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Article

DRUG FORMULATIONS

Eco-Friendly Chromatographic Methods for Determination of Acemetacin and Indomethacin; Greenness Profile Assessment

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Abstract

Background: The green chemistry approach was developed for the purpose of saving the environment by using green solvents. Applying green analytical chemistry principles to traditional methods is considered a challenge. Acemetacin is a commonly used analgesic prodrug that bioactivates to indomethacin.
Objective: Developing two simple, eco-friendly chromatographic methods for simultaneous determination of acemetacin and indomethacin.
Method: The first method is HPLC-DAD. Separation was performed on a Waters XBridge® Shield RP18 (250 × 4.6 mm, 5 μm) analytical column with ethanol–ammonium acetate buffer (50 mM, pH 3.5 ± 0.1; 60:40, v/v) as a mobile phase at a flow rate of 1 mL/min at 25 ± 0.5°C and UV detection at 254 nm. The other method is TLC coupled with densitometric quantification using pre-coated silica TLC plates and butanol–ethyl acetate (70:30, v/v) elution system. The plates were scanned at 254 nm.
Results: Both methods were validated according to International Conference on Harmonization guidelines. Linearity was confirmed for both over a concentration range of 1–100 μg/mL for the HPLC method and 0.2–7 μg/band for TLC-densitometric method. The methods' greenness was evaluated by the National Environmental Methods Index, Eco-Scale, Green Analytical Procedure Index metrics and Analytical GREEnness Metric Approach.
Conclusions: The proposed methods were found to be suitable for determination of studied drugs in their marketed formulations and is suggested for routine analysis in quality control laboratories.
Highlights: The developed HPLC method shortened the elution time of the analyzed drugs saving more time and money and the TLC method lowered the drugs' detection limit. HPLC and TLC methods were validated for the assay of acemetacin and indomethacin. The methods' greenness was evaluated and compared to published methods. The developed HPLC method shortened the elution time of the analyzed drugs, saving time and money and the TLC method lowered the drugs' detection limit.

The glycolic acid ester, acemetacin (ACE), is chemically known as ([[[1–(4-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetyl]oxy]acetic acid]) (1) (Figure 1). It is an orally absorbed analgesic prodrug, 50–90% of the absorbed molecules are bioactivated by the liver to the active metabolite indomethacin (IND; Figure 1) (1, 2). Both ACE and IND share their action mechanism as non-steroidal anti-inflammatory drugs (NSAIDs) by inhibition of cyclooxygenase (COX) enzymes. They are used

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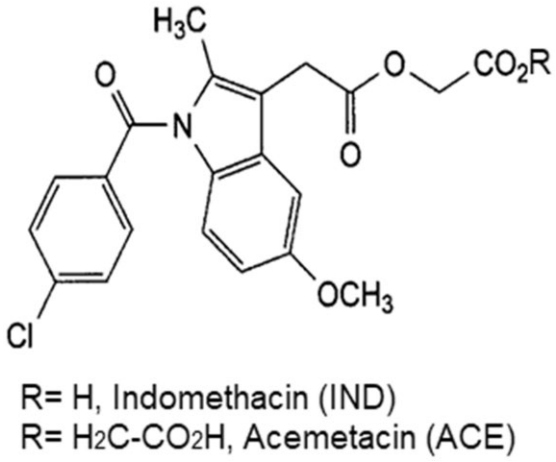

Figure 1. Structures of ACE and IND.

in treatment of rheumatoid arthritis, osteoarthritis, back pain, and post-operative pain. They exhibit the common side effects of NSAIDs: GIT (gastrointestinal tract) irritation and ulceration, but ACE is more tolerable compared with IND owing to esterification by glycolic acid which decrease the local effect on GIT (3–5). The stability indicating methods applied for ACE confirmed that IND is also its major degradation product (6–8).

ACE is a pharmacopeial drug. The British Pharmacopeia (1) reports IND as one of the main impurities of ACE. Several methods have been developed for determination of ACE in the presence of its active metabolite, IND, either in vitro or in body fluids; namely, HPLC (7, 9–16), TLC (8, 17), UPLC (6, 18), spectroscopic (7, 8, 19), and electrochemical (19–21) methods.

