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Short Review Article

A comprehensive Review of Analytical Methods for the Determination of Aceclofenac in Biological Fluids and Pharmaceutical Dosage Forms

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Abstract:

Method development is the process to prove that the analytical methods employed to measure the concentration of active pharmaceutical drug in a particular compounded dosage form is acceptable. This must be validated to provide accurate data for regulatory submissions. Aceclofenac (ACE) is an analog of diclofenac, a non-steroidal anti-inflammatory drug (NSAIDs). The drug is used in osteoarthritis, rheumatoid arthritis, ankylosing spondylitis ankylosing spondylitis, inflammation and relief of pain. The high importance of this class of drugs has prompted us to review the most important recent spectrophotometric methods for analyzing Aceclofenac in pure formulations, in various types of pharmaceutical dosage and in biological fluids published in the literature to date. They include spectrophotometry, high performance liquid chromatography, high performance thin layer chromatography, liquid chromatography-mass spectrometry, ultra high-performance liquid chromatography, mass spectrometry, and stability indicating methods. High sensitivity, speed, specificity and reproducibility make the use of these conventional methods for acetaminophen detection in routine analysis. They are time consuming, expensive and labour intensive though. Hence future research efforts are presumed to concentrate on developing novel methods to overcome these limitations.

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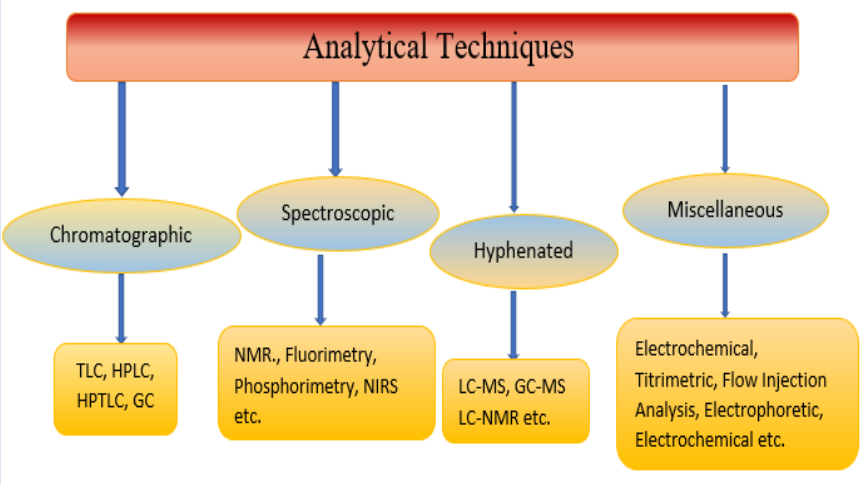
Keywords: Aceclofenac; NSAID; Estimation; Biological Sample; Pharmaceutical Formulations

Graphical Abstract:



Biography:

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1. Introduction

Development and validation of the analytical methods play significant roles in the research, production and manufacture of pharmaceuticals. Method validation is a wide range of validation parameters with specific strategies for specific requirement levels based on the planned use of analytical process, criticality and regulatory requirements. Aceclofenac (ACE) is the glycolic (hydroxy acetic) acid ester of diclofenac and is a non-steroidal anti-inflammatory drug (NSAID) with analgesic properties, typically utilized for osteoarthritis and similar afflictions. Chemically, Aceclofenac is 2-[2-[2-(2,6-dichloroanilino) phenyl] acetyl] oxy-acetic acid. [1-3]. Drug is official in Indian Pharmacopoeia, British Pharmacopoeia, European Pharmacopoeia and United States Pharmacopoeia [4-7].

Aceclofenac displays a high degree of enantio-selectivity with inhibitory effects on the arachidonic cyclooxygenase system. It is also reported to produce less GI bleeding than other NSAIDs such as indomethacin, ibuprofen or naproxen. After oral administration, aceclofenac is rapidly and completely absorbed as unchanged drug. Peak plasma concentrations are reached in approximately 1.25 to 3 h following ingestion. 4-hydroxyaceclofenac is the main metabolite detected in plasma [8]. The present review attempts to collect the maximum information available on analytical methods of ACE and with other drugs and elucidates the summary of all analytical methods which are reported in the literature for the estimation of ACE not only in bulk, pharmaceutical formulations but also in biological matrices. The analytical methods implemented in the studies on ACE are presented in Table 3 to 31.

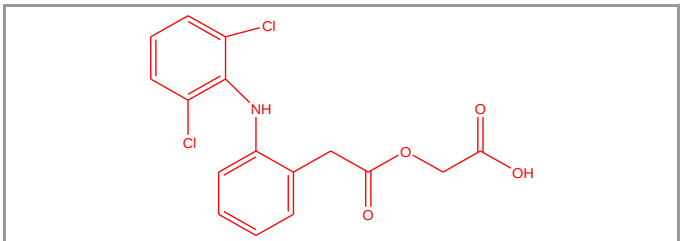

Figure 1. Structure of Aceclofenac.

2. Mechanism of Action

Aceclofenac converts into Diclofenac which inhibits the COX-2 enzyme and thus decreases the production of various inflammatory cytokines like prostaglandins E2 (PGE2), IL-1β, and TNF from the arachidonic acid pathway [9].

