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A Coherent Analytical Review of Indapamide

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ABSTRACT

Background: Indapamide is a diuretic of particular importance in an antihypertensive therapeutic regime that is profoundly applied to treat hypertension. Besides using as an individual drug for its diuretic and thereby antihypertensive effect, the drug is also a part of crucial combinations with Angiotensin-Converting Enzyme inhibitors. The recent combinations of Indapamide with Perindopril and Delapril work as the best therapies for heart patients.

Purpose: Considering the therapeutic and pharmaceutical importance of the drug molecule and its potential to be explored in future drug discovery and delivery, we made efforts to portray the pharmaceutical analytical profile of the drug molecule at ease.

Method: The present article is a composition entailing the comparative and critical evaluation of the various analytical approaches explored for the pharmaceutical estimation ofIndapamide as a particular drug in combinations and pharmaceutical as well as biological matrices. The analyses are reviewed for the specificapplications of analytical methods tested Indapamide alone or with other medications.

Result: The anticipated study revealed the comparative usage of different research techniques for Indapamide estimation. The study influences the possibility of constraints and focuses on the recent trend in Indapamide analysis. The article also provides an understanding of sample processing, drug extraction method, validation protocols/approaches, and stability studies, including but not limited to the bioanalytical perspectives.

Conclusion: This review can be explored thoroughly for the future analytical and pharmaceutical insights of Indapamide to the fullest.

1. Introduction

Indapamide (IND) is a diuretic resembling thiazide, and it is 4-chloro-*N*-(2-methyl-2,3-dihydroindol-1-yl)-3-sulfamoyl-benzamide a thiazide-like drug recognized to manage hypertension, as well as decompensate heart failure [Budavari 1996, Bataillard 1999]The molecular structure of IND is presented in (Figure 1). High blood pressure is being effectively managed using IND. It also reduces excessive body fluid (edema) aboutheart failure. Decreasing high BP aids stroke prevention and the possibility of heart attacks and kidney problems. Diuretics or water pillsare the class for which IND is well known[Ernst2022].

IND alone or in a mixture with other drugs used to manage hypertension [Waeber 2003]. IND is available in combination with Perindopril, an Angiotensin Converting Enzyme (ACE) inhibitor. Diuretics like thiazide (IND and chlorthalidone) are more effective in lowering the risk of cardiac disease in individuals facing elevated blood pressure than those used with thiazide diuretics (including hydrochlorothiazide). The adverse effect levels are thiazide-like, and thiazide-type diuretics are almost identical. It was patented in 1968 and approved for therapeutic purposes in 1977 [Asmar 2001]. IND is also available in combination with Atenolol [Divitiis 1983], Amlodipine [Jadhav *et al* 2014], and Delapril [Cavalieri 2007].

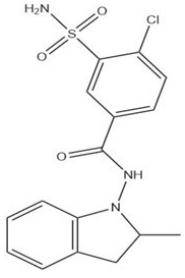

Figure 1: Chemical structure of Indapamide.

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2. Pharmacopoeial Insight

The IND is official as an Antihypertensive drug in the IP (Indian Pharmacopoeia) [IP 2018], BP (British Pharmacopoeia) [BP 2022], and USP (UnitedStates Pharmacopeia)[USP 2018].

3. Indian Pharmacopoeia (IP)

IP depicts the reportsfor HPLC (High-Performance Liquid-Chromatography) IND analysis. For the effective resolution of IND stainless steel column (15 cm 4.6 mm,packed with octadecylsilane bonded to porous silica (5 µm)was implemented. The solvent system comprises 6 volumes of a solution containing sodium dodecyl sulfate (5% *w/v*) andglacial acetic acid (3 % *v/v*), 10 volumes of triethylamine, 20 volumes of 2- butanol, 310 volumes of acetonitrile and 690 volumes of water, followed by the acquainting off the pH to 3.0 using orthophosphoric acid. The rate of flow of solvent system was kept at 1.6 ml/minute and monitored at 240 nm [IP 2018].

4. British Pharmacopeia (BP)

BP has presented on HPLC procedure for the investigation of IND. The separation of the IND has beenattained on column (0.15 m long and 4.6 mm wide,packed with octadecylsilyl silica gel for chromatography R (5 µm).The acetonitrile R (7 volumes) with tetrahydrofuran R (20 volumes) and 1.5 g/l solutions of trimethylamine R (73 volumes) were adjusted to 2.8 pH with phosphoric acid Ras the mixture was employed as a solvent system and the rate of flow of solvent system was tuned to 1.4 mL/min. The IND was identified at a wavelength of 305 nanometers. [BP 2022].

