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 of Indapamide as a particular drug in combinations and pharmaceutical as well as biological matrices. The analyses are reviewed for the specific applications 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) about heart failure. Decreasing high BP aids stroke prevention and the possibility of heart attacks and kidney problems. Diuretics or water pills are the class for which IND is well known [Ernst 2022].

IND alone or in a mixture with other drugs used to manage hypertension [Waerber 2003]. IND is available in combination with Perindopril, an Angiotensin Converting Enzyme (ACE) inhibitor. Diuretics like thiazide (IND and chlorothalidone) 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.
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 (United States Pharmacopeia)[USP 2018].

3. Indian Pharmacopoeia (IP)

IP depicts the reports for 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) and glacial 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 Pharmacopoeia (BP)

BP has presented on HPLC procedure for the investigation of IND. The separation of the IND has been attained on column (0.15 m long and 4.6 mm wide, packed with octadecylsilil 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 R as 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 of blend 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. HPLC Methods

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.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Analytes</th>
<th>Matrix</th>
<th>Chromatographic condition</th>
<th>Mobile Phase</th>
<th>Retention Time and Detection Wavelength,</th>
<th>Flow rate Injection volume</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ATN and IND</td>
<td>Tablet</td>
<td>(Hypersil Gold: 250mm x 4.6 mm, 5µm)</td>
<td>0.1% Triethyl Amine in water of pH 3.0 &amp; Methanol in the ratio 30:70 v/v</td>
<td>3.05 and 3.93 min, 240 nm</td>
<td>1.0 ml/min, 20 µl</td>
<td>ArindamBasu et al. 2011</td>
</tr>
<tr>
<td>2</td>
<td>ATN and IND</td>
<td>Tablet</td>
<td>Hypersil BDS C18 (250 mm x 4.6 mm, 5 µm particle)</td>
<td>(pH = 3.5, 0.01 M potassium dihydrogen orthophosphate buffer-acetonitrile (60:40; v:v)</td>
<td>5min, 231nm</td>
<td>1.0 ml/min, 20 µl</td>
<td>ThulasammaParusu&amp; VenkateswarluPonne ri 2012</td>
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<tr>
<td>3.</td>
<td>PDP and IND</td>
<td>Tablet</td>
<td>C18 (125 mm×4.0 mm i.d., with a particle size of 5 µm)</td>
<td>Acetonitrile, methanol and phosphate buffer of pH 3.0 (50:3:7/1/V/V/V)</td>
<td>2.9 and 4.6 min, 210 nm</td>
<td>0.7 ml/min, 20 µl</td>
<td>Anna gumieniczek et al. 2015</td>
</tr>
<tr>
<td>4.</td>
<td>ATN and IND</td>
<td>Tablet</td>
<td>C18 (250×4.6 mm 5 µm, 1.0 mm)</td>
<td>Methanol: water (adjusted to pH 2.7 with 1% ortho phosphoric acid) 80:20/V/V</td>
<td>1.766 min &amp; 3.407, 230 nm</td>
<td>1.0 ml/min, 20 µl</td>
<td>G. ruja rani et al. 2011</td>
</tr>
<tr>
<td>5.</td>
<td>PDE and IND</td>
<td>Bulk</td>
<td>Zorbax SB C18 Rapid Resolution (150 mm X 4.5 mm) column with 3.5 µm particle size</td>
<td>(Phosphate buffer:ACN52:48 V/V/V)</td>
<td>1.93 &amp; 3.17, 210 nm</td>
<td>1.0 ml/min, 5 µl</td>
<td>Ion Valen et al. 2015</td>
</tr>
<tr>
<td>6.</td>
<td>IND</td>
<td>Racemic Mixture</td>