Therefore, suppressed action of these inflammatory cytokines can decrease the production of reactive oxygen species. It also may reduce the production of nitrous oxide in human articular chondrocytes, inhibiting the expression of L-selectin (CD62L) (a cell adhesion molecule expressed on lymphocytes) by interfering with the neutrophil adhesion to endothelium. It is also intended to stimulate the synthesis of glycosaminoglycan in human

osteoarthritic cartilage which might be mediated through its inhibitory on IL-1 production and activity [10].

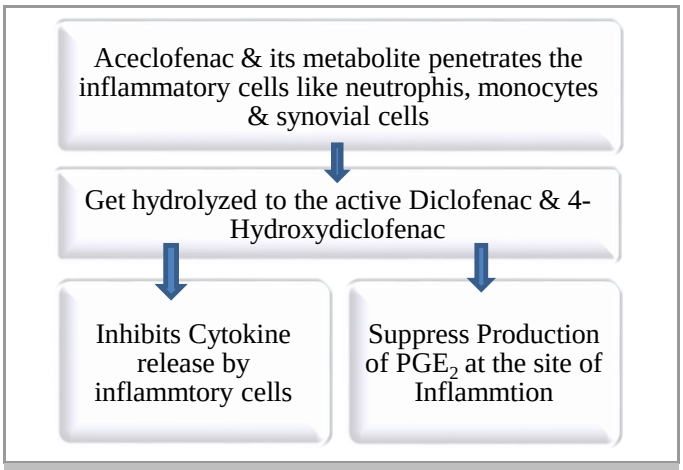

Figure 2. Schematic diagram of MOA of ACE (NSAIDs) [11].

3. Drug Profile

Using plant material for bio-fabrication of SeNPs has received an apt deal of attention due to its environmentally safe, cheap, swift, non-noxious, and procurable methodology which provides a concerted and single step technique for biogenic synthesis of SeNPs [3-4]. The green synthesis approach via plant extract involves many secondary metabolites such as flavonoids, alkaloids, phenols, saponins, carbohydrates, proteins, quinine, glycosides, tannins and steroids as natural reducers and/or stabilizers [5-6]. Some plants are already reported to facilitate SeNPs (Table 2). Several parts of plant such as buds, leaves, nuts, peel, fruit, seed and pulp can be used for synthesis of SeNPs with different morphologies and sizes by biological approaches. The aqua soluble chemical components are mainly responsible for creation and stabilization of SeNPs. Thereafter, the fabricated SeNPs need to be characterized using numerous known techniques.

Table 1. Drug profile of ACE [12-15].

Entry	Parameter	Aceclofenac
1	Category	NSAIDs & non-narcotic analgesic
2	Molecular formula	C16H13Cl2NO4
3	Molecular Weight	354.2 g/mol
4	CAS registry number	89796-99-6
5	Solubility	Freely soluble in acetone, soluble in ethanol (95%)
6	Melting Point	149-153 °C
7	pKa value	3.44
8	Storage	At a temp not exceeding 30 °C
9	Uses	Treat pain & swelling

4. Marketed Formulations of ACE

Table 2. Marketed formulations of ACE and its formulations with other drugs.

Entry	Brand name	Drug	Formulation	Dose
1	FERNACE SR	Aceclofenac	Tablet	200 mg
2	ACTIVE-200 SR	Aceclofenac	Tablet	200 mg
3	AFENAC	Aceclofenac	Tablet	100 mg
4	ACEZO-SR 200	Aceclofenac	Tablet	200 mg
5	M-NAC MD	Aceclofenac	Tablet	100 mg
6	AC- RUB	Aceclofenac	Gel	1 % w/w
7	ACCLORACE	Aceclofenac	Injection	150 mg
8	SAFRONAC	Aceclofenac	Tablet	100 mg
9	ALITRA	Aceclofenac	Tablet	100 mg
10	ACECLOFENAC STADA	Aceclofenac	Tablet	100 mg
11	XYNAC	Aceclofenac	Tablet	200 mg
12	FLAMACE 100	Aceclofenac	Tablet	100 mg
13	AIRTAL	Aceclofenac	Tablet	100 mg
14	VATOZIK-100	Aceclofenac	Tablet	100 mg
15	MOVON	Aceclofenac	Tablet	100 mg
16	HIFENAC	Aceclofenac	Tablet	100 mg
17	MOVIZ	Aceclofenac	Tablet	100 mg
18	SALNAC-100	Aceclofenac	Tablet	100 MG
19	ACLOWIN – P	Aceclofenac + Paracetamol	Tablet	100+ 325 mg
20	CLOOXIN	Aceclofenac + Paracetamol	Tablet	100 + 325 mg
21	DIFEE – P	Aceclofenac + Paracetamol	Tablet	100 + 325 mg
22	ZOLNAC	Aceclofenac + Rabeprazole	Capsule	200 + 20 mg
23	LUCIDOL-SPAS	Aceclofenac + Drotaverine	Tablet	100 + 80 mg
24	ANAC-D	Aceclofenac + Drotaverine HCl	Tablet	100 + 80 mg
25	CUDOL-SP	Aceclofenac + Paracetamol + Serritopeptidase	TABLET	100 + 325 + 15 mg
26	ZEROFENAC- TH4	Aceclofenac + Paracetamol + Thiocholchicoside	Tablet	100 + 325 + 4 mg
27	DOLORYL-MR	Aceclofenac + Paracetamol + Chlorzoxazone	Tablet	100 +325 + 250 mg

5. Reported Methods

5.1. Analytical Methods

Many different analytical methods have been reported to estimate the ACECLOFEANC (ACE) in bulk and dosage form as well as in biological fluids.2222

5.2. UV Spectroscopic Methods

Nasr JJ, *et al*. [16] specifies the stability-indicating spectrophotometric determination of aceclofenac using

multivariate calibration using phosphate buffer pH 6 as a solvent. The UV absorption spectra measured in the range of 220-330 nm at the interval of 1.0 nm.