5. United States Pharmacopeia [USP]

USP stated reports HPLC procedure for the assay of IND at 242 nm. The separation of the IND along with internal standard 2'-chloroacetophenone has been executed on a stainless-steel column (4.5 mm x 10 cm) containing a 3 *µm* packing of octadecylsilane. The solvents system composed ofablend of sodium 1-octanesulphonate (1.08 gm)in 700 ml water with 10 mL of glacial acetic acid and 300 mL(acetonitrile), and the flow rate was tuned to 1.0 mL per minute [USP 2018].

5.1. The Merck index

Revealed information regarding the physical properties and solubility of IND. The reports displayed that IND is a white coloured powder drug practically insoluble in water, soluble in alcohol, and slightly soluble in ether. The drug is light sensitive and needs to protect from light[Budavari 1996].

6. Performance Review on Analytical Techniques Implemented for IND

For assessing IND both in the pharmaceutical matrix and in bio-samples, a range of separation methods includes HPLC, LC-MS/MS, HPTLC, and Spectrophotometric have been studied.

6.1. HPLCMethods

The appreciable explored analytical technique implemented for the determination of IND is HPLC. The exploratory report on the HPLC methods for studies was compiled in Table 1.

Table 1: HPLC methods for analysis of IND.

Sr. No.	Analytes	Matrix	Chromatographic condition	Mobile Phase	Retention Time and Detection Wavelength,	Flow rate Injection volume	Ref.
1.	ATN and IND	Tablet	(Hypersil Gold: 250mm x 4.6 mm, 5µm)	0.1% Triethyl Amine in water of pH 3.0 & Methanol in the ratio 30:70 v/v	3.05 and 3.93 min, 240 nm	1.0 ml/ min, 20 µl	ArindamBasu et al. 2011
2.	ATN and IND	Tablet	Hypersil BDS C18 (250 mm x 4.6 mm, 5 µm particle)	(pH = 3.5, 0.01 M potassium dihydrogen orthophosphate buffer-acetonitrile (60:40; v:v)	5min, 231nm	1.0 ml/ min, 20 µl	ThulasammaParusu& VenkateswarluPonneri 2012
		Milk					
		Human Blood					

3.	PDP and IND	Tablet	C18 (125 mm×4.0 mm i.d., with a particle size of 5 µm)	Acetonitrile, methanol and phosphate buffer of pH 3.0 (50:3:47V/V/V)	2.9 and 4.6 min, 210 nm	0.7 ml/ min, 20 µl	Anna gumieniczek et al. 2015
4.	ATN and IND	Tablet	C18 (250×4.6 mm 5 µm, I.D)	Methanol: water (adjusted to pH 2.7 with 1% ortho phosphoric acid) 80:20v/v	1.766 min & 3.407, 230 nm	1.0 ml/ min, 20 µl	G.tulja rani et al. 2011
5.	PDE and IND	Bulk	Zorbax SB C18 Rapid Resolution (150 mm X 4.5 mm) column with 3.5 µm particle size	(Phosphate buffer:ACN52:48 V/V)	1.93 & 3.17, 210 nm	1.0 ml/ min, 5 µl	Ion Valen et al. 2015
6.	IND	Racemic Mixture	(150 x 4.6 mm, 5 µm)	Na2HPO4 10 mM buffer, ACN (95:5)	5.5 & 7.09 242 nm	1.0 ml/ min, 5 µl	Ancagabrielacârje et al. 2016
7.	IND	Tablet	C18 (250 mm × 4.6 mm, 5 µm)	Na2EDTA 0.2 g/L and anhydrous acetic acid 0.1 mL/L,Acetonitrile and Methanol (65: 17.5 :17.5: 1.2) (V/V/V/V)	16.92, 254 nm	1.-1.3 ml/ min, 10 µl	Simonacodruţaheghеş et al. 2017
8.	IND	Human Blood	C18 (15 cm x 4.6 mm I.D.x 5 µm)	80 mM ammonium acetate, pH 3.5 (adjusted with concentrated hydrochloric acid acetonitrile-2-propanol (65:30:5, v/v/v)	5.2 & 241 nm	1.0 ml/ min, 40 µl	R. Brent Miller et al. 1993
9.	OSM and IND	Bulk and Tablet	C18 AR column (250 × 4.6 mm id, 5 µm particle size)	Sodium perchlorate and triethylamine buffer solution (at pH 3): Acetonitrile (60:40 v/v)	6.8 & 5.3, 280 nm	1.0 ml/ min, 10 µl	AvaniSheth et al. 2013
10.	PDA and AMD and IND	Bulk and Tablet	BDS Hypersil C18 column (100 × 3 mm, 5 µm)	0.05 M potassium dihydrogen phosphate buffer (pH 2.6)– methanol (50 and 50, v/v	3.4, 6.0, 2.0 & 215 nm	0.6 ml/ min, 100 µl	Ramzia I. El-Bagary et al. 2015
11.	CP and IND	Bulk and Tablet	250 X4.6mm terra RP8 column, 5µm	26mM pentane-1-sulfonic acid sodium salt in 30mM potassium dihydrogen phosphate (pH 2.8, adjusted by phosphoric acid):methanol: acetonitrile (6:2:2 v/v/v).	1.8, 1.3min 210 nm	2.0 ml/ min, 20 µl	Alaa El-Gindy et al 2014