Chromatographic methods are mostly used for qualitative and quantitative analysis, especially HPLC, with high accuracy and precision. Unfortunately, those methods utilize various organic chemicals and produce too much waste which may induce hazardous effects on the environment. Recently, chemists concerned about the environment and human health (Environmental Protection Agency Staff) developed the term "green chemistry" to design safer analytical methods using less hazardous, toxic, or bio-accumulative solvents and decreasing the amount of produced waste (e.g., decrease analysis time or perform waste treatment) (22). Many metrics were raised to assess methods' greenness and their possible effect on health and the environment, such as the National Environmental Methods Index (NEMI) (23), analytical Eco-Scale (24), the Green Analytical Procedure Index (GAPI) (25), and most recently the Analytical GREEnness Metric Approach (AGREE) (26).

The aim of this work is to develop green and simple separation methods for the assay of ACE and IND in the presence of each other and in their pharmaceutical preparations.

Experimental

Materials and Methods

(a) *Chemicals and reagents*.—ACE was kindly obtained from Multi-Apex Pharmaceutical Co. (Cairo, Egypt) and IND was obtained from Kahira Pharmaceuticals Co. (Cairo, Egypt). Ost-map® capsules (batch No. MT9291019) manufactured by Multi-Apex Pharmaceutical Co. (Cairo, Egypt) and Indomethacin® capsules (batch No. 201684) manufactured by Pharco Pharmaceuticals Co. (Alexandria, Egypt), were purchased from the Egyptian local market. Each capsule claimed to contain 60 mg ACE and 50 mg IND. All solvents were of HPLC grade. Ethanol, methanol, butanol, ethyl acetate, and glacial acetic acid were purchased from Sigma Aldrich (St. Louis, MO, USA). Ammonium acetate was obtained from Alfa Aesar (Massachusetts, USA). Ultra-pure HPLC grade water purified by New Human Power 1 device, Human Corp. (Seoul, Korea).

(b) *Instruments and chromatographic conditions*.

(1) *HPLC method*.—An Agilent 1260 infinity series liquid chromatograph equipped with a quaternary pneumatic pumping system (model No. G1311C) and a Rheodyne injector (model No. 1328C) with 20-μL injector loop and photodiode array detector (model No. G1315D; Agilent, Waldbronn, Germany). Chromatographic separation was done on a Waters XBridge® Shield RP18 (250 × 4.6 mm, 5 μm) analytical column (Wexford, Ireland) utilizing a mobile phase composed of ethanol and ammonium acetate buffer (50 mM, pH 3.5 ± 0.1) in the ratio 60:40 (v/v), pumped at a flow rate of 1 mL/min at ambient temperature (25 ± 0.5°C) with PDA (Photo-diode array) -detection at 254 nm. The buffer was filtered through a 0.22 μm membrane filter (Sartorious Stedium Biotec, GmbH, Goettingen, Germany) and degassed ultrasonic vibration (Sonix TVss-series ultrasonicator, Sonix, Springfield, VA, USA) for 5 min. Jenway digital ion analyzer model 3330 with Jenway pH glass electrode (Essex, UK) were used for pH adjustments .

(2) *TLC method*.—TLC aluminum plates (20 × 20 cm, 0.25 mm) pre-coated with silica gel 60 F_{254} (E. Merck, Darmstadt, Germany) were used for the studied drug separation. The mobile phase composed of butanol–ethyl acetate in the ratio 70:30 (v/v). It was left to saturate in the tank for 15 min before development. Samples bands of lengths ~6 mm were applied, separated 4 mm apart from each other, placed 1 cm from the plate bottom edge, using Camag Linomat 5 autosampler (Muttenz, Switzerland) coupled with Camag microsyringe (100-μL) and Camag software were used for performing this procedure.

Samples were developed at ~25°C in a glass TLC tank in ascending mode. The air-dried plates were scanned using a Camag scanner model 3S/N 130319 programmed with winCATS software at 254 nm with slit dimensions (3 × 0.5 mm) at a scan speed of 20 mm/second.