Srujani CH, *et al*. [17] validated UV spectrophotometric methods for the estimation of Aceclofenac in bulk and pharmaceutical formulation using methanol and water (40: 60) as a solvent system. Three methods were developed, zero order at 274.65 nm, first order derivative at 259 nm and area under curve method was measured at 269-279 nm wavelength.

Table 3. Summary of validation parameters [17].

Parameters	Method A	Method B	Method C
R2	0.9994	0.9991	0.9995
% Recovery	99.20-99.38	100.22-100.3	99.85-99.91
Precision			
Intraday (%RSD)	0.16-0.42	0.61-1.32	0.021-0.049
Interday (%RSD)	0.39-0.84	0.87-1.41	0.082-0.296

Valambhia KR, *et al*. [18] describes validation of UV spectroscopic method of analysis for assay and dissolution of aceclofenac tablet using methanol for assay and phosphate buffer pH 6.8 for dissolution as a solvent. The maximum absorbance was observed at 276 nm with the linearity range of 0-120 µg/mL.

Table 4. Validated parameters [18].

Parameters	Observations
R2	0.9997
Regression equation	Y=0.003X+0.006
Slope	0.0036
Intercept	0.0062

Susmitha A, *et al*. [19] studied the analytical method development and validation of aceclofenac in pharmaceutical dosage dorm by UV spectroscopy technique using ethanol as a solvent. The maximum absorbance was observed at 277.7 nm in the linearity range of 2-60 µg/mL.

Table 5. Reported validated parameters [19].

Parameters	Observations
R2	0.996
%Recovery	99%
% Deviation	0.3-1.7

Golhar MK, *et al*. [20] specified development and validation of two spectrophotometric methods to determine the Aceclofenac in tablets using methanol as a solvent. The zero-order spectrum method was detected at 277.2 nm and first derivative method was detected at 261.2 nm with the 5-25 µg/mL linearity range.

Table 6. Validated parameters reported by Golharet [20].

Parameters	Method A	Method B
R2	0.9987	0.9995
%Recovery	99.01-99.64	101.3-101.6
LOD (µg/ml)	0.25	0.25
Intraday (SD)	1.02	1.32
Interday (SD)	1.07	1.32
Robustness	100.64±0.73	100.29±0.47

Bose A, *et al*. [21] evaluated the simple spectrophotometric methods for estimating the aceclofenac from bulk and formulations using p-dimethylaminocinnamaldehyde (PDAC) and 3-Methyl-2-benzothiazolinone hydrazine hydrochloride (MBTH). The two methods were developed using the PDAC and MBTH with detection at 658 nm and 592 nm, respectively. The beer's law obeyed in the concentration range of 1-200 and 1-100 µg/mL.

Table 7. Reported validation parameters by Bose *et al*.[21].

Parameters	Method A	Method B
R2	0.9986	0.999
Slope	0.011	0.012
Intercept	0.0135	0.018
%Assay (%RSD)	0.659	0.558
LOD (µg/ml)	0.9	0.6875
LOQ (µg/ml)	2.727	2.097
Intraday	99.39±0.68	99.38±0.52
Interday	99.24±0.47	99.25±0.60
%Recovery	99.29-99.63	98.91-99.45

Shah R, *et al*. [22] specified the validated spectroscopic method for estimating the Aceclofenac from tablet formulation using phosphate buffer pH 7.4 as a solvent. The detection was done at 273 nm and the linearity was obtained in the concentration range of 0-20 µg/mL.

Table 8. Summary of validation parameters [22].

Parameters	Observations
R2	0.9998
Slope	0.025052
Intercept	0.025141

5.3. Colorimetry Method

Kalavadiya B, *et al*. [23] investigated the development of colorimetric method and validation for determination of Aceclofenac in bulk and marketed formulation. In this method, cerric ammonium sulphate has been used for Aceclofenac, in excess amount at the presence of sulphuric acid. Remaining amount of oxidizing agents oxidizes standard amount of crystal violet which produces violet colour. Absorbance maxima was found to be 585 nm. Linearity range was found to be 2-18 µg/mL of drug concentration, respectively.

