Review Article

Valsartan - A Review of Analytical Methods

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ABSTRACT

This review focuses on the recent developments in analytical techniques for estimation of Valsartan alone or in combinations with other drugs in various biological media like human plasma and urine. This review will critically examine the analytical methods UV Spectroscopy, high performance liquid chromatography (HPLC), ultra performance liquid chromatography (UPLC), high performance thin layer chromatography (HPTLC), liquid chromatography coupled to tandem mass spectrometry (LC-MS).

Keywords: Analytical Techniques, Valsartan, Solid phase extraction, HPLC, Spectrophotometry.

INTRODUCTION

Valsartan is a new potent, highly selective and orally active antihypertensive drug belonging to the family of Angiotensin II type I receptor antagonists. Angiotensin II receptor type I antagonists have been widely used in the treatment of hypertension, heart failure, myocardial infarction and diabetic nephropathy. It is a lipophilic drug and it was first developed by Novartis and has a wide market in the developed and developing countries. It is available as single and in combination with other antihypertensive drugs. Valsartan is rapidly absorbed after oral administration. Volume of distribution at steady state has been estimated 17L and mean absolute Bioavailability is 23%. Food decreases the exposure of Valsartan by about 40% and peak plasma concentration by about 50%. 94%-97% of drug bound to serum protein mainly albumin. This review focuses on the recent developments in analytical techniques for estimation of Valsartan alone or in combinations with other drugs in various biological media like human plasma and urine, Various analytical techniques are discussed, from simple colorimetric methods of intermediate selectivity and sensitivity to sophisticated highly selective and sensitive, chromatographic methods applied in a modern analytical laboratory. This review will critically examine the (a) sample pretreatment method such as solid phase extraction (SPE), (b) separation methods such as thin layer chromatography (TLC), high performance liquid chromatography (HPLC), ultra performance liquid chromatography (UPLC), high performance thin layer chromatography (HPTLC), liquid chromatography coupled to tandem mass spectrometry (LC-MS) and capillary electrophoresis (CE), other methods such as spectrophotometry, diffuse reflectance near infrared spectroscopy and electrochemical methods.

Physicochemical Properties

Valsartan is N-(1-oxopentyl)-N-[[2-(1H-tetrazol-5- yl) [1, 1-biphenyl]-4-yl] methyl]-l-valine [14]. It is a white powder with empirical formula $C_{24}H_{29}N_5O_3$ and molecular weight 435.52g/mol. It is synthesized from L-valine methyl ester hydrochloride. Key step involves palladium catalysed Suzuki coupling. Melting range of 105-110 °C and specific rotation [α]D/20 in methanol is 68° and partition coefficient of Valsartan is 0.033 (logP=1.499) indicating that the compound has a rather hydrophilic characteristic at physiological pH. Due to its fine particle size, Valsartan absorbs water reversibly from ambient atmosphere. The compound is stable when stored under dry conditions [2]. For ionizable molecules, pH plays a crucial role. The charge state that a molecule exhibit at particular pH is characterized by ionization constant pKa of the molecules. Buffer affects pH gradients weakly acidic and weakly basic drug exhibit pH dependent solubility. Valsartan is a tetrazole derivative that contains two weakly acidic function groups (acid and carboxylic acid) with pKa value of 4.7 and 3.9. These groups making compound stable in the neutral pH range [3].

Determination Methods

Many analytical methods have been developed for the determination of Valsartan in pharmaceutical formulations and in biological fluids. Such as UV spectroscopy[13,19-23], HPLC[24-31], RP-HPLC[12,32-50], HPTLC[51-53], TLC[54], absorption ratio method[55,56] voltammetry[57] has been developed. Methods such as HPLC, Capillary electrophoresis and simultaneous UV spectroscopic methods of Valsartan are reported for estimation of Valsartan alone or in combination with other drugs. The advantages of UV- spectroscopic methods over HPLC is significantly shortening analysis time, low cost of analysis, widespread access to the apparatus, while the HPLC procedure is time consuming, require too many solvents and expensive apparatus. HPLC-MS/MS [58] and LCMS/ MS [59] methods have been developed for analysis of ACE inhibitors in plasma.