12.	PERI and IND	Bulk and Tablet	RP-YMC pack ODS A-132 C18 (5 µm, 15 cm×6.0 mm i.d.) column.	phosphate buffer pH 2.4 and acetonitrile (7:3 v/v)	5.8 min 215 nm	1.0 ml/ min, 20 µl	NevinErk et al 2001
13.	ATL and IND	Bulk and Tablet	C18 column	methanol: water (60:40) with 0.1%v/v of Ammonium Hydroxide	7.5 and 8.9 min 260 nm	1.0 ml/ min, 20 µl	Naveen Kadian et al 2012
14.	ATL and IND	Bulk and Tablet	Symmetry X-terra C8 (4.6mm x 100mm, 5µm) column	Potassium di hydrogen phosphate buffer and Acetonitrile in the ratio 40:60 v/v	2.1 and 3.6 min 240 nm	1.0 ml/ min, 20 µl	K Madhavi et al (2014)
15.	LIS and IND	Bulk and Capsule	C18 column	methanol:water (50:50, v/v)	4.71±0.2 18.51±0.3, 206nm	1.0 ml/ min, 100 µl	Sofía Negro et al (2014)
16.	PERI and IND	Bulk and Tablet	C-18 column (150mm x 4.6mm, 5µm	acetonitrile: 5mM sodium phosphate buffer (pH 7.5) (50:50)	2.5 and 4.7 min 202 nm	1.0 ml/ min, 20 µl	Menna I. Ezzeldina et al (2013)
17.	AML and IND	Bulk and Tablet	C18 Column	Acetonitrile: Water contains 0.2% of Triethyl amine and adjusting the pH to 4.0 with orthophosphoric acid (70:30, v/v, pH 4.0)	3.27 and 4.7 min 238 nm	0.8 ml/ min, 20 µl	Mehul M. Patel et al (2012)
18.	AML and IND	Bulk and Tablet	Brownlee C-18	0.02 M potassium dihydrogen phosphate– methanol (30: 70, v/v)	5.9 min and 3.6 min 242 nm	1.0 ml/ min, 20 µl	Deval B. PATEL et al (2012)
19.	IND	Rat whole blood	Chromosil ODS column(250 × 4.6 mm id, 5 µm particle size)	methanol–acetonitrile–tetrahydrofuran–0.2% trifluoroacetic acid (170:20:15:38, v/v/v/v)	2.1 and 3.6 min 240 nm	0.8 ml/ min, 20 µl	XubinSuo et al (2013)
20.	PERI and IND	Bulk and Tablet	BDS hypersil C18 column (25cm×4.6mm, 5)	potassium dihydrogen phosphate buffer (pH 2.6) and acetonitrile (65:35, v/v)	210 nm	1.5 ml/ min, 10 µl	A.K. Pathak et al (2011)
21.	PERI and IND	Bulk and Tablet	Kromosil C18 column (250×4.6mm× 5µ	Phosphate buffer: ACN: methanol (40:25:35 v/v/v) pH 4.5	2.350 and 3.490 min 223 nm	1.0 ml/ min, 20 µl	S. Soujanya (2017)
22.	IND	Bulk and Tablet	LiChrospher RP- 18 column	acetonitrile-distilled water (35: 65)	8.25-8.30 min 254 nm	1.5 ml/ min, 20 µl	TUNCEL OZDEN et al (1998)