<td>(150 x 4.6 mm, 5 µm)</td>
<td>Na2HPO4 10 mO buffer, ACN (95:5)</td>
<td>5.5 &amp; 7.09 242 nm</td>
<td>1.0 ml/min, 5 µl</td>
<td>Ancagabrielacárje et al. 2016</td>
</tr>
<tr>
<td>7.</td>
<td>IND</td>
<td>Tablet</td>
<td>C18 (250 mm × 4.6 mm, 5 µm)</td>
<td>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)</td>
<td>16.92, 254 nm</td>
<td>1.3 ml/min, 10 µl</td>
<td>Simonacodruţahegheş et al. 2017</td>
</tr>
<tr>
<td>8.</td>
<td>IND</td>
<td>Human Blood</td>
<td>C18 (15 cm x 4.6 mm 1.D.x 5 µm)</td>
<td>80 mM ammonium acetate, pH 3.5 (adjusted with concentrated hydrochloric acid) acetonitrile-2-propanol (65:30:5, v/v/v)</td>
<td>5.2 &amp; 241 nm</td>
<td>1.0 ml/min, 40 µl</td>
<td>R. Brent Miller et al. 1993</td>
</tr>
<tr>
<td>9.</td>
<td>OSM and IND</td>
<td>Bulk and Tablet</td>
<td>C18 AR column (250 × 4.6 mm id, 5 µm particle size)</td>
<td>Sodium perchlorate and triethylamine buffer solution (at pH 3): Acetonitrile (60:40 v/v)</td>
<td>6.8 &amp; 5,3 280 nm</td>
<td>1.0 ml/min, 10 µl</td>
<td>AvaniSheth et al. 2013</td>
</tr>
<tr>
<td>10.</td>
<td>PDA and AMD and IND</td>
<td>Bulk and Tablet</td>
<td>BDS Hypersil C18 column (100 × 3 mm, 5 µm)</td>
<td>0.05 M potassium dihydrogen phosphate buffer (pH 2.6)–methanol (50 and 50, v/v)</td>
<td>3.4, 6.0, 2.0 &amp; 215 nm</td>
<td>0.6 ml/min, 100 µl</td>
<td>Ramzia I. El-Bagary et al. 2015</td>
</tr>
<tr>
<td>11.</td>
<td>CP and IND</td>
<td>Bulk and Tablet</td>
<td>250 X4.6 mm terra RP8 column, 5µm</td>
<td>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),</td>
<td>1.8, 1.3 min 210 nm</td>
<td>2.0 ml/min, 20 µl</td>
<td>Alaa El-Gindy et al. 2014</td>
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<td>12.</td>
<td>PERI</td>
<td>Bulk and Tablet</td>
<td>RP-YMC pack ODS A-132 C18 (5 µm, 15 cm×6.0 mm i.d.) column.</td>
<td>phosphate buffer pH 2.4 and acetonitrile (7:3 v/v)</td>
<td>5.8 min 215 nm</td>
<td>1.0 ml/ min, 20 µl</td>
<td>NevinErk et al 2001</td>
</tr>
<tr>
<td>13.</td>
<td>ATL and IND</td>
<td>Bulk and Tablet</td>
<td>C18 column</td>
<td>methanol: water (60:40) with 0.1%v/v of Ammonium Hydroxide</td>
<td>7.5 and 8.9 min 260 nm</td>
<td>1.0 ml/ min, 20 µl</td>
<td>Naveen Kadian et al 2012</td>
</tr>
<tr>
<td>14.</td>
<td>ATL and IND</td>
<td>Bulk and Tablet</td>
<td>Symmetry X-terra C8 (4.6mm x 100mm, 5µm) column</td>
<td>Potassium di hydrogen phosphate buffer and Acetonitrile in the ratio 40:60 v/v</td>
<td>2.1 and 3.6 min 240 nm</td>
<td>1.0 ml/ min, 20 µl</td>
<td>K Madhavi et al (2014)</td>
</tr>
<tr>
<td>15.</td>
<td>LIS and IND</td>
<td>Bulk and Capsule</td>
<td>C18 column</td>
<td>methanol:water (50:50, v/v)</td>
<td>4.71±0.2 18.51±0.3, 206nm</td>
<td>1.0 ml/ min, 100 µl</td>
<td>Sofia Negro et al (2014)</td>
</tr>
<tr>
<td>16.</td>
<td>PERI and IND</td>
<td>Bulk and Tablet</td>
<td>C-18 column (150mm x 4.6mm, 5µm)</td>
<td>acetonitrile: 5mM sodium phosphate buffer (pH 7.5) (50:50)</td>
<td>2.5 and 4.7 min 202 nm</td>
<td>1.0 ml/ min, 20 µl</td>
<td>Menna I. Ezzeldina et al (2013)</td>
</tr>
<tr>
<td>17.</td>
<td>AML and IND</td>
<td>Bulk and Tablet</td>
<td>C18 Column</td>
<td>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)</td>
<td>3.27 and 4.7 min 238 nm</td>
<td>0.8 ml/ min, 20 µl</td>
<td>Mehul M. Patel et al (2012)</td>
</tr>
<tr>