UV spectroscopic method

Absorbance ratio method, First order derivative spectrophotometric, Simultaneous equations method, continuous wavelet transform (CWT), Q-value analysis method, H-point standard additions method (HPSAM) and partial least squares (PLS) calibration methods were described for simultaneous determination of Valsartan.

Title	Method	Wavelength	Linearity and r^2	Recovery	Ref
Spectrophotometric method for the determination of Valsartan in bulk and pharmaceutical preparations	UV	720 nm	0.999	99.6-100.8	4
Spectroscopic method for the estimation of valsartan in pure and pharmaceutical dosage form	UV	250nm	0.9968	98.64%	5
Spectrofluorimetric method for the drug combination of Amlodipine with Valsartan	Conventional and Synchronous fluorescence spectroscopy	460nm and 385 nm 390nm and 227nm	0.9999 and 0.9998 0.9997 and 0.9997	100.16 and 99.95 % 99.5 and 99.7 %	6
Determination of valsartan and hydrochlorothiazide in tablets by UV Spectroscopy	absorption ratio method	270.5 nm and 231.5 nm	0.9997 and 0.9993	97.42-102.23%	7
Spectrophotometric method for the simultaneous estimation of Valsartan and Nifedipine	First derivative method	248.43 nm and 216.52 nm	0.9994 and 0.9963	99.50-100.50%	8
UV-spectrophotometric methods for simultaneous estimation of valsartan and hydrochlorothiazide	Simultaneous equations and absorbance ratio method	249.4 nm and 272.6 nm 258.4nm and 272.6nm	0.9998 and 0.9999	97.96% - 100.20%	9
simultaneous spcetroptometric determination of valsartan and Amlodipine	Wavelet transform (CWT) Method	258.5 and 263.3 265.7 and 270 nm	0.9999 and 0.9998	99.40% - 101.20%	10
Simultaneous UV spectrophotometric method for the estimation of amlodipine besylate, valsartan and hydrochlorothiazide	simultaneous equation, Q-analysis and area under curve method	359 nm, 317 nm and 250 nm	0.9999, 0.9999 and 0.9998	99.32–102.2%	11
Spectrophotometric method for simultaneous determination of Amlodipine and valsartan	zero order UV spectrophotometry Method	360.5 nm and 290 nm	0.9996 and 0.9997	99.15 – 100.90 %	12
Simultaneous estimation of Nebivolol hydrochloride valsartan and hydrochlorothiazide	simultaneous equation and Q-analysis method	270.4 nm, 280.2nm and 270 nm	0.9998, 0.9999 and 0.9998	99.0 – 101.2 %	`13
Spectrophotometric method for the simultaneous estimation of Valsartan and Ramipril	Second order derivative spectroscopy method	289.36 and 226.89 nm	0.9973 and 0.9987	98.10 – 99.25 %	14
Estimation of valsartan in pure and pharmaceutical formulation	UV-Method	250.80nm	0.9996	99.26% - 100.7%	15
Spectrophotometric method for estimation of Valsartan	UV-Method	250nm	0.9998	99.18- 99.77 %	16
Simultaneous determination of valsartan and hydrochlorothiazide	H-point standard additions method and partial least squares	216 and 228 nm	0.9981 and 0.9978	92.6 - 109.1 %	17

Chromatographic Methods:

HPLC methods were widely used chromatographic methods in the analysis of valsartan in Formulation. LC-MS/MS, LC-MS and UPLC use for estimation of valsartan in Plasma. HPTLC method also developed for determination of valsartan in pharmaceutical dosage form and plasma.

