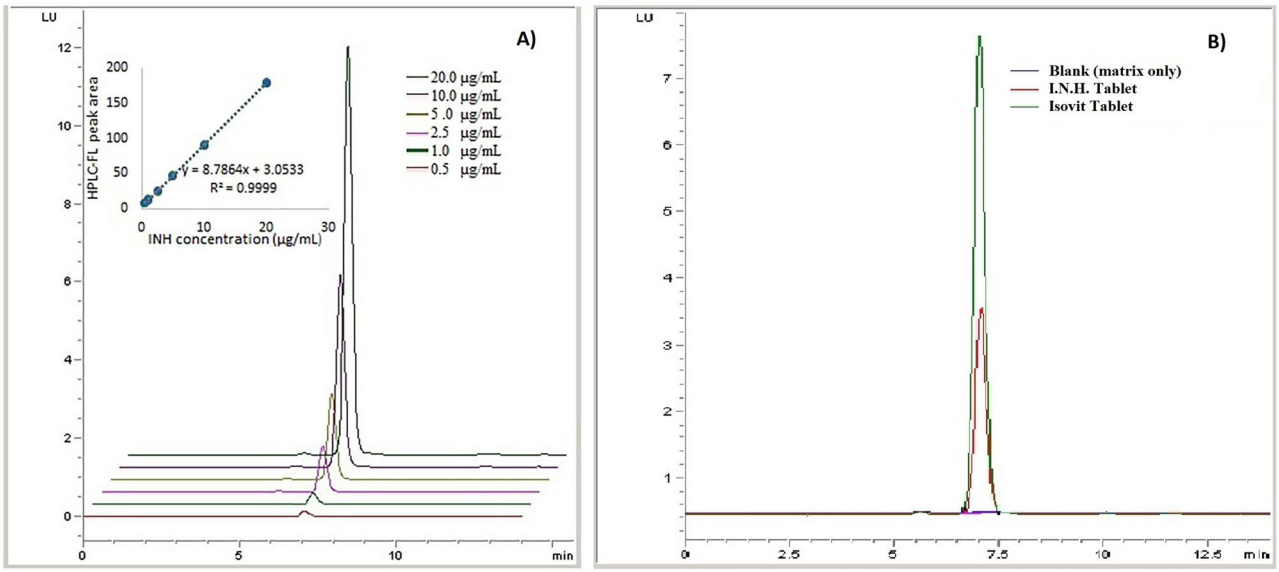


Fig. 3 **A** HPLC-FL chromatograms of **A** INHAA (0.5–20 µg/mL INH) **B** blank (matrix only) and real samples. The chromatographic conditions were: methanol-Milli-Q grade water (40:60 v/v) mobile phase, 1 mL/min flow rate, λex:390 nm and λem:489 nm

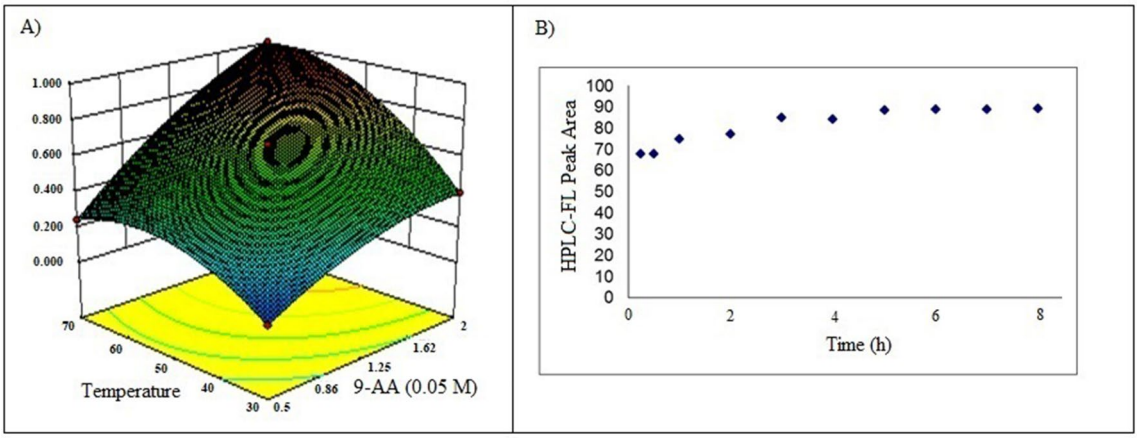


Fig. 4 **A** Three-dimensional plot of the response surface for peak area (Y). **A** Variation of the response Y as a function of A and B. **B** Graph of change of HPLC-FL peak areas of INHAA containing 10 µg/mL INH with time

The adjusted R2 was found to be 0.8343, which is within the acceptable limits of $R2 \geq 0.80$, according to the statistical parameters obtained from the ANOVA for the reduced models [31]. The P-value for the reduced models was found to be 0.0077. This model is significant with a P-value of < 0.05.

Optimal values for each factor were determined to be 1.97 mL (0.05 M) 9-AA and 68 °C. In addition, reaction time was determined under optimized HPLC-FD method conditions in order to determine the formation, equilibration and stability of INHAA with the condensation reaction of INH and 9-AA. The peak area–time curves for the INHAA were plotted under the reaction conditions containing 1.97 mL (0.05 M) 9-AA and 68 °C (Fig. 4A). The change in HPLC-FL peak areas with time is shown in Fig. 4B, and it was observed that 3 h was required. This time was taken into account throughout the study.

3.2 Method Validation

The proposed method was validated according to the ICH Q2B Validation of Analytical Procedures Method [32].