<td>18.</td>
<td>AML and IND</td>
<td>Bulk and Tablet</td>
<td>Brownlee C-18</td>
<td>0.02 M potassium dihydrogen phosphate– methanol (30: 70, v/v)</td>
<td>5.9 min and 3.6 min 242 nm</td>
<td>1.0 ml/ min, 20 µl</td>
<td>Deval B. PATEL et al (2012)</td>
</tr>
<tr>
<td>19.</td>
<td>IND</td>
<td>Rat whole blood</td>
<td>Chromosil ODS column(250 × 4.6 mm id, 5 µm particle size)</td>
<td>methanol–acetonitrile–tetrahydrofuran–0.2% trifluoroacetic acid (170:20:15:38, v/v/v/v)</td>
<td>2.1 and 3.6 min 240 nm</td>
<td>0.8 ml/ min, 20 µl</td>
<td>XubinSuo et al (2013)</td>
</tr>
<tr>
<td>20.</td>
<td>PERI and IND</td>
<td>Bulk and Tablet</td>
<td>BDS hypersil C18 column (25cm×4.6mm, 5)</td>
<td>potassium dihydrogen phosphate buffer (pH 2.6) and acetonitrile (65:35, v/v)</td>
<td>210 nm</td>
<td>1.5 ml/ min, 10 µl</td>
<td>A.K. Pathak et al (2011)</td>
</tr>
<tr>
<td>21.</td>
<td>PERI and IND</td>
<td>Bulk and Tablet</td>
<td>Kromosil C18 column (250×4.6mm× 5µ</td>
<td>Phosphate buffer: ACN: methanol (40:25:35 v/v/v) pH 4.5</td>
<td>2.350 and 3.490 min 223 nm</td>
<td>1.0 ml/ min, 20 µl</td>
<td>S. Soujanya (2017)</td>
</tr>
<tr>
<td>23.</td>
<td>PERI and IND</td>
<td>Bulk and Tablet</td>
<td>BEH C18 (1.7 µm, 2.1×50 mm)</td>
<td>0.01% v/v formic acid in water adjusted to pH 4 with acetic acid and acetonitrile (40:60 v/v)</td>
<td>4.5 min 227 nm</td>
<td>0.3 ml/min, 1 µl</td>
<td>Naser F. Al-Tannak et al (2018)</td>
</tr>
<tr>
<td>24.</td>
<td>HCTZ and IND</td>
<td>Bulk drug and Tablet</td>
<td>Hypersil-Gold C18 (100 x 4.6 mm, 3 µm)</td>
<td>58% buffer (5 mM KH2PO4, containing triethylamine 0.25 ml/L), 25% acetonitrile and 17% methanol (pH adjusted to 2.8 ± 0.1)</td>
<td>3.4 and 6.6 min 215 nm.</td>
<td>1.0 ml/min, 10 µl</td>
<td>Ashok K. Shakya et al (2014)</td>
</tr>
<tr>
<td>25.</td>
<td>AML and IND</td>
<td>Bulk and Tablet</td>
<td>C-18 ODS bonded column (25cm x 4.60 mm, 10 µl)</td>
<td>methanol: water (95:5 % v/v)</td>
<td>8.780 and 2.850 min, 238 nm</td>
<td>1.0 ml/min, 10 µl</td>
<td>Varsha Kashaw et al (2016)</td>
</tr>
<tr>
<td>26.</td>
<td>IND</td>
<td>Bulk and Tablet</td>
<td>RP C-18 Column (25cm x 4.6 mm i.d., 5 µm)</td>
<td>o-phosphoric acid (0.05%) buffer of pH 3.0 and Acetonitrile in the ratio of 60:40 (v/v)</td>
<td>6.76±0.0145 min 240 nm.</td>
<td>1.0 ml/min, 20 µl</td>
<td>Sathish Kumar Shetty A. et al (2011)</td>
</tr>
<tr>
<td>27.</td>
<td>IND</td>
<td>Human Whole Blood</td>
<td>YMC ODS-A reverse column (5 lm particle size, 4.6-150 mm i.d.)</td>
<td>Acetonitrile - 2-propanol (0.1 triethylamine in water (adjusting to pH 3.75 with 85% phosphoric acid) (35:5:60, v/v/v).</td>
<td>12 min, 240 nm</td>
<td>1.2 ml/min, 20 µl</td>
<td>Xinguo Jiang et al (2005)</td>
</tr>
<tr>
<td>28.</td>
<td>AML and IND</td>
<td>Bulk drug and Tablet</td>
<td>ODS (C18), 250 mm × 4.6 mm &amp; 5 µm</td>
<td>Phosphate buffer (pH 4.0): Acetonitrile (40: 60 v/v)</td>
<td>3.5 min and 4.8 min, 247 nm</td>
<td>1.0 ml/min, 20 µl</td>
<td>G.V.S. Kumar et al (2012)</td>
</tr>
<tr>
<td>29.</td>
<td>AML and IND</td>
<td>Bulk and Tablet</td>
<td>C18 column (Phenomenex C18, 5µ, 250 mm x 4.6 mm)</td>
<td>Methanol: Water in the ratio of (95:5 v/v)</td>
<td>8.722 and 2.855 min 238 nm</td>
<td>1.0 ml/min, 20 µl</td>
<td>Manish C. Raj et al (2012)</td>
</tr>
</tbody>
</table>