23.	PERI and IND	Bulk and Tablet	BEH C18 (1.7 µm, 2.1×50 mm)	0.01% v/v formic acid in water adjusted to pH 4 with acetic acid and acetonitrile (40:60 v/v)	4.5 min 227 nm	0.3 ml/ min, 1 µl	Naser F. Al-Tannak et al (2018)
24.	HCTZ and IND	Bulk drugand Tablet	Hypersil-Gold C18 (100 × 4.6 mm, 3 µm	58% buffer (5 mM KH2PO4, containing triethylamine 0.25 ml/L), 25% acetonitrile and 17% methanol (pH adjusted to 2.8 ± 0.1)	3.4 and 6.6 min 215 nm.	1.0 ml/ min, 10 µl	Ashok K. Shakya et al (2014)
25.	AML and IND	Bulk and Tablet	C-18 ODS bonded column (25cm × 4.60 mm, 10 µl	methanol: water (95:5 % v/v)	8.780 and 2.850 min, 238 nm	1.0 ml/ min, 10 µl	VarshaKashaw et al (2016)
26.	IND	Bulk and Tablet	RP C-18 Column (25cm x 4.6 mm i.d.,5 µm)	o-phosphoric acid (0.05%) buffer of pH 3.0 and Acetonitrile in the ratio of 60:40 (v/v)	6.76±0.0145 min 240 nm.	1.0 ml/ min, 20 µl	Sathish Kumar Shetty A. et al (2011)
27.	IND	Human Whole Blood	YMC ODS-A reverse column (5 lm particle size, 4.6·150 mm i.d.)	Acetonitrile - 2-propanol)0.1 triethylamine in water (adjusting to pH 3.75 with 85% phosphoric acid) (35:5:60, v/v/v).	12 min, 240 nm	1.2 ml/ min, 20 µl	Xinguo Jiang et al (2005)
28.	AML and IND	Bulk drugand Tablet	ODS (C18), 250 mm × 4.6 mm & 5 µm	Phosphate buffer (pH 4.0): Acetonitrile (40: 60 v/v)	3.5 min and 4.8 min, 247 nm	1.0 ml/ min, 20 µl	G.V.S. Kumar et al (2012)
29.	AML and IND	Bulk and Tablet	C18 column (Phenomenex C18, 5µ, 250 mm x 4.6 mm)	Methanol: Water in the ratio of (95:5 v/v)	8.722 and 2.855 min 238 nm	1.0 ml/ min, 20 µl	Manish C. Raj et al (2012)

IND in a mixture with other drugs is also available in the market. The detailed account of HPLC analysis for IND in combination with other medications is as follows;

Basu A. *et al.* established theHPLC analysis forthe parallel quantification of Atenolol (ATL) and IND tablet dosage and validated the method. The systematic separation of analytes was accomplished on the L1 Hypersil Gold column (250 4.6 mm and particle size 5 µm) flushed with methanol: water (70:30 % *v/v)* as a solvent system.The pH was acclimatized to 3.0 using triethylamine (0.1%). The system was run in an isocratic mode of elution. The detection was performed wavelength of 240nm. ATL and IND, Rt (retention time) were reported at 3.05 and 3.93 min, correspondingly. The approach has been tested successfully within harmony for specificity, precision, robustness, and accuracy. The studied approach was effectively explored for the tablet formulation [Basu 2011].

Valentin *et al.* illustrated HPLC and CZE to study and separate Perindopril Erbumine (PER) and IND. The resolution of selection candidates was achieved ona C18 Zorbax SB column having a particle size of 3.5 µm. The rational separation was executed using a solvent system comprisedof potassium dihydrogen phosphate buffer of pH 2.8 (5 mM) and ACN (52:48 %*v/v*). The estimation of the drug was performed at 215 nm. The electrophoretic migration was governed by ideal conditions such as borate buffer (50 mM) having a pH (9.2). The voltage applied was 25kV;whereas,the capillary temperature was monitored at 25^{0}C.The injection was performed at 30 mbar - 3 seconds. For both these methods, the total run duration was less than 5 min. The LOD and LOQ values for PER and IND were established (2 µg, 200 µg, 0.4 µg; 25 µg and 4 µg, 250 µg, 4 µg, 50 µg), respectively, for HPLC and CZE. [Valentin 2015].

An RP-HPLC protocol was studied and tested for validation for quantification of Amlodipine (AML), IND, and PER, alone and in pharmaceutical preparation by El-Bagary, R.I. *et al.* A C_{18} column of BDS Hypersil (100 3 mm, 5 µm) was exploited for effective separation**.**The analysis was executed using a solvent system comprising 0.05 M (potassium dihydrogen phosphate buffer; pH 2.6) and methanol in the proportion (50:50 % *v/v*at0.6 mL/min)and isocratic elution was reported. Further, the column temperature was monitored at 50^0C. A 100µL solution was injected as a sample and detected ata wavelength of 215 nm. The IND calibration plot was studied in the range of 0.5 - 20 µg/mL concentrations.

The study has also acknowledged that the method currently developed has been systematically correlated with standard approaches. The accuracy outcome was identified to be 99.53-102 % for PER, 98.13-101.08 % for AML, and 98.00-101.43 % for IND [El-Bagary 2017].

Madhavi K. *et al.* have explained a simple reversed-phase-HPLC method for concurrently assessing ATL and IND in the pharmaceutical matrix. The separation of the analyte was achieved on the Symmetry X-terra C8 column with specifications as 5µm (particle size) and (4.6 mm 100 mm) and a solvent system comprised of (60:40% *v/v*at 0.7 mL/min rate of flow)acetonitrile and potassium dihydrogen phosphate.The effective identification was made ata 240nm using a UV detector. The linearity study was calculated by plotting the linearity in the concentration range of 1-5 µg/mL (IND) and 20-100 µg/mL (ATL). For ATL and IND, the limit of detection and quantification was found to be 0.22, 0.67, and 0.28, 0.86 µg, correspondingly. The reported protocol was also treated to estimate analytes in a marketed pharmaceutical formulation. The determining drug content was 100.20 % for ATL and 99.11 % for IND, respectively [Madhavi 2014].