Solutions Preparation

(a) *Standard stock solutions of ACE and IND (each 1 mg/mL)*.—A mass of 50 mg of each pure drug was transferred, separately, into 50 mL measuring flasks and the volume was completed with ethanol in the HPLC method and methanol in the TLC method. The solutions were kept away from light and refrigerated at 8°C when not in use, keeping them stable for 5 days.

(b) *Dosage form stock solutions (1 mg/mL)*.—Ten capsules of Ost-map were emptied, mixed well, and weighed. A mass of 395.8 mg, equivalent to 250 mg ACE, was transferred to 250 mL measuring flasks, then dissolved, and the volume was completed to the mark with ethanol and methanol for HPLC and TLC methods, respectively. Ten IND soft gelatin

capsules were cut, and their contents were transferred into 250 mL beakers filled with 200 mL ethanol for the HPLC method and methanol for the TLC method. The solutions were then sonicated for 15 min to assure complete dissolving. A volume equivalent to 250 mg IND (100 mL) was transferred to a 250 mL measuring flask and the volume completed with solvent.

(c) *Laboratory prepared mixtures*.—Different calculated aliquots of ACE and IND solutions were transferred to 10 mL measuring flasks and volumes were completed to the mark with mobile phase for the HPLC method and methanol for the TLC method.

(d) *Construction of calibration curves and assessment of validation parameters*.—For the HPLC method, working and calibration solutions were prepared by transferring different volumes of stock solutions to 10 mL volumetric flasks and volumes were completed to the mark with the mobile phase, giving samples in the concentration range of 1–100 μg/mL. From each sample, a volume of 20 μL was injected and chromatographed in triplicate. The calibration curve was constructed by plotting the average peak area obtained against the corresponding concentration then the regression equation was computed.

For the TLC method, from the stock solutions, aliquots equivalent to 0.2–7 mg were transferred into 10 mL volumetric flasks and volumes were completed to the mark with methanol. From each solution, 10 μL were applied in triplicate on TLC silica plates and chromatographed as mentioned giving a spot concentration range of 0.2–7 μg/spot. The average peak area obtained was plotted against the corresponding concentration to obtain the calibration curve and the regression equation was computed.

For accuracy, precision, and robustness determinations, solutions were prepared and tested according to the International Conference on Harmonization (ICH) guidelines (27).

Results and Discussion

Method Development and Optimization

HPLC method.—This study aimed to design a green HPLC method for simultaneous determination of ACE and IND with optimum resolution and acceptable peak shape. Different columns and mobile phase compositions with various buffer pH values were tried. The most suitable conditions were obtained by using an XBridge Shield RP18 (250 × 4.6 mm, 5μm) column with a mobile phase composed of ethanol–ammonium acetate buffer (50 mM, pH 3.5 ± 0.1) in the ratio of 60:40 (v/v) at a flow rate of 1 mL/min at 25 ± 0.5°C. Increasing the buffer pH to 4 or increasing the buffer ratio broadened the separated peaks. At pH values of more than 5, peak interference and poor separation were observed. Despite the fact that ethanol developed a higher back pressure than more commonly used solvents methanol and acetonitrile (28), it was preferred for its acceptable eco-friendly characteristics. To achieve maximum sensitivity with minimum noise, scanning of the chromatogram at different wavelengths was carried out to select the optimum detection wavelength. Although 210 and 230 nm have higher absorptivity based on the studied molecules' absorption spectra, they showed high baseline noise which may affect the method reproducibility. So, a wavelength of 254 nm was selected to detect both drugs which gave optimum sensitivity and least baseline noise. The ACE peak was separated at 4.52 ± 0.2 min and the IND peak at 5.61 ± 0.2 min (Figure 2). The proposed HPLC method decreased the elution time of the studied drugs compared to the previously reported HPLC methods. The method system suitability parameters were calculated. The obtained values showed compliance with resolution, selectivity, and peak symmetry as presented in Table 1, in accordance with the USP (29).