Title	Method	Mobile phase	Stationary phase	Wave length	Ref
Development and validation of HPLC method to determine valsartan in nanoparticles	HPLC	Ammonium formate and Acetonitrile (57:43v/v)	Phenomenex C18, 250 mm × 4.6 mm id, 5 µ	250 nm	`18
Determination of Valsartan for stability indicating studies	HPLC	Methanol and Phosphate buffer pH 3 (65:35v/v)	Microbondapak,C18, 25cm 4.6mm i.d, 5µm	210 nm	19
Simultaneous determination of Valsartan and Hydrochlorothiazide in Pharmaceutical Formulation	HPLC	Acetonitrile: Methanol: Phosphate buffer pH 3 (65:35v/v)	Phenomenex Luna C18, 150 mm × 4.6 mm i.d., 5 µ	250 nm	20
Comparative study on the degradation behavior of Valsartan and Losartan	HPLC	Acetonitrile: Phosphate buffer, pH 3.5, (60: 40 v/v)	ACEC18, 250 mm × 4.6 mm i.d, 5µ	225 nm	21
Simultaneous estimation of atenolol, hydrochlorothiazide, losartan and valsartan	HPLC	Phosphate buffer: Acetonitrile, pH 3.0, (50: 50 v/v)	Nucleodur100C18, 250 × 4.6 mm i.d., 5 µ	210 nm	22
Method Development for Quantification of Valsartan in Tablet Dosage Form	HPLC	Acetonitrile: Phosphate buffer, pH 3.5, (50: 50 v/v)	KromasilC-18, 250 × 4.6 mm i.d., 5µ	250 nm	23
Analysis of Valsartan in Pharmaceutical Dosage Forms	HPLC	Phosphate buffer: Acetonitrile, pH 3.0, (50: 50 v/v)	Xterra C18 100×4.6 mm i.d., 5 µ	210 nm	24
Determination of Valsartan in Tablet Dosage Form	HPLC	Water: Acetonitrile: glacial acetic acid (500:500:01).	Thermo-hypersil ODS 150 mm×4.6 mm i.d., 5 µ	273 nm	25
Analytical Method Development and Validation of Valsartan	HPLC	Methanol and phosphate buffer pH 2.5, (75:25 v/v)	Phenomenex C18 250×4.6 mm, 5µ	250 nm	26
Simultaneous Determination of Amlodipine, Valsartan, Telmisartan, Hydrochlorothiazide and Chlorthalidone	HPLC	0.05 M sodium dihydrogen phosphate buffer and Acetonitrile, Gradient mode	Cosmosil PAQ 150 mm × 4.6 mm i.d., 5 µ	220 nm	27
Estimation of Valsartan in Pure and Tablet Dosage Form	HPLC	Phosphate buffer and Acetonitrile (55:45 v/v)	Kromasil C18, 250 × 4.6 mm i.d., 5 µ	233 nm	28
Estimation of Valsartan in Bulk Drug	HPLC	Phosphate buffer: Acetonitrile, pH 3.0, (50: 50 v/v)	Acquity HSS Y- 3, 2.1× 100 mm i.d., 1.8 µ	205 nm	29
Determination of Hypertensive Drug Products	HPLC	Ammonium acetate buffer and Acetonitrile, Gradient mode	XTerra C18 150 × 4.6 mm i.d., 5 µ	230 nm	30
Estimation and Separation of Valsartan, Losartan and Irbesartan in Bulk and Pharmaceutical formulation	HPLC	Acetonitrile and Phosphate buffer (40:60 v/v)	Eurospher, C8 250 × 4.6 mm i.d., 5 µ	254 nm	31
Estimation of Valsartan in Solid Oral Dosage Forms	HPLC	Acetate buffer:Acetonitrile:methanol (38:24:38 %, v/v)	ODS C8 250 × 4.6 mm i.d., 5 µ	248 nm	32
Determination of valsartan in human volunteers and its application in bioequivalence study	HPLC	Phosphate buffer: Acetonitrile, pH 3.0, (50: 50 v/v)	Zorbax Extend-C18 150 × 4.6 mm i.d., 5 µ	230and 370 nm	33
Estimation of Valsartan in Pharmaceutical Dosage Forms	HPLC	Methanol: water: THF 60:35:05 (v/v/v).	Inertsil ODS C-18 250 × 4.6 mm i.d., 5 µ	269 nm	34
Stability Indicating Method for Simultaneous Estimation of Nebivolol HCL and Valsartan	HPLC	Acetonitrile, methanol and phosphate buffer (pH 4.0) (50:20:30 v/v)	Inertsil ODS C-18 150 × 4.6 mm i.d., 5 µ	210 nm	35
Simultaneous estimation of Aliskiren and Valsartan in Tablet Dosage Form	HPLC	Methanol, Phosphate buffer (pH 3.0) Acetonitrile, (50:20:30 v/v)	Lichrosphere C-18 150 × 4.6 mm i.d., 5 µ	271 nm	36
Stability-Indicating Method for the Simultaneous Determination of Valsartan and Ezetimibe	HPLC	Phosphate buffer: Acetonitrile, pH 3.15, (58: 42 v/v)	Symmetry C18, 250 × 4.6 mm i.d., 5 µ	230 nm	37
Stability Indicating Method for Quantification of Valsartan and hydrochlorothiazide	HPLC	Ammonium acetate buffer pH 5.6, and Acetonitrile, Gradient mode	XTerra C18 250 × 4.6 mm i.d., 5 µ	265 nm	58
Determination of triple drug combination of valsartan,	HPLC	Acetonitrile and ammonium formate, pH 3.5, Gradient	Gemini C18 250 × 4.6 mm i.d., 5 µ	254 nm	39