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 the HPLC analysis forth the 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 240 nm. 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 on C18 Zorbax SB column having a particle size of 3.5 µm. The rational separation was executed using a solvent system comprised of 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°C. The injection was performed at 3 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 C18 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) 0.05 M (potassium dihydrogen phosphate buffer; pH 2.6) and methanol in the proportion (50:50 % v/v) at a flow rate of 0.6 mL/min and isocratic elution was reported. Further, the column temperature was maintained at 50°C. A 100µL solution was injected as a sample and detected at a 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 ethanol 0.7 mL/min rate of flow) acetonitrile and potassium dihydrogen phosphate. The effective identification was made at 240 nm 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 LiChroRPHPLC-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 a UV 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 UHPLC-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 using 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].


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

Mahant, B.D. et al. have validated 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: 237 nm (λ max AML) and 242 nm (λ max IND). The drugs obeyed Beer’s-Lambert’s law at 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.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Drug</th>
<th>Method</th>
<th>Matrix</th>
<th>Linearity (µg/ml)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IND on condensation with p-dimethylaminocinnamaldehyde (PDAC) and p-dimethylaminobenzaldehyde (PDAB)</td>
<td>Area Under Curve 682.0nm and 602.0nm</td>
<td>Bulk and Tablet</td>
<td>6-16µg/ml, 50-250µg/ml and 1-18µg/ml</td>
<td>Jyoti B. Pai et al (2011)</td>
</tr>
<tr>
<td>2</td>
<td>ATL and IND</td>
<td>Simultaneous 266 nm and 270.2 nm UV</td>
<td>Bulk and Tablet</td>
<td>100-350 and 5-17.5 µg/mL</td>
<td>N. Fernandes et al (2008)</td>
</tr>
<tr>
<td>3</td>
<td>AML and IND</td>
<td>First-Order Derivative UV Spectrophotometry 242 and 238 nm Absorption Correction Method</td>
<td>Bulk and Tablet</td>
<td>10-70 µg/ml and 2-16 µg/ml</td>
<td>Mehul M. Patel et al (2012)</td>
</tr>
<tr>
<td>4</td>
<td>Aceclofenac and IND</td>
<td>642.6 nm 783.2 nm</td>
<td>Bulk and complex</td>
<td>80-160 µg/ml</td>
<td>Singhavi et al (2007)</td>
</tr>
<tr>
<td>5</td>
<td>IND</td>
<td>Two derivative spectrophotometric 252.8 nm and 260.4 nm</td>
<td>Bulk and Tablet</td>
<td>1-30 µg/mL and 1-35 µg/mL</td>
<td>SacideAltınoz et al (2002)</td>
</tr>
<tr>
<td>6</td>
<td>TEL and IND</td>
<td>Simultaneous 295 nm and 239 nm</td>
<td>Bulk and Capsule</td>
<td>2-10 µg/ml and 2-14 µg/ml</td>
<td>Purvesh K Patel et al (2012)</td>
</tr>
<tr>
<td>7</td>
<td>PERI and IND</td>
<td>Simultaneous 210.4nm and 241.2nm</td>
<td>Bulk and Tablet</td>
<td>24 – 56 µg/ml and 7.5 – 17.5 µg/mL</td>
<td>Darshana K. Modi et al (2011)</td>
</tr>
<tr>
<td>8</td>
<td>IND</td>
<td>Simple UV 240 nm and 223 nm</td>
<td>Bulk and tablet</td>
<td>5 – 40 µg/ml</td>
<td>TarkaseKailash N et al (2012)</td>
</tr>
<tr>
<td>9</td>
<td>TEL and IND</td>
<td>Simultaneous and Q-Absorption Ratio Method</td>
<td>Bulk and tablet</td>
<td>4-14µg/ml</td>
<td>J.M. Chavda et al (2012)</td>
</tr>
</tbody>
</table>

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 nm are 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. An equal 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 the IND in tablets. The first approach was the absorption correction which needed 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 for telmisartan (TEL) and IND in a pure and combined matrix. The simultaneous
equations method implements two wavelengths, 295 nm, and 239 nm, as absorbance maxima (λ_max) 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 robustness under ICH guidelines [Nazareth 2013].