TLC method.—TLC offers a great analytical tool for simple drugs' assays, either qualitatively by analyte separation and their

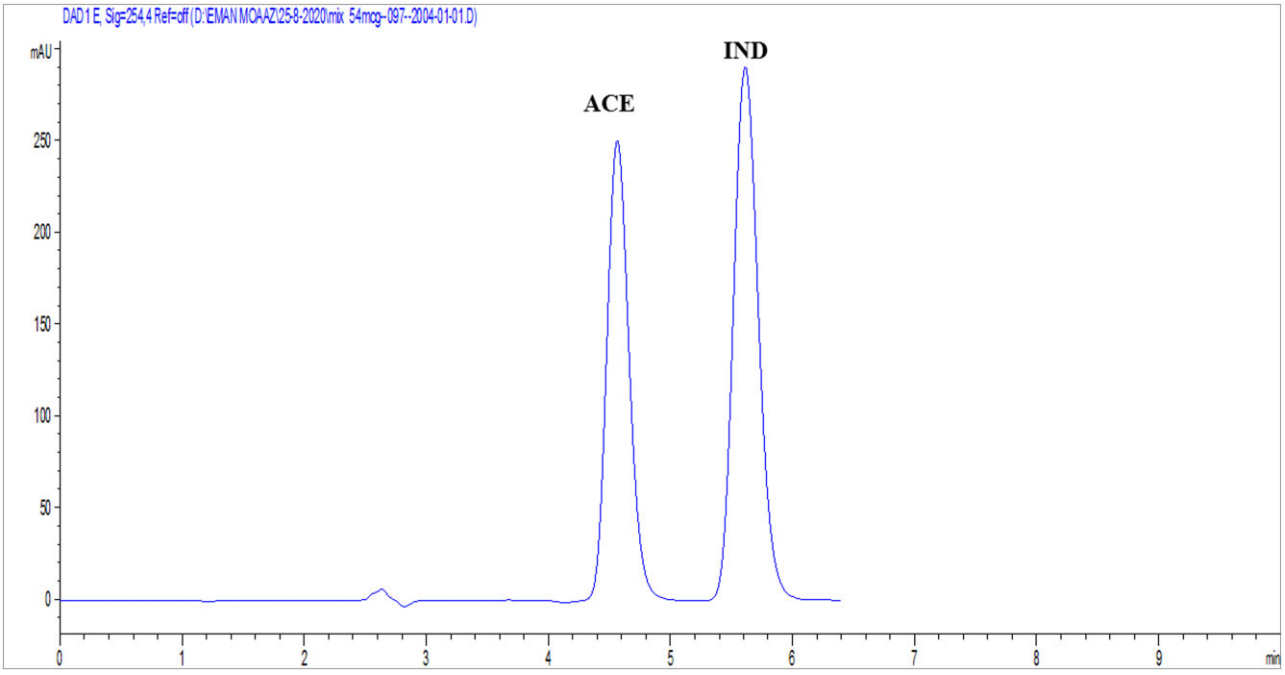

Figure 2. HPLC chromatogram of ACE (60 μg/mL, t_R 4.56) and IND (60 μg/mL, t_R 5.61) using the proposed conditions.

Table 1. System suitability parameters of the proposed HPLC and TLC methods

HPLC method				TLC method		
	Obtained value				Obtained value	
Parameter	ACE	IND	Reference value	Parameter	ACE	IND
Capacity factor (k')[a]	11	13.692		Retardation factor (R_f)	0.33 ± 0.03	0.84 ± 0.05
Selectivity (α)[b]	1.245		<1	Capacity factor (K')	60	159
Resolution (R_s)[b]	1.75		R_s <1.5	Selectivity (α)[c]	2.65	
Tailing factor (T)[a]	1	1	≈1	Resolution (R_s)[c]	4.95	
Number of theoretical plates (N)	1202	1206	Increase with efficiency of separation	Tailing factor (T)	1	1
Height equivalent to theoretical plates (HETP)	0.0208	0.0207	The smaller the value, the higher the column efficiency			
Retention time (min ± 0.2) t_R	4.518	5.611				