Amlodipine and hydrochlorothiazide in plasma		mode			
Simultaneous estimation of Nebivolol and Valsartan in Tablet Dosage Form	HPLC	Acetonitrile and Phosphate buffer (60:40 v/v)	Inertsil ODS C-18 250 × 4.6 mm i.d., 5 µ	278 nm	40
Stability-Indicating Method for the Determination of Aliskiren Hemifumarate and Valsartan	HPLC	Phosphate buffer and Methanol pH 3.0, (70 : 30 v/v)	Nucleosil ODS C-18 250 × 4.6 mm i.d., 5 µ	225 nm	41
Stability Indicating Method for Quantification of Impurities in Amlodipine and Valsartan	HPLC	Water, Acetonitrile and Methanol (70:20:10 v/v)	Zorbax SB C8 150 × 4.6 mm i.d., 3.5 µ	240 nm	42
Simultaneous Determination of Amlodipine, Valsartan, Hydrochlorothiazide in Dosage Form and Spiked Human Plasma	HPLC	Acetonitrile and Phosphate buffer pH 2.8 (40:60 v/v)	Phenomenex Kinetex 150 × 4.6 mm i.d., 5 µ	227 nm	43
Stability indicating Simultaneous Determination of Valsartan and Ramipril in binary combination	HPLC	Acetonitrile and Water(55:45 v/v)	Hypersil C-18 250 × 4.6 mm i.d., 5 µ	215 nm	44
Determination and validation of ketoprofen, pantoprazole and valsartan in human plasma	HPLC	Phosphate buffer and Acetonitrile pH 3.15, (58 : 42 v/v)	Kromasil C18 250 × 4.6 mm i.d., 5 µ	225 and 272nm.	45
Stability indicating method for the estimation of Valsartan	HPLC	Methanol and Phosphate buffer pH 3.0 (65:35 v/v)	Phenomenex C18 250 × 4.6 mm i.d., 5 µ	210 nm	46
Estimation of valsartan in bulk and tablet dosage forms	HPLC	Water, Acetonitrile and Glacial acetic acid (55:45:1 v/v)	XTerra C18 250 × 4.6 mm i.d., 5 µ	240 nm	47
Estimation of Valsartan in bulk formulation and human serum	HPLC	Acetonitrile and Phosphate buffer pH 3.0, (40 : 60 v/v)	Eurospher, C 18 250 × 4.6 mm i.d., 5 µ	254 nm	48
Inherent Stability of Valsartan by Stress Degradation and Its Validation	HPLC	Water and Acetonitrile (60:40 v/v)	Kromasil C18, 250 × 4.6 mm i.d., 5 µ	265 nm	49
Quantitative Determination of three Angiotensin-II-receptor Antagonists in Presence of Hydrochlorothiazide	HPLC	Phosphate buffer and Acetonitrile pH 6.0, (65 : 35 v/v)	Hypersil C-18 250 × 4.6 mm i.d., 5 µ	220 nm	50
Determination and validation of valsartan and its degradation products	HPLC	Methanol and Water pH 7.2 (60:40 v/v)	HIQ sil C18 ODS 250 × 4.6 mm i.d., 5 µ	250 nm	51
Simultaneous determination of Propranolol and valsartan in bulk drug and gel formulation	HPLC	Acetonitrile, Methanol and Phosphate buffer pH 3.5 (50 : 35 : 15 v/v)	Hypersil C-18 ODS 250 × 4.6 mm i.d., 5 µ	250 nm	52
Analysis of Some Antihypertensive Agents in their Pharmaceutical Dosage Forms	HPLC	0.2 % v/v Triethylamine buffer (pH 3.0) and Acetonitrile. Gradient mode	Purosphere Star 250 × 4.6 mm i.d., 5 µ	215 nm	53
Specific Stability Indicating method for Valsartan	HPLC	Phosphate buffer : Acetonitrile pH 2.5, (58 : 42 v/v)	Symmetry C18, 250 × 4.6 mm i.d., 5 µ	250 nm	54
Stability-Indicating Determination of Valsartan and Hydrochlorothiazide Using Quality by Design	HPLC	Water, Methanol and Acetonitrile (50:38:12 v/v)	Hypersil C-18 ODS 250 × 4.6 mm i.d., 5 µ	271 nm	55
Simultaneous Estimation of Nebivolol HCL and Valsartan in bulk and pharmaceutical dosage form	HPLC	Phosphate buffer and Acetonitrile pH 6.0, (52 : 48 v/v)	Altima C18, 150 × 4.6 mm i.d., 5 µ	282 nm	56
Simultaneous estimation of ramipril and valsartan in combined dosage form	HPLC	Phosphate buffer and Acetonitrile pH 3.2, (40 : 60 v/v)	Hypersil C18 250 × 4.6 mm i.d., 5 µ	25 nm	57
Simultaneous Estimation of Antihypertensive and Antidiabetic Drugs	HPLC	Acetic acid and Acetonitrile (60 : 40 v/v)	Phenomenex C18 250 × 4.6 mm i.d., 5 µ	240 nm	58
Improved analytical validation and pharmacokinetics of valsartan	HPLC	Acetonitrile and Phosphate buffer pH 2.0, (42 : 58 v/v)	Phenomenex C18 250 × 4.6 mm i.d., 5 µ	220 nm	59
Method Development of Aliskiren Hemifumarate and Valsartan in bulk drug	HPLC	Acetonitrile, Phosphate buffer and Methanol pH 4.0 (45 : 40 : 15 v/v)	Waters C18, 250 × 4.6 mm i.d., 5 µ	220 nm	60
Rapid determination of valsartan in human plasma by protein precipitation	HPLC	Acetonitrile and Phosphate buffer pH 2.0, (45 : 55 v/v)	Nucleosil C-18 120 × 4.6 mm i.d., 5 µ	234 nm	61