5.4. RP-HPLC Methods

Hinz B, *et al*. [24] discussed the simultaneous determination of aceclofenac and three of its metabolites in human plasma by high-performance liquid chromatography using acetonitrile and phosphate buffer pH 2.5 as a mobile phase with 1 mL/min flow rate. The detection was carried out at 282 nm with UV detector. The retention times for

aceclofenac, diclofenac, 4-hydroxy-aceclofenac, 4-hydroxy-diclofenac and ketoprofen (internal standard) were 69.1, 60.9, 46.9, 28.4, and 21.2 min, respectively. The validated quantitation range of the method was 10-10,000 ng/mL for aceclofenac, 4-hydroxyaceclofenac and diclofenac, and 25–10,000 ng/mL for 4-hydroxy-diclofenac.

Ravisankar P, *et al*. [25] studied development and validation of a reverse phase HPLC method to determine the aceclofenac in bulk and pharmaceutical dosage forms using WELCHROM C18 Column (4.6 X 250 mm, 5 µm), SHIMADZU LC-20AT prominence liquid chromatograph. The separation was carried out with phosphate buffer pH 6.8 and acetonitrile (50: 50 v/v) at a 5.0 mL/min flow rate. The detection was observed at 278 nm wavelength with 8.767 min retention time using SHIMADZU SPD-20A prominence UV-Vis detector.

Table 9. Summary of validation parameters [25].

Parameters	Observations
R2	0.999
Intraday(%RSD)	0.060
Interday(%RSD)	0.035
%Recovery	99.91-101.26
LOD (µg/ml)	0.12
LOQ (µg/ml)	0.37

Gupta CR, *et al*. [26] described the development and validation of the RP-HPLC method for the determination of aceclofenac in plasma using Ibuprofen as an internal standard. Phosphate buffer of pH 6.8: acetonitrile (30: 70 v/v) was used as a mobile phase with the C18 column for the separation. The detection was done at 282 nm with the retention time 7.20 min and 5-12 µg/ml linearity range.

Table 10. Summary of validation parameters [26].

Parameters	Observations
R2	0.992
LOQ (µg/ml)	0.5
%Recovery	85-20-95.75

Jat RK, et al. [27] describes the RP-HPLC method for the estimation of aceclofenac in tablet dosage form using Water: acetonitrile (55: 45 v/v) as a mobile phase at 1 ml/min flow rate. The separation was carried out from hypersil C18 column with the detection at 277 nm. The linearity was observed in the concentration range of 1-10 µg/ml.

Table 11. Summary of validation parameters [27].

Parameters	Observations
R2	0.999
Intercept	0.497
Slope	0.996
Intraday(%RSD)	0.257-0.712
Interday(%RSD)	0.438-1.080
%Recovery	99.06-101.03
LOD (µg/ml)	0.23
LOQ (µg/ml)	0.86
Repeatability(%RSD)	0.195

Shah RR, *et al*. [28] discussed the RP-HPLC method for the determination of aceclofenac in from bulk and microemulsion formulations. The separation was carried out with acetonitrile and 25mM of trishydoxylmethyl aminomethane (50:50 v/v) in phosphate buffer pH 7.0. The detection was done at 276 nm with concentration range of 0-100 µg/mL.

Table 12. Summary of validation parameters [28].

Parameters	Observations
R2	0.9994
Precision (%RSD)	< 0.25 %
%Recovery	99.98-101.50
LOD (µg/ml)	0.07
LOQ (µg/ml)	0.21

5.5. LC-MS Method

Kang W, *et al*. [29] assessed the simultaneous determination of the aceclofenac and its three metabolites in plasma using the liquid chromatography-tandem mass spectrometry using reverse phase C18 column. The separation was carried out by acetonitrile and 0.1 % formic acid (80: 20 v/v) as a mobile phase with the flow rate of 0.2 mL/min. The linearity was observed in the concentration range of 0.1-20 µg/mL.

5.6. HPLC-MS Method

Reddy SR, *et al*. [30] describes the development and validation of high performance liquid chromatography Tandem mass spectrometric method for quantification of Aceclofenac in human plasma in the concentration range of 0.106-14.060 µg/mL. Separation was done by using buffer pH 6.8 and acetonitrile and C18 (4.6 X 50 mm, 50 µm, 60 A0) column with the flow rate of 0.350 mL/min. Retention time were 1.20 and 1.21 min, respectively.

Table 13. Summary of validation parameters [30].

Parameters	Observations
R2	0.999
Sensitivity	5.6 & 100.3%
Precision	2.1-6.8
% Recovery	96.5-103.8

5.7. UPLC-MS/MS Method

Bagary R, *et al*. [31] described the UPLC-MS/MS determination of aceclofenac and diclofenac in bulk, dosage forms and in At-line Monitoring of Aceclofenac synthesis using Acetonitrile, water and formic acid (80: 20: 0.5 v/v/v) as a mobile phase and UPLC C18 column (2.1 X 50 mm, 1.7 µm). The flow rate was 0.2 mL/min for the elution. The temperature was maintained at 5 oC in Auto-sampler to prevent any further degradation of ACL. Electrospray positive ionization (ESI +Ve) in multiple-reaction monitoring mode (MRM) was used

for the simultaneous determination of ACL and DCL. Monitoring was performed at [M+H]+ 354.23: 250.09 and 296.13:250.1 *m/z*, respectively.

5.8. HPTLC Method

William H, *et al*. [32] discussed the validated high-performance thin layer chromatographic estimation of Aceclofenac in bulk and pharmaceutical dosage Forms using silica gel 60F254 as a stationary phase. Hexane, chloroform and methanol (6: 2: 2 v/v) was used as a mobile phase. The Rf value was 0.3 and was measured at 271 nm detection wavelength.