[a] Calculated for each individual peak.
[b] Calculated for each of two successive peaks.
[c] Calculated for each of two successive peaks.

characteristic retardation factors or quantitatively by densitometric measurements of band intensity. Various elution systems with different mixtures and ratios of methanol, butanol, ethyl acetate, ammonia, and acetic acid were tried. The most suitable results were obtained by butanol–ethyl acetate (70:30, v/v) as developing system at ~25°C and scanning was performed at 254 nm. The ACE band separated at an R_f value of 0.33 ± 0.03 and the IND band at 0.81 ± 0.05 (Figure 3a). The bands were separated with optimum resolution, symmetry, and other system suitability parameters (Table 1).

Method Validation

The proposed methods were validated for linearity, accuracy, precision, robustness, and specificity according to the ICH guidelines (27) and are summarized in Table 2.

Linearity and range.—The linearity ranges of both drugs in the HPLC method were figured to be 1–100 μg/mL by plotting the peak area of separated drugs against their corresponding concentration using linear regression equations:

$$y = 51.618x + 61.366$$

for ACE, and

$$y = 60.586x + 95.601$$

for IND. The LOQ were 1 and 0.8 μg/mL for ACE and IND, respectively, while the LOD were 0.8 and 0.5 μg/mL, respectively, as calculated by S/N.

While the obtained linearity ranges in the TLC method for the studied drugs were 0.2–7 μg/band (Figure 3b), by applying polynomial equations:

$$y = -3.8571x^2 + 65.557x + 18.988$$

for ACE, and

$$y = -2.6124x^2 + 66.931x - 8.4757$$

for IND, where "y" = the peak area and "x" = the concentration of drugs in μg/mL for the HPLC method and in μg/band for the TLC method.

The LOQs were 0.15 and 0.2 μg/mL, while the LODs were 0.1 and 0.15 μg/mL for ACE and IND, respectively, as calculated by S/N.

Accuracy and precision.—The accuracy of each method was tested by assaying three different concentrations within the linearity range three times and calculating their mean recovery percentages for each drug. Precision of the proposed methods was evaluated by the mentioned steps on the same day for intraday assessment and on three subsequent days for interday assessment.

Robustness.—For the robustness study, minor variations of the proposed method conditions were carried out to evaluate their accuracy and reliability with undeliberate changes in normal usage. For the HPLC method the following changes were tested: flow rate was decreased to 0.9 mL/min, mobile phase ratio (ethanol–ammonium acetate buffer 50mM pH 3.5) was altered to 63:37 (v/v) and the buffer pH increased to 3.7. The performed variations for the TLC method were: decreasing the developing temperature to ~18°C and modifying the eluting system (butanol–ethyl acetate) to 75:25 (v/v) and 65:35 (v/v).

ACE and IND peaks were well separated with accepted parameters, recovery percentages and standard deviations in all performed methods' variations.

Specificity.—Method specificity was tested by assaying both drugs in the presence of each other and in their dosage forms with the co-formulated excipients. Different concentration percentages of ACE and IND were mixed and assayed by the proposed methods and the results (given in Supplemental Table S1) revealed that both drugs could be determined together without interference in wide a wide range of percentages. Both methods efficiently separated and assayed the studied drugs in their mentioned pharmaceutical preparations (Supplemental Table S2). The method validity was assessed by standard addition technique and the accurate results (shown in Supplemental