Determination of irbesartan and valsartan in human urine	HPLC	0.3 % Formic acid and Methanol (30:70 v/v)	C-18 120 × 4.6 mm i.d., 5 µ	236 nm	62
Determination of losartan, Telmisartan, and valsartan by direct injection of human urine	HPLC	Phosphate buffer, Acetonitrile and Methanol pH 3.8 (65 : 20 : 15 v/v)	LiChrocart 250 × 4.6 mm i.d., 5 µ	259 and 399nm	63
Determination of Amlodipine, Hydrochlorothiazide and Valsartan	HPLC	Phosphate buffer pH 5.5 and methanol (38 : 62 v/v)	Waters C18, 250 × 4.6 mm i.d., 5 µ	234 nm	64
Monitoring of Impurity Level of Valsartan and Hydrochlorothiazide	HPLC	Acetonitrile and Water pH 2.5 Gradient mode	Hypersil – ODS 250 × 4.6 mm i.d., 5 µ	256 nm	65
Simultaneous determination of valsartan and hydrochlorothiazide	LC	Phosphate buffer, Acetonitrile pH 3.2 (55 : 45 v/v)	Symmetry C18, 250 × 4.6 mm i.d., 5 µ	225 nm	66
Quantitative Estimation of Valsartan in Bulk and Dosage Forms	HPLC	Phosphate buffer, Acetonitrile (20 : 80 v/v)	Venusil XBP C-18 250 × 4.6 mm i.d., 5 µ	273 nm	67
Stability Indicating Method for Determination of Valsartan in Pure and Pharmaceutical Formulation	HPLC	Phosphate buffer and Methanol pH 3.5 (50 : 50 v/v)	Phenomenex Gemini C18 250 × 4.6 mm i.d., 5 µ	210 nm	68
Concurrent Estimation of Amlodipine Besylate, Hydrochlorothiazide and Valsartan	HPLC	Acetonitrile and Water (50 : 50 v/v)	Kromasil KR-5 C18 250 × 4.6mm i.d., 5 µ	232 nm	69
Determination of Valsartan, Amlodipine Besylate, and Hydrochlorothiazide	UPLC	Methanol : Phosphate buffer pH 3.0 (70:30 v/v)	Acquity RP18 100 mm × 2.1 mm i.d.,1.7 µ	239 nm	70
Simultaneous Determination of Valsartan & Hydrochlorothiazide in Drug Products	UPLC	Triethylamine buffer : Methanol (75:25 v/v)	Kromasil eternity C-18 50 mm×2.1 mm i.d.,3.5 µ	225 nm	71
Determination of Valsartan and their degradation products in pharmaceutical dosage forms	UPLC	Acetic acid : Acetonitrile Gradient mode	Waters Acquity C18 100mm×2.1mm i.d.,1.7 µ	225 nm	72
Quantitative Analysis Of Valsartan And hydrochlorothiazide	HPTLC	Chloroform, ethyl acetate and acetic acid, 5:5:0.2 (v/v)	Aluminium plates precoated silica gel 60F254	248 nm	73
Concurrent Estimation of Amlodipine Besylate, Hydrochlorothiazide and Valsartan	HPTLC	Ethyl acetate, Methanol, Toluene and ammonia (7.5:3:2:0.8, v/v/v/v)	Aluminium plates precoated silica gel 60F254	242 nm	69
Simultaneous Estimation Of Cilnidipine And Valsartan In Bulk And Tablet Dosage Form	HPTLC	Toluene: Methanol: Ethyl acetate: Glacial Acetic acid in the ratio 8:1:1:0.1 (v/v/v/v)	Aluminium plates precoated silica gel 60F254	240 nm	74