Table 14. Summary of validation parameters [32].

Parameters	Observations
R2	0.9998
Regression equation	Y=3171.6x + 3030.70
LOD (ng/spot)	10
LOQ (ng/spot)	20
Intraday (%RSD)	0.07-0.3
Interday (%RSD)	0.06-0.3

6. REPORTED METHODS (Aceclofenac and its other combinations)

6.1. UV Spectroscopic Methods

Basnett H, *et al*. [33] investigated the estimation of paracetamol and aceclofenac in tablets by a novel ratio difference method using methanol as a solvent. The developed method was estimated at 245 nm and 270 nm as λ1 and λ2 for Paracetamol and 214 nm and 242 nm as λ1 and λ2 for Aceclofenac. The linearity was obtained in the concentration range of 3-40 µg/mL for Paracetamol and 3-10 µg/mL for Aceclofenac.

Table 15. Summary of validation parameters [33].

Parameters	Paracetamol	Aceclofenac
R2	0.997	0.998
Slope	0.1691	0.1373
LOD (µg/ml)	0.144	0.156
LOQ (µg/ml)	0.439	0.473
Intraday (%RSD)	1.20	1.47
Interday (%RSD)	1.14	1.48
%Recovery	90-102	97-103.2

Jeeboi L, *et al*. [34] described the UV spectrophotometric method for simultaneous estimation of tramadol hydrochloride and Aceclofenac in bulk and tablet dosage form with detection wavelengths 214.8 nm and 275.6 nm for tramadol hydrochloride and Aceclofenac, respectively. The analysis was performed using the methanol: water (60: 40 v/v) as a solvent. The linearity was obtained in the concentration range of 5-30 µg/mL for both the drugs.

Table 16. Summary of validation parameters [34].

Parameters	Tramadol	Aceclofenac
R2	0.999	0.999
Slope	0.026	0.027
Intercept	0.019	0.002
LOD (µg/mL)	2.412	0.244
LOQ (µg/mL)	7.308	0.741
Precision	< 2	< 2
%Recovery	98.12-101.00	98.01-98.36

Suryawanshi SS, *et al*. [35] investigated the development and validation of UV-spectrophotometric method for simultaneous estimation of Aceclofenac and Pantoprazole in bulk and tablet dosage forms using the hydrotropic solvent with the detection wavelengths 273 nm and 293 nm, respectively. Linearity was observed at the range of 5-40 µg/mL for Aceclofenac and 2-16 µg/mL for pantoprazole. Hydrotropic solvents were chosen as a solvent i.e. 0.1 M sodium bicarbonate and 0.1 M urea solution (50: 50 v/v).

Table 17. Summary of validation parameters [35].

Parameters	Pantoprazole	Aceclofenac
R2	0.9998	0.9998
Absorptivity at 273 nm	230.06	222.37
Absorptivity at 293 nm	561.14	133.27
LOD (µg/ml)	0.05	0.47
LOQ (µg/ml)	0.16	1.43
Intraday (%RSD)	1.49	0.84
Interday (%RSD)	1.40	1.23
%Recovery	99-100.9	99.50-101.7
(Analyst 1-2)	98.1-101.3	99-100.9
%Assay	99.54	101.33

Parmar AR, *et al*. [36] specified the simultaneous estimation of Aceclofenac and Serratiopeptidase in tablet dosage form by Absorbance ratio method using the visible spectrophotometry using the ethanol: water as a solvent. The detection was done at 316 nm and 375 nm with the linearity range of 30-70 and 100-30 µg/mL for Aceclofenac (ACE) and Serratiopeptidase (SER), respectively.

Table 18. Summary of validation parameters [36].

Parameters	ACE	SER
R2	0.9968	0.9955
Slope	0.005	0.001
Intercept	0.075	0.004
LOD (µg/ml)	2.33	12.50
LOQ (µg/ml)	7.07	37.88
Intraday (%RSD)	1.81	0.43
Interday (%RSD)	0.35	1.58
%Recovery	99.19 ± 0.95	99.15 ± 0.40
%Assay	98.32	100.12

Gondane SJ, *et al*. [37] described the spectrophotometric method development and validation for the estimation of Tizanidine and

Aceclofenac in bulk drug and tablet formulation by two different spectroscopic methods including the Viedort's method and 1st order UV derivative method. The maximum absorbance was measured at 318 nm for Tizanidine and at 274 nm for Aceclofenac using the methanol and phosphate buffer as a solvent system. The linearity was obtained in the concentration range of 1-10 µg/mL and 2-20 µg/mL for Tizanidine and Aceclofenac, respectively.

Table 19. Summary of validation parameters [37].