Ezzeldin, M.I. *et al.* Documented HPLC and spectrophotometric methods for the real-time estimation of PER and IND in bulk powder and the tablets matrix. The effective serration of the drug candidate has been done on an Econosphere C18 column (150 4.6 mm, particle size 5µm) comprising acetonitrile: 5mM sodium phosphate buffer (pH 7.5) in the proportion of 50:50 % *v/v* as a solvent system. The detection was done using a UV detector at a wavelength of 202 nm when the flow rate(0.5 mL/min) was adjusted.

Two methods, the ratio subtraction, and the first derivatives, were used in respect of the spectrophotometric techniques. In the method of ratio subtraction, absorbance readings were taken in methanol at two wavelengths of 277.48 nm (ALK, lambda max) and 315 nm (HTZ extended-spectrum).

The subtraction proportion technique implemented the two wavelengths, 277.48 nm and 315 nm (extended-spectrum), to get absorbance. The solvent used was methanol. The area around the wavelengths 237.2 nm (for ALK) and 275.8 nm (for HTZ) was employed. The proposed method was tested for validation as per the guidelines of ICH Q2 (R1) [Ezzeldin 2013].

The specific high-performance liquid chromatography technique for estimating IND in the pharmaceutical matrix on the Turkish market has been developed by Ozden, T. *et al.*

The investigation was performed on LiChrospher C18 column and acetonitrile and distilled water (35:65 % *v/v*) as a solvent system,and the flow rate (1.5 mL/min) was adjusted.The detection at 254 nm using aUV detector was done. The retention time was 8-9 minutes, and the total retention time was under 10 minutes [Ozden 1998].

Al-Tannak, N. F., has developed UHPL-UV methods for the simultaneous analysis of PER and IND in a tablet dosage form and validated for stability.

A BEH C18 column (50 2.1 mm, 1.7µm) was used for the estimation usinga mobile phase consisting of water (0.01 % formic acid) and acetonitrile in a ratio of 40:60 % *v/v,* and the pH was kept at 4.0 using acetic acid. In total, the run time was reported to be below 5 min. The wavelength of measurement was 227 nm. The product samples were also subject to different stresses such as acidic, basic, and thermal.

Besides, UHPLC-Quadrupole time for Flight-Mass spectrometry (UHPLC-QToF-MS) has elucidated the degradation products of the combination [Al-Tannak 2018].

Dawud, E.R., and Shakya, A.K. notified an accurate and HPLC method for the simultaneous estimation of ACE inhibitors with HCTZ and IND in pharmaceutical formulations.

The Design of Experiments, specifically central composite design, had successfully implemented for method development and optimization [Dawud 2019].

Mahant, B.D. *et al.* havevalidated UV-spectrophotometric and stability-indicating RP-HPLC procedure for quantifying AML and IND simultaneously in combined tablets in the presence of degradation products generated from stress degradation studies.

The measurement of absorbance was observed for the simultaneous equation method. The method relies upon the two wavelengths; 237nm(λ max AML) and 242nm (λ max IND). The drugs obeyed Beer's-Lambert's lawon a scale of 5-25 µg/mL and 1-11 µg/mL, respectively.The correlation coefficient obtained was 0.99 for AML and 0.99 for IND [Mahant 2016].

6.2. Spectrophotometric method

Spectrophotometric methods with UV-Visible detection have been studied for IND analysis with or without combination, as illustrated in (Table 2).

Table 2: UV-Spectrophotometric methods for determination of IND.

Sr. No.	Drug	Method	Matrix	Linearity (µg/ml)	Ref.
	IND on condensation with p-dimethylaminocinnamaldehyde (PDAC) and p-dimethylaminobenzaldehyde (PDAB)	Area Under Curve 682.0nm and 602.0nm	Bulk and Tablet	6-16µg/ml, 50-250µg/ml and 1-18µg/ml	Jyoti B. Pai et al (2011)
	ATL and IND	Simultaneous 266 nm and 270.2 nm UV	Bulk and Tablet	100-350 and 5-17.5 µg/mL	N. Fernandes et al (2008)
	AML and IND	First-Order Derivative UV Spectrophotometry 242 and 238 nm Absorption Correction Method	Bulk and Tablet	10-70 µg/ml and 2-16 µg/ml	Mehul M. Patel et al (2012)
	Aceclofenac and IND	642.6 nm 783.2 nm	Bulk and complex	80-160 µg/ml	Singhavi et al (2007)
	IND	Two derivative spectrophotometric 252.8 nm and 260.4 nm	Bulk and Tablet	1-30 µg/mL and 1-35 µg/mL	SacideAltınoz et al (2002)
	TEL and IND	Simultaneous 295 nm and 239 nm	Bulk and Capsule	2-10 µg/ml and 2-14 µg/ml	Purvesh K Patel et al (2012)
	PERI and IND	Simultaneous 210.4nm and 241.2nm	Bulk and Tablet	24 – 56 µg/mLand 7.5 – 17.5 µg/mL	Darshana K. Modi et al (2011)
	IND	Simple UV 240 nm and 223 nm	Bulk and tablet	5 –40 *µg*/ml	TarkaseKailash N et al (2012)
	TEL and IND	Simultaneous and Q-Absorption Ratio Method	Bulk and tablet	4-14µg/ml	J.M. Chavda et al (2012)