Vyas, N et al. studied the accurate and reliable high-performance thin-layer chromatography procedure for simultaneously 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].

Bhoir and 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 for assessment 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.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Drugs</th>
<th>Matrix</th>
<th>Stationary phase plates</th>
<th>Mobile phase Composition</th>
<th>Linearity (ng/spot)</th>
<th>Rf</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>OML and IND</td>
<td>Bulk drug and Tablet</td>
<td>Silica gel 60 F_{254}</td>
<td>Toluene: Chloroform: Ethanol (4:4:1 v/v)</td>
<td>100 to 700 ng/spot and 100 to 600 ng/spot</td>
<td>0.15 and 0.47</td>
<td>Celina Nazareth et al (2013)</td>
</tr>
<tr>
<td>2.</td>
<td>NEB and IND</td>
<td>Bulk drug and Tablet</td>
<td>Silica gel 60 F_{254}</td>
<td>Ethyl acetate: methanol: dil. ammonia, (8.5: 0.8: 1.0 v/v/v)</td>
<td>500–4000 ng/spot and 300–1050 ng/spot</td>
<td>0.43 and 0.64</td>
<td>Niraj Vyas et al (2012)</td>
</tr>
<tr>
<td>3.</td>
<td>ATL and IND</td>
<td>Bulk drug and Tablet</td>
<td>Silica gel 60 F_{254}</td>
<td>Toluene: ethyl acetate: methanol: ammonia 5:3:3:0.1 (v/v/v/v)</td>
<td>200–1200 ng/spot and 100–600 ng/spot</td>
<td>0.27 and 0.71</td>
<td>Janhavi R Rao et al (2011)</td>
</tr>
<tr>
<td>4.</td>
<td>AML and IND</td>
<td>Bulk drug and Tablet</td>
<td>Silica gel 60 F_{254}</td>
<td>Dichloromethane: methanol: ammonia 8.5: 1.5: 0.1 (v/v/v)</td>
<td>300–1500 ng/spot and 100–500 ng/spot</td>
<td>0.3 and 0.8</td>
<td>A.K. Desai et al (2012)</td>
</tr>
<tr>
<td>5.</td>
<td>PERI and IND</td>
<td>Bulk drug and Tablet</td>
<td>Silica gel 60 F_{254}</td>
<td>Dichloromethane: Methanol: Glacial acetic acid in the ratio of 9.5:0.5:0.1 (v/v/v)</td>
<td>1000–5000 ng/band and 200–1000 ng/band</td>
<td>0.30 and 0.60</td>
<td>Mrinalini C. Damle et al (2014)</td>
</tr>
<tr>
<td>6.</td>
<td>TEL and IND</td>
<td>Bulk drug and Tablet</td>
<td>Silica Gel 60 F_{254}</td>
<td>Toluene: Ethyl Acetate: Acetone: Methanol (7: 4: 3: 1, v/v/v/v)</td>
<td>30–10000ng/spot and 600–200 ng/spot</td>
<td>0.61 and 0.34</td>
<td>Raval Manan A. et al (2013)</td>
</tr>
</tbody>
</table>

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 examine the specificity of analysis, it is the most credible to examine active pharmaceutical 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.
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.**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Drugs</th>
<th>Matrix</th>
<th>Extraction method</th>
<th>m/z ratio</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.</td>
<td>IND</td>
<td>Human plasma</td>
<td>liquid–liquid extraction</td>
<td>364.3</td>
<td>Li Ding et al (2006)</td>
</tr>
<tr>
<td>9.</td>
<td>IND</td>
<td>Human whole blood</td>
<td>liquid–liquid extraction</td>
<td>364.0</td>
<td>Guilherme Araújo Pinto et al (2013)</td>
</tr>
</tbody>
</table>

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 tested sustained-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 ZnSO₄. 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 UPLC-MS/MS allowed reliable screening with significantly less analysis time [Murray 2009].

Woo, H. et al. investigated an HPLC and LC-MS/MS protocols for determining 17 (diuretics) from dietary supplements. The chromatographic analysis and resolution were performed under the RP mechanism on the HSS-T3 column. A total of 16 dietary supplements are involved. In all sample analyses, diuretics were not detected [Woo 2013].

Zeng, Y. et al. demonstrated that 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. investigated a 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 depicted good 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 oxidized 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 determine IND 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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Conflict of Interest

The authors do not have any conflict of interest

Declaration

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