The selectivity of the method was evaluated by analyzing the 9 AA, INH (Fig. 2), blank (matrix only) and real samples (Fig. 3). INH showed no response to the fluorescence detector, whereas 9AA showed fluorescence at a different retention time. No interfering peaks from endogenous compounds were observed in the chromatogram of INHAA, demonstrating the specificity of the developed method.

The linearity of the HPLC-FL method was determined in order to obtain sample results with a precise mathematical relationship to the INH concentration. The linearity of the method according to the response for INHAA was determined in the concentration range 0.5–20 µg/mL of INH (Fig. 3A). The calibration curves ($n = 6$) were plotted the INH concentration versus peak area of INHAA. The mean linear regression equation was calculated based as $PA = 8.7864C\text{-}3.0533$. C is the INH concentration (µg/mL), and PA is the obtained HPLC-FL peak area at 489 nm emission wavelength corresponding to the excitation wavelength at 390 nm. In addition, the standard deviation of the intercept, the standard deviation of the slope and mean correlation coefficient of the linear regression equations were found to be 0.292, 0.0638 and 0.9999, respectively. The rather high correlation coefficient values obtained indicate that the method is linear within the proposed range.

Furthermore, the F-test shows that the calibration curve obtained is linear with a calculated F value of 0.69 (Ft: 3.7). The accuracy and precision of the HPLC-FL method were determined by analyzing the QC samples of INHAA containing 1, 5 and 15 µg/mL INH with intra-day (6 times per day) and inter-day (two times daily for 3 days) measurement. The intra- and inter-day precisions of the HPLC-FL method were given the RSD % and found as less than 1.96% and 2.47%, respectively. The intra- and inter-day accuracies of the HPLC-FL method were expressed as RE % and found to be less than $\pm 2.40\%$ and $\pm 3.40\%$ respectively (Table 1).

The sensitivity of the an HPLC-FL method was given as LOD and LOQ values. LOD and LOQ were determined to be 3.3 σ/S and 10 σ/S, respectively (σ: SD of the intercept of the regression line, S: the slope of the regression line). The LOD and LOQ were 0.11 µg/mL and 0.33 µg/mL INH, respectively.

3.3 Application and Comparison of the Proposed Methods

In order to demonstrate the feasibility of the developed and validated chromatographic method, the drug content of commercial Isovit® (100 mg) and I.N.H.® (300 mg) tablets containing INH was analyzed. Drug solutions were prepared as

Table 1 Intra-day and inter-day precision and accuracy of HPLC-FL method

Added (µg/mL)	Intra-day			Inter-day		
	Found ± SD (µg/mL)	Accuracy RE %	Precision RSD %	Found ± SD (µg/mL)	Accuracy RE %	Precision RSD %
1.0	1.02 ± 0.02	2.01	1.96	0.98 ± 0.02	− 2.00	2.04
5.0	4.88 ± 0.09	− 2.40	1.84	4.83 ± 0.08	− 3.40	1.67
15.0	15.13 ± 0.27	0.86	1.80	14.96 ± 0.37	− 0.27	2.47

SD standard deviation (n = 6), *RSD* relative standard derivation (n = 6), *RE* relative error

Table 2 Determination of INH in commercial tablets obtained by using the HPLC-FL

Commercial Preparation	N	Mean (mg) ± SD	Recovery %	RSD %
Isovit (100 mg)	6	100.18 ± 2.14	100.2	2.14
I.N.H (300 mg)	6	295.6 ± 8.54	98.53	2.89

SD standard deviation (n = 6), *RSD* relative standard derivation (n = 6)

described in the 'Tablet Procedure' section. The obtained solutions were injected into the HPLC system with 20 µL, chromatograms were recorded (Fig. 3B), and quantification was performed by placing the peak area on the calibration curve. The percentage recovery of the result obtained was greater than 98.53% (Table 2). Good agreement was defined between the assay results and the label claim of the product. In addition, the RSD % values for all tablets were ≤ 2.89, indicating the precision of the analytical method.

4 Conclusion

In the study described, a new HPLC-FD method based on the condensation reaction of INH with 9-AA, which produces the yellow fluorescent INHAA product of INH, was developed and validated. The central composite design method was used to optimise the conditions of the formation reaction. Two factors (9-AA concentration and temperature) that play important roles in the formation reaction were simultaneously optimised by applying a response surface methodology based on central composite design, which can save time and effort by estimating the optimum conditions. Furthermore, the reaction time was determined with the kinetic study and then the method validation study supported the selection of the method conditions by confirming that the method was sensitive, specific, precise and accurate. Although several validated methods exist, we believe our novel method, based on the formation of a coloured fluorescent product of INH, provides an alternative to existing methods by using a common stationary phase, such as a C18 column, and cheap and easily obtainable reagents for the preparation of the mobile phase, and involves a simple process which can be implemented in most laboratories. The proposed HPLC-FL method also has the advantages of being specific, making it suitable for use by quality control laboratories for the analysis of INH.

Author Contributions FDM designed the study. FDM and BB performed experimental studies. FDM, BB and analyzed the data and interpreted the results. FDM and BB wrote the paper. All authors read and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of Interest No potential conflict of interest was reported by the authors.

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Authors and Affiliations

Fatma Demirkaya Miloglu[1] · Burak Bayrak[1] · Yucel Kadioglu[1]

Burak Bayrak
burak.bayrak@atauni.edu.tr

Yucel Kadioglu
yucel@atauni.edu.tr; yucelkadi@yahoo.com

[1] Department of Analytical Chemistry, Faculty of Pharmacy, Ataturk University, 25240 Erzurum, Turkey