The UV-method for evaluating IND in bulk and pharmaceutical formulation was reported by **Pai, J. B. et al.** IND yields bottle-green and blue coloured complex when it condenses with p-dimethylaminobenzaldehyde (PDAB) and p-dimethylaminocinnamaldehyde (PDAC) in an acidic media. Methods A, B, and C used Area Under Curve (AUC) for the assessment of IND in the range of wavelength (238 - 248 nm [Pai 2011].

ATL and IND in their combined dose form have been simultaneously determined using a UV spectroscopic technique, which has been tested by Fernandes, N., and co-workers. In the first method, two wavelengths 246.4 nm and 266 nmare analyzed as potential candidates for establishing simultaneous equations.The use of two wavelengths to create a situation in which the absorbance variation kept zero for the other drug was the basis behind the second concept. Anequal absorbance was found at 246.4 nm and 254.2 nm for ATL. Subsequently, the absorbance variability was monitored in order to estimate the IND. ATL determination was evaluated at 266 nm and 270.2 nm as well [Fernandes 2008].

Shah, R.N., and colleagues have studied UV-Spectrophotometry for the assessment of AML and theIND in tablets. The first approach was the absorption correction which neededa direct determination of AML at 360 nm. Because at this wavelength, zero absorbance was found for IND and the drug exhibited no visible disruption. For the determination of IND, the corrected absorbance was determined wavelength of 242 nm due to the intervention of AML at this wavelength. First-order derivative spectrophotometry was the method under study in the second section. The wavelengths chosen for the measurements were 238 nm for IND and 242 nm for AML (zero-crossing point for IND) (zero-crossing point for AML) [Shah 2012].

Patel, P. K. et al. investigated the rapid and economical spectrophotometric procedure fortelmisartan (TEL) and IND in a pure and combined matrix.The simultaneous

equations method implements two wavelengths, 295 nm, and 239 nm, as absorbance maxima (λmax) for TEL and IND, respectively. The analysis was performed using methanol-distilled water mixture [Patel 2012].

Chavda, J.M. *et al.*studied the two methods, by UV-Spectrophotometric tool for analysis of TEL and IND present in combined matrix [Chavda 2012].

7. High-Performance Thin-Layer Chromatography (HPTLC)

HPTLC exploration has been briefed for IND analysis alone or in the combined dosage form,as depicted in (Table 3).

Nazareth, C., and co-authors established the procedure for the measurement of Olmesartan (OLM) and IND in their combined formulation. The method has been tested for validation parameters *viz* accuracy, precision, specificity, and robustnessunder ICH guidelines [Nazareth 2013].

Vyas, N *et al.* studied the accurate and reliable high-performance thin-layer chromatography procedure forsimultaneously determining Nebivolol (NEB) and IND in pharmaceutical formulation. The method has been studied on silica gel 60 F_{254}thin layer chromatography foil and validated as per the ICH guidelines [Vyas 2012].

Bhoirand co-workers have explored the HPTLC approach, which depends on separating two drugs on plates of aluminium-backed pre-coated silica gel $60F_{254}$. The customized operational conditions gave a compact spot for PER and IND at retention factor (R_f) 0.30 ± 0.02 and 0.60 ± 0.02, respectively [Bhoir 2014].

Patel, N.M. *et al.* demonstrated a new stability-indicating HPTLC approach forassessment of TEL and IND simultaneously in the presence of their degradation material and in their marketed matrix. In the stationary phase, the procedure was performed on aluminium-backed thin-layer chromatography foil (silica Gel $60F_{254}$) [Patel 2013].

Table 3: Overview on HPTLC methods for quantification of IND.