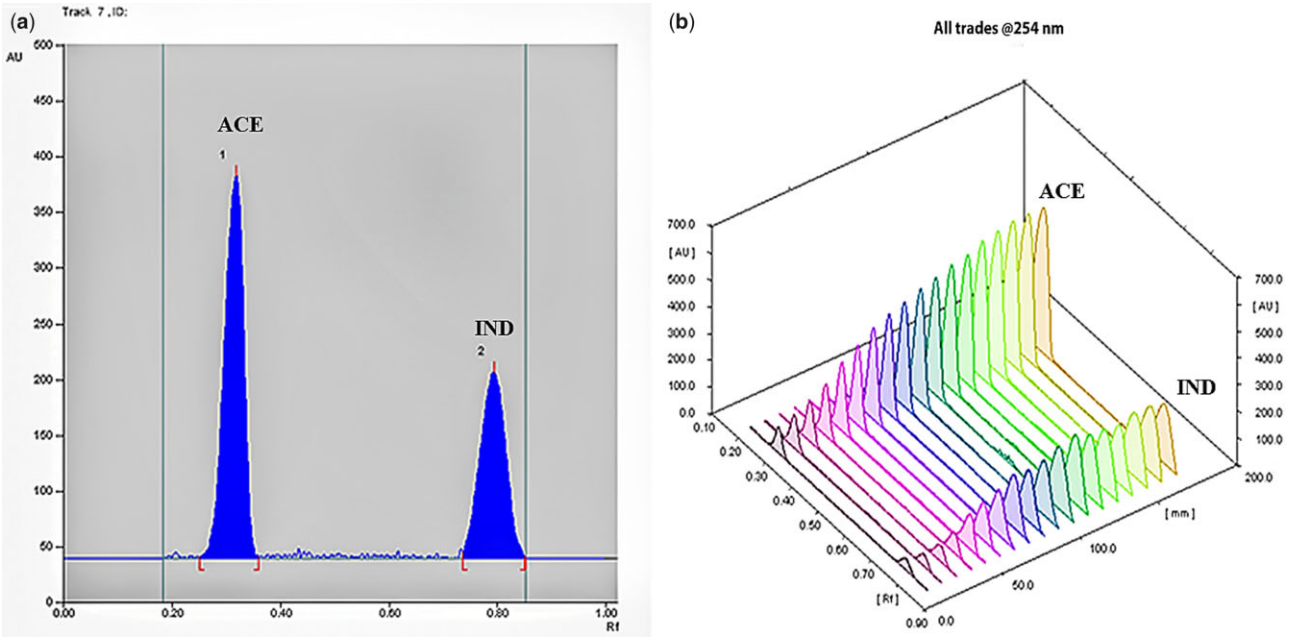

Figure 3. (a) TLC chromatogram of ACE (1.7 μg/band, R_f 0.33) and IND (1.7 μg/band, R_f 0.81) and (b) linearity range for ACE and IND (0.2–7 μg/band).

Table 2. Validation of the proposed HPLC and TLC-densitometric methods for the determination of Acemetacin and Indomethacin

	HPLC method		TLC-densitometric method	
Parameter	ACE	IND	ACE	IND
Range	1–100 μg/mL	1–100 μg/mL	0.2–7 μg/band	0.2–7 μg/band
Regression equations parameters				
Slope (b)[a]	51.618	60.586		
Coefficient 1 (b1)[b]			−3.8571	−2.6124
Coefficient 2 (b2)[b]			65.557	66.931
Intercept (a)[a,b]	61.366	95.601	18.988	−8.4757
Correlation coefficient (r)	0.9999	0.9999	0.9995	0.9999
Accuracy (mean ± SD)	100.10 ± 0.87	100.33 ± 0.54	99.83 ± 1.07	99.69 ± 0.96
Specificity [c]	100.44 ± 0.72	99.26 ± 1.12	99.89 ± 0.73	100.02 ± 0.95
Precision				
RSD, %[d]	0.95	0.91	0.63	1.01
RSD, %[e]	0.12	1.10	1.21	1.11
Robustness[f]	0.93	1.27	1.03	1.38

[a] Regression equation for HPLC: $A = a + bc$, where 'A' is the area and 'c' is the concentration of ACE and IND.
[b] Coefficients 1 and 2 are the coefficients of X^2 and X, respectively. Following a polynomial regression: $A = b1c^2 + b2c + a$, where 'A' is the peak area, 'c' is the concentration of ACE and IND (μg/band), 'b1' and 'b2' are coefficients 1 and 2, respectively, and 'a' is the intercept.
[c] Recovery of ACE and IND in laboratory prepared mixtures.
[d] Intraday precision [average of three different concentrations of three replicate each ($n = 9$) within the same day].
[e] Interday precision [average of three different concentrations of three replicate each ($n = 9$) repeated on three successive days].
[f] Robustness; RSD, % (average of three different concentrations of three replicate each ($n = 9$) analyzed in different conditions mentioned before).