Parameters	Method I		Method II	
	TZN	ACF	TZN	ACF
R2	0.999	0.998	0.996	0.997
Slope	0.034	0.105	0.031	0.356
Intercept	0.001	0.001	0.001	0.001
Intraday	0.61	0.05	0.74	0.10
Interday	0.30	0.07	0.43	0.09

Modak VG, *et al*. [38] specified the spectrophotometric determination of Drotaverine and Aceclofenac in combined tablet dosage form by ratio derivative spectroscopy (Method A) and area under curve (AUC) (Method B) spectrophotometric methods using the methanol and Double distilled water as a solvent. Method A was estimated at 330.13 nm and 228.06 nm to determine the Drotaverine and Aceclofenac, respectively. In Method B, the determination of Aceclofenac and Drotaverine were done in the wavelength range of 299-305 nm and 270-277 nm, respectively. Linearity was observed in the concentration ranges of 4-20 µg/mL for DRT and 5-25 µg/mL for ACE in Method A while 4-24 µg/ml for DRT and 5-30 µg/mL for ACE in Method B.

Table 20. Summary of validation parameters [40].

Parameters	Drotaverine		Aceclofenac	
	A	B	A	B
R2	0.999	0.999	0.999	0.999
Slope	0.496	0.114	0.499	0.161
Intercept	0.248	0.025	0.103	0.029
Intraday	0.46	0.72	1.15	0.88
Interday	0.37	0.49	1.10	0.60
&Assay	99.48	100.0	99.89	99.52

Suchithra TJ, *et al*. [39] specified the simultaneous estimation of Aceclofenac and Pregabalin in combined dosage form by solubility based separation method using the methanol. The linearity was observed at the concentration range of 10-50 µg/mL with detection at 276 nm for aceclofenac and 50-500 µg/mL for pregabalin with detection at 406 nm.

Table 21. Summary of validation parameters [49].

Parameters	Aceclofenac	Pregabalin
R2	0.992	0.997
Slope	0.015	0.004
Intercept	0.0013	0.727
LOD (µg/mL)	0.50	0.65
LOQ (µg/mL)	2.06	4.03
Intraday	1.27	1.66
Interday	1.20	1.67
%Recovery	99.79	100.44

6.2. RP-HPLC Methods

Shaikh KA, *et al*. [40] investigated the sensitive LC method for the simultaneous determination of diacerein and aceclofenac in tablet dosage form using Kromasil C18 (150 x 4.6 mm, 3.5 µm) column and Double distilled water (pH 2.7 with glacial acetic acid): ACN (45: 55 v/v) as a mobile phase. The detection was done at 256 nm. The linearity was observed in the concentration range of 2.5-75 µg/mL and 5-150 µg/mL for Diacerein and Aceclofenac, respectively.

Table 22. Summary of validation parameters [40].

Parameters	Diacerein	Aceclofenac
R2	0.9999	0.9997
LOD (µg/ml)	0.0033	0.007
LOQ (µg/ml)	0.01	0.021
Repeatability	0.26	0.52
Intermediate Precision	0.35	0.64
%Recovery		
50%	99.5	100.2
100%	99.8	100.5
150%	100.3	100.0
%Assay	100.3	100.1

Rao CM, *et al*. [41] specified the simultaneous estimation of zinc carnosine and Aceclofenac in bulk and tablet dosage form by HPLC method using C18 column (250 x 4.6 mm, 5 µm). The separation was carried out using the Potassium di-hydrogen phosphate buffer, ACN and methanol (50: 30: 20 v/v) with 1 mL/min flow rate. The detection was done at 215 nm and 275 nm. The retention time were found to be 2.258 min and 6.690 min for zinc carnosine and Aceclofenac, respectively. The linearity was obtained at the concentration range of 2-10 µg/mL for both the drugs.

Table 23. Summary of validation parameters [41].

Parameters	Zinc Carosine	ACE
R2	0.999	0.999
Slope	0.1120	3505.52
Intercept	63.86	-406.105
LOD (ng/mL)	33.4	101.3
LOQ (ng/mL)	2.473	7.495
%Recovery	99.5-100.36	99-99.83

Kumar RS, *et al*. [42] described a validated reversed phase HPLC-method for the determination of Aceclofenac and Tizanidine in tablets using ACN: Methanol: 20 mM phosphate buffer pH 3.5 (40: 30: 30 v/v/v) as a mobile phase. The analysis was performed using the C18 column (250 x 4.6 mm, 5 µm) in isocratic mode with the detection wavelength 230 nm. The linearity was obtained in the concentration ranges of 120-280 µg/mL and 2-40 µg/mL for Aceclofenac and Tizanidine, respectively.

Table 24. Summary of validation parameters [42].

Parameters	Tizanidine	ACE
R2	0.9999	0.9998
LOD (µg/mL)	0.40	20
LOQ (µg/mL)	0.80	50
Selectivity	--	1.60
%Recovery	99.45-100.61	99.56-101.32

Ojha A, *et al*. [43] assessed the simultaneous HPLC–UV determination of Rhein and Aceclofenac in human plasma using the RP-ODS column as a stationary phase. Separation was carried out using the Acetate buffer: ACN as a mobile phase at 1 ml/min flow rate. Detection was done at 258 nm wavelength with the linearity ranges of 0.1-7 µg/mL and 0.5-20 µg/mL for Rhein and Aceclofenac, respectively, using 500 µL plasma samples.

Rajamahanti SG, *et al*. [44] investigated a new stability indicating method for determination of Aceclofenac and Thiocolchicoside in pharmaceutical dosage form by RP-HPLC. The separation was carried out by using Agilent Zorbax column (150 × 4.6 mm, 5 µm) with methanol: 0.1% o-phosphoric acid (75: 25 v/v) as a mobile phase at detection wavelength 275 nm and flow rate of 1 mL/min.