Sr. No.	Drugs	Matrix	Stationary phase plates	Mobile phase Composition	Linearity (ng/spot)	Rf	Ref
1.	OML and IND	Bulk drug and Tablet	Silica gel 60 F254	Toluene: Chloroform: Ethanol (4:4:1 v/v)	100 to 700 ng/spot and 100 to 600 ng/spot	0.15 and 0.47	Celina Nazareth et al (2013)
2.	NEB and IND	Bulk drug and Tablet	Silica gel 60 F254	Ethyl acetate: methanol: dil. ammonia, (8.5: 0.8: 1.0 v/v/v)	500–4000 ng /spot and 300–1050 ng/spot	0.43 and 0.64	Niraj Vyas et al (2012)
3.	ATL and IND	Bulk drug and Tablet	Silica gel 60F254	Toluene: ethyl acetate: methanol: ammonia 5:3:3:0.1 (v/v/v/v)	200-1200 ng/spot and 100-600 ng/spot	0.27 and 0.71	Janhavi R Rao et al (2011)
4.	AML and IND	Bulk drug and Tablet	Silica gel 60F254	Dichloromethane: methanol: ammonia 8.5: 1.5: 0.1 (v/v/v)	300-1500 ng/spot and 100-500 ng/spot	0.3 and 0.8	A.K. Desai et al (2012)
5.	PERI and IND	Bulk drug and Tablet	Silica gel 60 F254	Dichloromethane: Methanol: Glacial acetic acid in the ratio of 9.5:0.5:0.1 (v/v/v)	1000-5000 ng/band and 200-1000 ng/band	0.30 and 0.60	Mrinalini C. Damle et al (2014)
6.	TEL and IND	Bulk drug and Tablet	Silica Gel 60F254	Toluene: Ethyl Acetate: Acetone: Methanol (7: 4: 3: 1, v/v/v/v)	30-1000ng/spot and 600-200 ng/spot	0.61 and 0.34	RavalManan A. et al (2013)

8. Hyphenated Approaches

The HPLC coupling with an MS or MS-MS is a highly responsive hyphenation. Such coupling can be used to analyze the multiple components. Later, to examinethe specificity of analysis, it is the most credible to examine activepharmaceutical ingredients from samples of biological origin. A sample's ionization was followed by an LC/MS/MS technique for IND analysis. It was carried out as API, separated from the mass analyzer's high vacuum. Two

widely used procedures for the examination are atmospheric pressure chemical ionization (APCI) and electrospray ionization (ESI). The different phases of mass analysis are involved in tandem-mass spectrometry (MS/MS). The speculations are presented in (Table 4).

Table 4: LC-MS/MS protocols for measurement of IND.

Sr. No.	Drugs	Matrix	Extraction method	m/z ratio	References
1.	IND	Human serum	SPE	366	NatalijaNakov et al (2013)
2.	IND	Human serum	SPE	364	Jingling Tang et al (2005)
3.	IND	Human plasma	liquid–liquid extraction	364	Lin Xie et al (2006)
4.	IND	Human plasma	liquid–liquid extraction	364.3	Li Ding et al (2006)
5.	IND	human whole blood	liquid–liquid extraction	366.10	Deepak S. Jain et al (2006)
6.	IND	human serum	SPE	366	Hideyuki Morihisa et al (2008)
7.	Beta blockers	Human urine	SPE	–	Gordon J. Murray et al (2009)
8.	IND	human whole blood	SPE	366.1	N. Nakov et al (2013)
9.	IND	human whole blood	liquid–liquid extraction	364.0	GuilhermeAraújoPinto et al (2013)
10.	Diuretics	Dietary supplements	SPE	363.90	J.W. Kim et al (2013)
11.	Compounds	In metabolites	SPE	366.1	Yun Zeng et al (2016)
12.	IND	Human whole blood	SPE	366	Libo Zhao et al (2013)

Nakov, N., and co-authors explored the automated SPE procedure together with fast LC-MS/MS for serum determination of IND. The SPE analyses were performed with the help of polymeric mixed-mode sorbent using the positive mode electrospray technique of ionization [Nakov 2013].

Tang, J. *et al.* have tested LC-ESI-MS detection for analyzing IND in human blood. Consequently, the explored work was efficiently applied to a bioequivalence approach in which 20 healthy volunteers received 3 mg as a single oral dose reference and testedsustained-release IND formulations in an open, two-period, randomized crossover protocol. The test tablets showed relative bioavailability of 110:1 34:5% compared to the reference tablets [Tang 2005].

Chen, W.D. *et al.* investigated LC–ESI–MS approach for the quantification of IND in human plasma. A liquid-liquid extraction protocol was referred to by injecting extracts onto column (C-18) in gradient elution [Chen 2006].

Jain, D.S. *et al.* evaluated the highly precise and sensitive procedure for determining IND in whole human blood with the help of LC-MS/MS. A lower limit of measurement for the method under investigation is a sensitivity of 0.5 ng/mL in the human whole blood specimen.

The protocol adopted for the isolation and extraction of IND includes haemolysis and deprotonation of whole blood. The agent used was using $ZnSO_4$.The liquid-liquid extraction procedure utilized ethyl acetate as a extracting medium. Post drying sample extracts were reconstituted and analysed using LC-MS/MS, supported with a turbo ion spray (TIS) source[Jain 2006].