Table S2) revealed that no interference from the excipients added to the tested dosage forms.

Supplementary Table S3 shows the statistical comparison of the pure compound analysis results by the proposed methods against their official ones, which was done by calculating the student's *t*-test and *F*-value with 95% confidence level. The results revealed that there was no significant difference between the proposed and official methods in their accuracy and precision.

Green Profile Assessment Metrics

Three monitoring metrics were used to assess the greenness of the proposed methods, namely, NEMI, Eco-scale, and GAPI. NEMI is one of the first metric tools developed to assess method greenness, and does so according to four terms: *(1)* PBT (solvent persistence, bio-accumulation and toxicity), *(2)* hazardous effect (the presence of used chemicals in D, F, P, or U lists for being corrosive, ignitable, reactive, toxic, or acutely hazardous, *(3)* corrosive effects (pH not less than 2 or more than 12), and *(4)* produced waste amount (less than 50 g per sample). For the proposed HPLC method, utilizing ethanol and ammonium phosphate buffer (pH 3.5) with waste less than 50 g per sample,

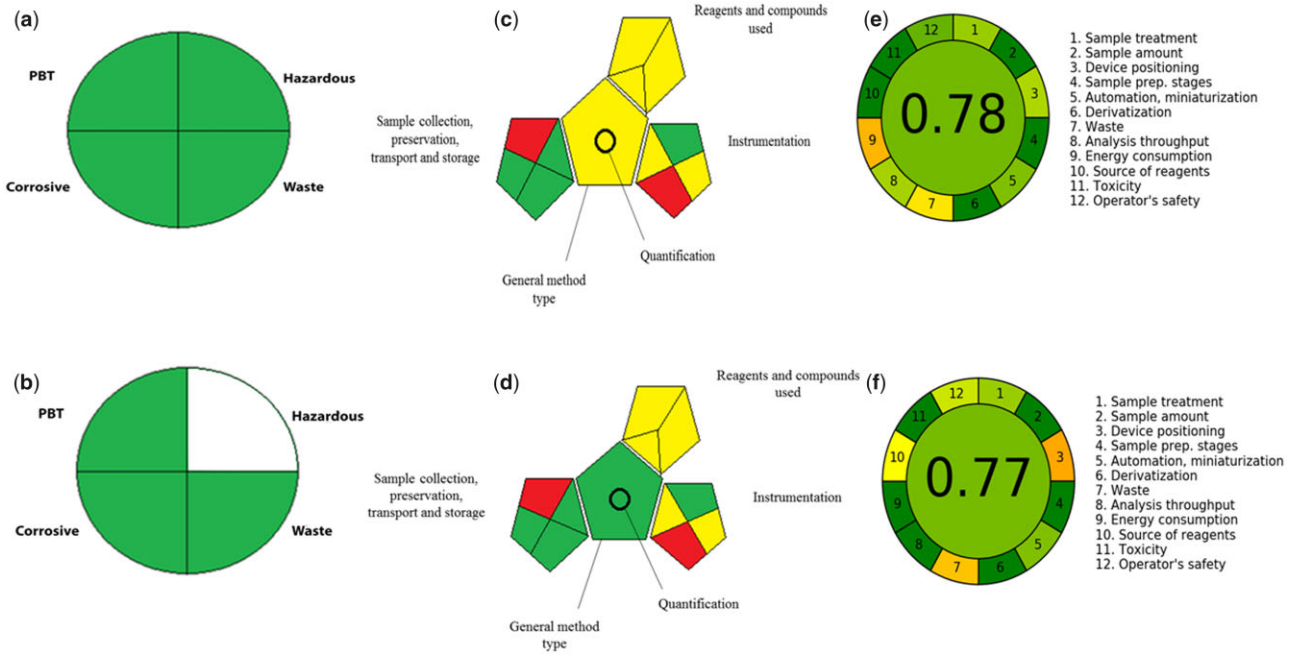

Figure 4. NEMI green profile assessment of (a) the proposed HPLC method and (b) the proposed TLC method, the GAPI green profile assessment of (c) the proposed HPLC method and (d) the proposed TLC method, and the AGREE green profile assessment of (e) the proposed HPLC method and (f) the proposed TLC method.