Table 25. Summary of validation parameters [44].

Parameters	Thiocolchicoside	ACE
R2	0.9972	0.9994
Slope	41081	33295
Intercept	-16755	60388
LOD (µg/mL)	1.83	3.61
LOQ (µg/mL)	1.81	3.54

Jawale A, *et al*. [45] specified novel bio-analytical RP-HPLC method for simultaneous estimation of aceclofenac and drotaverine hydrochloride in human plasma by DOE approach using Kromasil C8 column (150×4.6 mm, 5 µm). The separation was carried out by ACN: Ammonium acetate buffer pH 3.5 (53:47 v/v) as a mobile phase with the flow rate of 1 mL/min. The detection was done at 230 nm and the linearity was obtained in the concentration range of 30-9000 ng/mL for aceclofenac and 50-180 ng/mL for drotaverine hydrochloride (DRT).

Table 26. Summary of validation parameters [45].

Parameters	DRT	ACE
R2	0.9926	0.9952
Slope	20.745	27.558
Intercept	1999.2	-281.57
Intraday (%CV)	0.39-1.26	0.61-1.17
Interday (%CV)	3.36-7.21	1.20-1.25
Accuracy(%CV)	1.23-1.82	1.06-1.18

Adhao VS, *et al*. [46] studied the RP-HPLC method development and validation for the simultaneous estimation of Aceclofenac and Rabeprazole sodium in the bulk and marketed formulation using methanol, water and ACN (60: 30: 10 v/v/v) as a mobile phase. The analysis was performed using the Hypersil BDS column with C18 packaging (250 × 4.6 mm, 5 µm) with the flow rate of 1 ml/min. The detection was done at the wavelength of 283 nm.

Bhavsar A, *et al*. [47] provided the detail about development and validation of RP- HPLC method for simultaneous estimation of Aceclofenac and Pregabalin in combined tablet dosage form BDS hypersil C18 column. The analysis was performed using phosphate buffer pH 4: Methanol (60: 40 v/v) as a mobile phase with the 1 mL/min flow rate. The detection was done at 210 nm with 3.67 min and 6.73 min retention time for Aceclofenac and Pregabalin, respectively. The linearity was observed in the concentration range of 25-75 µg/mL for Aceclofenac and 18.75-56.25 µg/mL for Pregabalin.

Table 27. Summary of validation parameters [47].

Parameters	Pregabalin	ACE
R2	0.9969	0.9978
Slope	71.109	21.765
Intercept	-98.811	-29.773
LOD (µg/mL)	25.127	4.533
LOQ (µg/mL)	76.142	13.739

Ventrapragada B, *et al*. [48] describes the Method development and validation for the simultaneous estimation of aceclofenac and paracetamol in solid dosage form by using RP –HPLC using Cosmicsil Adze C18 (150x4.6nm, 5µm) as a column. The separation was carried out by using 2 M phosphate buffer pH 7 and ACN (75: 25 v/v) as a mobile phase with 1 mL/min flow rate. Estimation was done at 265 nm with 6.03 min and 2.80 min retention time for Aceclofenac and Paracetamol, respectively.

Patel RD, *et al*. [49] specifies the Liquid Chromatographic Estimation of Cyclobenzaprine Hydrochloride and Aceclofenac in Pharmaceutical Formulation using Luna C18 column (250 x 4.6 mm id, 5 µm) as a column and Methanol: 0.02 M dihydrogen potassium phosphate pH 3 (75: 25 v/v) as a mobile phase. The detection was carried out at 280 nm with 4.2 min and 9 min retention time for Cyclobenzaprine hydrochloride (CBP) and Aceclofenac, respectively.

Table 28. Summary of validation parameters [49].

Parameters	CBP	ACE
R2	0.9990	0.999
Slope	22012.40	52764.60
Intercept	16560.40	22999
Intraday	0.49-1.02	0.51-0.93
Interday	0.50-1.13	0.58-1.08
%Recovery	99.57-101.10	99.78-101.81
LOD & LOQ	0.003,0.01	0.03,0.1

Gawande V, *et al*. [50] assessed the validated RP-HPLC method for the estimation of Rabeprazole and Aceclofenac from human plasma using HiQ SiL C8 column (250 x 4.6 mm id, 5 µm). The analysis was

performed using 0.05 M Potassium diphosphate, ACN and Methanol (4: 4: 3 v/v/v) as a mobile phase with 1 mL/min flow rate and 215 nm detection wavelength. The linearity was observed in the concentration range of 0.5–7.5 µg/mL.

Table 29. Summary of validation parameters [50].

Parameters	Rabeprazole	ACE
R2	0.990	0.997
Slope	10222	12509
Intercept	77049	14664
Intraday	3.34	1.01
Interday	1.76	1.97
%Recovery	100.66	100.25

Manasa B, *et al*. [51] described the development and validation of RP-HPLC method for the simultaneous estimation of aceclofenac and rabeprazole sodium in bulk and capsules using SUNFIRE C18 column (250 x 4.6mm×5µ) with UV detector. Ammonium acetate buffer and ACN (50: 50 v/v) used as a mobile phase with 1 mL/min flow rate and 300 nm detection wavelength. The retention time found to be 2.72 min and 3.95 min and linearity were obtained 10-60 and 1-6 µg/mL for Aceclofenac and Rabeprazole sodium, respectively**.**

Table 30. Summary of validation parameters [51].