Morihisa, H. *et al.* assessed IND in human serum was examined using LC-ESI-MS/MS. Using SPE and Oasis HLB 96-well plates, IND and 4-diethylaminobenzoic acid (internal standard) were concurrently extracted from serum samples and quantified by LC-MS/MS [Morihisa 2008].

Murray, G.J., and Danaceau, J. P. have exhibited two common screening protocols for the assessment of 49 exogenous compounds, including 21 (diuretics) with 19 (beta-blockers) and 8(stimulants) and 2(steroids) compounds simultaneously in human urine as biological fluid by HPLC-MS/MS and UPLC-MS/MS. The samples were extracted using SPE. Samples were injected onto RP-HPLC and UPLC columns and instruments capable of polarity switching. The method was validated as per ISO 17025 international standards.

Sixty urine samples submitted were checked, and the results were correlated with previously validated procedures. Both methods were found to be helpful. The use of UPLCMS/MS allowed reliable screening with significantly less analysis time [Murray 2009].

Woo, H. *et al.* investigated an HPLC and LC-MS/MS protocols for determining17 (diuretics) from dietary supplements. The chromatographic analysis and resolution were performed under the RP mechanism on the HSS-T3 column.Atotal of (16) dietary supplements are involved. In all sample analyses, diuretics were not detected [Woo 2013].

Zeng, Y. *et al.* demonstratedthat the LC-MS/MS procedure improved product ion (EPI) method. The study analyzed 40 compounds simultaneously with a weight loss effect and included bisacodyl, phenolphthalein, sibutramine, and metabolites [Zeng 2016].

Zhao, L. *et al.*established a distinction between LC-UV and LC-MS/MS for IND. The similar methodology was used for bioequivalence investigations. The criteria used to compare the two approaches were their levels of selectivity, linearity, precision, and limit of quantification. The two approaches have thus far proven to be reliable and compatible. Additionally, the LC-MS/MS methodology was around 25 times more sensitive than the other method while requiring only a quarter of the blood volume. In contrast to the previous method, which required 11 minutes to run each sample, the LC-MS/MS method only required 3.5 minutes. As participants, 40 healthy Chinese men volunteers were chosen. The second half received 1.5 mg IND sustained-release coated pills, while the first half received 2.5 mg IND immediate-release tablets [Zhao 2010].

8. Infrared Spectrophotometry Method

Sirbu, C. *et al.* investigateda NIR-chemometric method to estimate IND as API (Active Pharmaceutical Ingredient). The method also involved the two leading excipients. The components were determined from the pharmaceutical powder used as a blend for manufacturing IND sustained-release (SR) tablets. Calibration models were developed for IND, hydroxyl propyl methylcellulose (HPMC) assay, and lactose. The 25 series of powder blends (prepared according to an experimental design) were used, and the NIR spectra were recorded. The methods were validated as per ICH regulations. The validation findings depictedgood precision, trueness, and accuracy [Sirbu 2014].

8.1. Calorimetric Analysis

Saleh, H.M. *et al.* reported two strategies for IND estimation in bulk and marketed matrix. These approaches mostly focused on IND being oxidised with iron (III) in an acidic solution. As a result of the freed iron (II) reacting with 10-phenanthroline (Method A), the ferroin complex was calorimetrically compared to the reagent blank at lambda max 509 nm. The drug's lowering of Fe (III) is a component of method (B). With 2, 20-bipyridyl, iron (III) forms a colourful complex with a maximum radius of 522 nm [Saleh 2001].

8.2. Kinetic Spectrofluorimetric Method

A simple and precise kinetic spectrofluorimetric approach was published by Guo, Y., and colleagues for simultaneously evaluating sibutramine, IND, and HCTZ in commonly found weight-loss supplements. Cerium (IV) ammonium sulphate that was dissolved in an acidic solution oxidised the analytes. At the excitation wavelength, the kinetic-fluorescence spectrum of the generated cerium (III) was examined between 0 and 600 s of reaction time at 250 nm i.e., excitation wavelength [Guo 2016].

Conclusions

The present review highlights specific typical and atypical methodological approaches to assessing IND in bulk, pharmaceutical, and biological matrices. Thorough literature searches were conducted for HPLC, Bio-analytical, HPTLC, UV/Vis-Spectroscopy, Spectrofluorimetric analysis, TLC-densitometric analysis, LC-MS/MS, etc. for assessment of IND in bulk and its combined pharmaceutical formulations and plasma.

HPLC assisted with UV detection was a highly explored methodology by many authors for estimating IND in bulk and for pharmaceutical formulations. The hyphenated techniques such as LS-MS/MS have been studied to determineIND and its metabolite in plasma and other biological matrices. Also, these techniques were studied for pharmacokinetic as well as bioequivalence studies.

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The authors do not have any conflict of interest

Declaration

It is an original data and has neither been sent elsewhere nor published anywhere.

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