Table 3. Penalty points of the proposed HPLC method

	Penalty points
Reagents	
Ethanol	6
Ammonium acetate	1
Ultrapure Water	0
	Σ7
Instrument	
Energy (< 1.5 kWh per sample)	1
Occupational hazard	0
Waste (1–10 ml)	3
	Σ4
Total penalty points	11
Analytical Eco-scale score	89
t_R of analytes	ACE: 4.518 IND: 5.611

Table 4. Penalty points of the proposed TLC method

	Penalty points
Reagents	
Butanol	8
Ethyl acetate	6
	Σ14
Instrument	
Energy (< 1.5 kWh per sample)	1
Occupational hazard	0
Waste (1–10 ml)	3
	Σ4
Total penalty points	18
Analytical Eco-scale score =	82

fulfills the four terms (Figure 4a), while the proposed TLC dropped out of the hazard quadrant due to the presence of butanol and ethyl acetate in U and F lists due to their ignitability, but succeeded in the rest of the terms (Figure 4b). The Eco-Scale method is a semi-quantitative tool based on calculating penalty points for used solvents and different method's parameters and subtracting from a base of 100, analytical eco-scale score more than 75 is considered as excellent green method (24). The analytical Eco score of the proposed HPLC method was found to be 89 (Table 3) which proves that the method's greenness is superior for the used solvents or the analytes retention time over the reported methods (Supplemental Table S4a–d). The calculated Eco score for the proposed TLC method is 82 (Table 4). This score proved the greenness of the method because butanol was used in the eluting system rather than hexane, as in the reported TLC methods (Supplemental Table S5). The greenness assessment tool, GAPI, is a visual presentation method consisting of five pentagrams, used to evaluate the environmental effects of main steps of the method (sample collection, preservation, transport and storage, general method type, sample preparation, reagent and compounds used, and instrumentation) using red, yellow, and green colors which stand for high, medium, and low hazardous effects, respectively. For the developed methods there is no sample preparation step, so the relevant pentagram is removed. The GAPI pentagrams of the proposed methods (Figure 4c and d) vary between medium and low hazardous effects, except for sample storage (sample is refrigerated at 8°C when not in use) and the inability to carry out a waste treatment step, although the methods produce a low amount of waste (HPLC run time 6.5 min and TLC 10 ml per sample). The most recent greenness assessment tool, AGREE, is a calculator assessment approach where the assessment criteria considers the 12 principles of green analytical chemistry and translates these to a score from 0 to 1 with a clock-like colored pictogram indicating the greenness of each principle and a middle circle showing the method AGREE score. When the score

is closer to 1 the circle becomes greener. The pictograms of the proposed methods scored 0.78 and 0.77 for the HPLC and TLC methods, respectively (Figure 4e and f), indicating that the methods are green. The proposed methods showed better green profiles compared to the related reported methods, based on the results from the four greenness assessment tools (Supplemental Tables S4 and S5).

Conclusions

The proposed HPLC/DAD and TLC-densitometric methods separated and quantified ACE and IND simultaneously in pure form and in their tested pharmaceutical formulations. They were validated according to the ICH guidelines and statistically compared to the official methods, where the results proved that there was no significant difference between the compared methods. The greenness of both methods was evaluated by three assessment metrics, namely NEMI, Eco-Scale, GAPI, and AGREE. All confirmed the methods' greenness. The eco-friendly proposed methods can be used for routine analysis and drug monitoring in quality control labs. The HPLC method's mobile phase enables further studies with mass spectroscopic detection.

Supplemental Information

Supplemental Information is available on the *J. AOAC Int.* website.

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Conflict of Interest

The authors have declared no conflict of interest.

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