Parameters	Rabeprazole	ACE
R2	0.999	0.999
Method Precision	0.22	0.08
System Precision	0.33	0.15
LOD	0.44	0.98
LOQ	1.38	3.07
%Recovery	99.2	99.62

Chitlange SS, *et al*. [52] evaluated the simultaneous estimation of Thiocolchicoside and Aceclofenac in pharmaceutical dosage form by spectrophotometric and LC method by area under the curve method and RP-HPLC method. The area under the curve method was developed under the wavelength range of 264.5-254.5 nm for THC and 279-269 nm for ACE with the linearity range of 4-36 µg/mL for both the drugs. The RP-HPLC method developed using Thermo C18 column (250 x 4.6 mm, 5 µm) as a stationary phase and ACN: Water: 0.025 M potassium dihydrogen orthophosphate buffer pH 3 (70: 10: 20 % v/v/v) as a mobile phase with the linearity ranges 1-6 µg/mL and 25-150 µg/mL for THC and ACE, respectively.

Baishya H, *et al*. [53] reversed phase UHPLC method for simultaneous estimation of aceclofenac and paracetamol in bulk and pharmaceutical dosage form using the stainless steel column (25 cm × 4.6 mm×5 µm) packed with octadecylsilane chemically bonded to porous silica column. The separation was carried out with acetonitrile and buffer pH 7.5 (60: 40 v/v) at 1.5 mL/min flow rate and detection was done at 272 nm. The retention time was found to be 1.698 and 2.548 min for Paracetamol and Aceclofenac, respectively. The linearity was obtained in the concentration range of 10-100 µg/mL and 100-500 µg/mL for Aceclofenac and Paracetamol, respectively.

Table 31. Summary of validation parameters [52].

Parameters	Paracetamol	ACE
R2	0.999	0.999
Slope	0.252	0.411
Intercept	0.034	0.147
Intraday	0.660	0.897
Interday	0.589	0.856
%Recovery	99.48±0.653	99.42±0.543
LOD & LOQ	0.08,0.25	0.02,0.06
%Assay	95.8	96.5

6.3. UPLC-MS Method

Khan H, *et al*. [54] evaluated the validated UPLC/Q-TOF-MS method for simultaneous determination of aceclofenac and paracetamol in human plasma and its application to pharmacokinetic study. The analysis was performed using the UPLC BEH C18 (100.0 x 2.1 mm, 1.7 µm) column with acetonitrile and 2 mM ammonium acetate (50: 50 v/v) mobile phase. The detection was done with 0.20 mL/min flow rate. Quantitation was done at m/z 354.07 to 215.07 for aceclofenac and 152.07 to 110.06 for paracetamol. The linearity obtained in the range of 1-1000 ng/mL.

Table 32. Summary of validation parameters [54].

Parameters	Paracetamol	ACE
R2	0.9997	0.9995
LOD (µg/mL)	0.01	0.01
LOQ (µg/mL)	1	1

6.4. RP-UPLC Method

Balan P, *et al*. [55] described the development and validation of stability-indicating RP-UPLC method for simultaneous estimation of Thiocolchicoside and Aceclofenac in combined dosage form. The analysis was done using thermo scientific hypersil gold C18 (50 x 2.1 mm, 1.9 µm) column and 5 ammonium acetate buffers: Methanol (40: 60 v/v) pH 5 % as a mobile phase. The detection was done at 276 nm with the flow rate of 250 µL/min. Retention time was found to be 0.697 min and 1.125 min for TCC and ACF, respectively. The linearity was obtained in the concentration range of 4.8-7.2 µg/mL for TCC and 63.8-96 µg/mL for ACF.

6.5. HPTLC Method

Patil A, *et al*. [56] investigated the development and validation of HPTLC method for the simultaneous estimation of paracetamol and aceclofenac in combined dosage form using Toluene: Methanol (3.5: 1 v/v) as a mobile phase. The separation was carried out using silica gel 60 F254 as a stationary phase and Rf values

were found to be 0.48 for PCM and 0.62 for ACF with the linearity 33-1800 and 100-600 ng/spot, respectively.

7. Conclusion

The present review discussed the summary of all analytical methods which are reported in the literature for the estimation of ACE no only in bulk, pharmaceutical formulations but also in biological matrices. The study of analytical data revealed that the HPLC and UV methods were predominant for the estimation of Aceclofenac alone or in combinations. However, very few analytical methods are obtainable on LC-MS, HPLC-MS, UPLC-MS/MS and HPTLC for ACE single and HPTLC and UPLC-MS methods for ACE with other combination of drugs. All the above analytical methods are important for both qualitative and quantitative determination of Aceclofenac. These methods are found to be accurate, rapid, sensitive, reproducible, and economic. With the help of these analytical techniques, quantification and identification of the impurities, stability assessment and dosage selection can also be carried out.

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Disclosure statement

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