Simultaneous Estimation of Ramipril and Valsartan	HPTLC	Chloroform: ethyl acetate: methanol: glacial acetic acid (5.0:5.0:1.0:02 v/v/v/v).	Aluminium plates precoated silica gel 60 F254	210 nm	75
Simultaneous Estimation of Ramipril & Valsartan in Tablets by	HPTLC	Ethyl acetate: chloroform: glacial acetic acid, (8:2:0.2, v/v)	Aluminium plates precoated silica gel 60 F254	220 nm	76
Analysis of angiotensin II receptor antagonist and protein markers	LC-MS-MS	Acetonitrile : Formic acid (45 : 55 v/v)	RP C18 nano-flow column 150 µ inner diameter 375 µ outer diameter 3 µ	-	77
Simultaneous Estimation of Amlodipine and Valsartan in Human Plasma	LC-MS-MS	Acetonitrile : Ammonium formate (80 : 20 v/v)	Luna C18 100A 150 x 4.6 mm, 5 µ	--	78
Simultaneous quantification of valsartan and hydrochlorothiazide in human plasma	LC-MS-MS	Acetonitrile : Ammonium Acetate pH 4.5 (60 : 40 v/v)	Zorbax SB-Aq C18 150 x 4.6 mm, 5 µ	--	79
Bio- analytical method development of Valsartan by precipitation method	HPLC-MS/MS	0.1% formic acid and Methanol (25:75, v/v)	Hypurity C18 150 × 4.6 mm i.d., 5 µ	-	80
Optimization and validation of bioanalytical method for estimation of Valsartan in rat plasma	HPLC- ESI-MS-MS	0.1 % Formic acid and Methanol (25:75 v/v)	Ascentis Express C-18 50 × 4.6 mm i.d., 2.7 µ	-	81

CONCLUSION

In conclusion, a broad range of techniques are available for the analysis of valsartan in biological samples and pharmaceutical formulations. The analysis of the published data revealed that the HPLC methods were extensively used for the determination of valsartan in various matrices like plasma, serum and urine. For determination of valsartan in biological samples, were commend the HPLC–MS/MS method, since this method combines the HPLC separation ability with MS sensitivity and selectivity, allowing the unambiguous identification of valsartan and its metabolites. For analysis of valsartan in pharmaceuticals, HPLC with UV detection is applicable because this method provides accurate results and low cost compared to more advanced detection techniques. This review carried out an overview of the current state-of-art analytical methods for the determination of valsartan.

The review would help analytical chemists in knowing the key solvents and their combinations for their available set of instruments in the analytical laboratory. The effective combination of parameters should minimize the cost of the analysis and reduce the time required for producing are liable analytical method. The methods are also useful for determining parameters for in-process evaluation during the manufacturing of API.

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