Review Article

A Review on Analytical Methods of Antigout Agents

Abstract

The aim of this study was to provide information of the development in analytical perspective of impurity profiling, force degradation, and bioanalysis of pharmaceutical drug substance and drug products used for the treatment of gout. This information was discussed on the basis of year of publication, matrix (active pharmaceutical ingredient, dosage form, and biological fluid), sample preparation technique, column and types of elution in chromatography (isocratic or gradient), detector, and therapeutic categories of drug, which were used for analysis. It focuses mainly on analytical methods including hyphenated techniques for the identification and quantification of impurity, degradants, and metabolites in different pharmaceutical and biological matrices.

Keywords: *Bioanalysis and antigout drug, forced degradation study, impurity profiling*

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Introduction

Development of analytical methods and validation play an important role in the drug discovery, development, and manufacturing of pharmaceuticals. The number of drugs introduced into the market may be either new entities or partial structure modification of the existing one. There is a time lag from the date of introduction of a drug into the market to the date of its inclusion in pharmacopoeias due to possible unpredictability in the continuous and wider uses of such drugs, reports of new toxicities (resulting in their withdrawal from the market), development of patient resistance, and introduction of better drugs by competitors. Under such conditions, standard and analytical procedure of such drugs may not be available in the pharmacopoeias. Therefore, there is a scope to develop newer analytical methods for such drug. The choice of analytical methodology is based on many considerations such as chemical properties of the analyte and its concentration, sample matrix, the speed and cost of analysis, type of measurement, that is, quantitative or qualitative, and the number of samples. Analytical methods are used to perform identification tests, potency of assays, quantitative tests for impurities, limit test for the control of impurities, specific test (particle size analysis, X-ray diffraction, etc.), and quantitative determination of drugs and metabolites in biological matrices such as blood, serum, plasma, urine, and tissues.[1]

Analytical methods are intended to establish the identity, purity, physical characteristic, and potency of the drugs that we use. Methods may also support safety and characterization studies or evaluation of drug performance. Safety and efficacy of pharmaceutical product are fundamental aspects in drug therapy and these are dependent not only on the intrinsic toxicological properties of active ingredient but also on the impurities and degradation product that it may contain. The impurity profile of drug is an important in case of manufacturing of high purity drug. The degradation products may be provided through forced degradation studies, which provides information about possible degradation routes, evaluation of the factors that may interfere in the drug stability and critical analysis of the drug degradation profile. Bioanalysis is also an essential part in toxicological evaluation, pharmacokinetic (PK) and pharmacodynamic (PD) studies during drug development.[2]

Impurity profile

Impurity is any component of the new drug substance that is not the chemical entity, which is defined as the new drug substance, and impurity profile is a description of the identified and unidentified impurities present in new drug substance.[3-9] Various terms that have been commonly used to describe impurities are as follows:

- By-product
- Degradation product

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- Interaction product
- Intermediate
- Penultimate intermediate
- Related product
- Transformation product

Classification of impurities

1. Organic impurities: They arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or nonvolatile, and include the following:
   - Starting materials
   - By-products
   - Intermediates
   - Degradation products
   - Reagents, ligands and catalysts
2. Inorganic impurities: They can result from the manufacturing process. They are normally known and identified and include the following:
   - Reagents, ligands, and catalysts
   - Heavy metals or other residual metals
   - Inorganic salts
   - Other materials (e.g., filter aids and charcoal)
3. Residual solvents: They are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of new drug substance. As these are generally of known toxicity, the selection of appropriate controls is easily accomplished.

Elemental impurity

Elemental impurities[7] in drug products may arise from several sources; they may be residual catalysts that were added intentionally in synthesis or may be present as impurities (e.g., through interactions with processing equipment or container/closure systems or by being present in components of the drug product). Because elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits.

Classification of elemental impurity is as following:

Class 1: As, Cd, Hg, and Pb
Class 2A: Co, Ni, and V
Class 2B: Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se, and Tl
Class 3: Ba, Cr, Cu, Li, Mo, Sb, and Sn
Other: Al, B, Ca, Fe, K, Mg, Mn, Na, W, and Zn

International Conference on Harmonization guidelines

- Q1A (R) Stability testing of new drug substance and products
- Q3A (R) Impurities in drug substance
- Q3B Impurities in drug product
- Q3C Impurities: residual solvent
- Q3D Elemental impurities
- Q6A Specification

According to International Conference on Harmonization (ICH) guidelines on impurities in new drug products, identification of impurities below 0.1% level is not considered to be necessary, unless potential impurities are expected to be unusually potent or toxic [Table 1] [Figure 1].

Forced degradation study

Forced degradation studies[10-14] are used to facilitate the development of analytical methodology, to gain a better

Table 1: Thresholds according to International Conference on Harmonization Q3A (R2)

Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
≤2 g/day	0.05%	0.10% or 1 mg per day intake (whichever is lower)	0.15% or 1 mg per day intake (whichever is lower)
>2 g/day	0.03%	0.05%	0.05%

Thresholds for degradation products in new drug products

Reporting thresholds

Maximum daily dose	Threshold
≤1 g	0.1%
>1 g	0.05%

Identification thresholds

Maximum daily dose	Threshold
<1 mg	1.0% or 5 µg TDI, whichever is lower
1–10 mg	0.5% or 20 µg TDI, whichever is lower
>10–2 mg	0.2% or 2 mg TDI, whichever is lower
>2 g	0.10%

Qualification thresholds

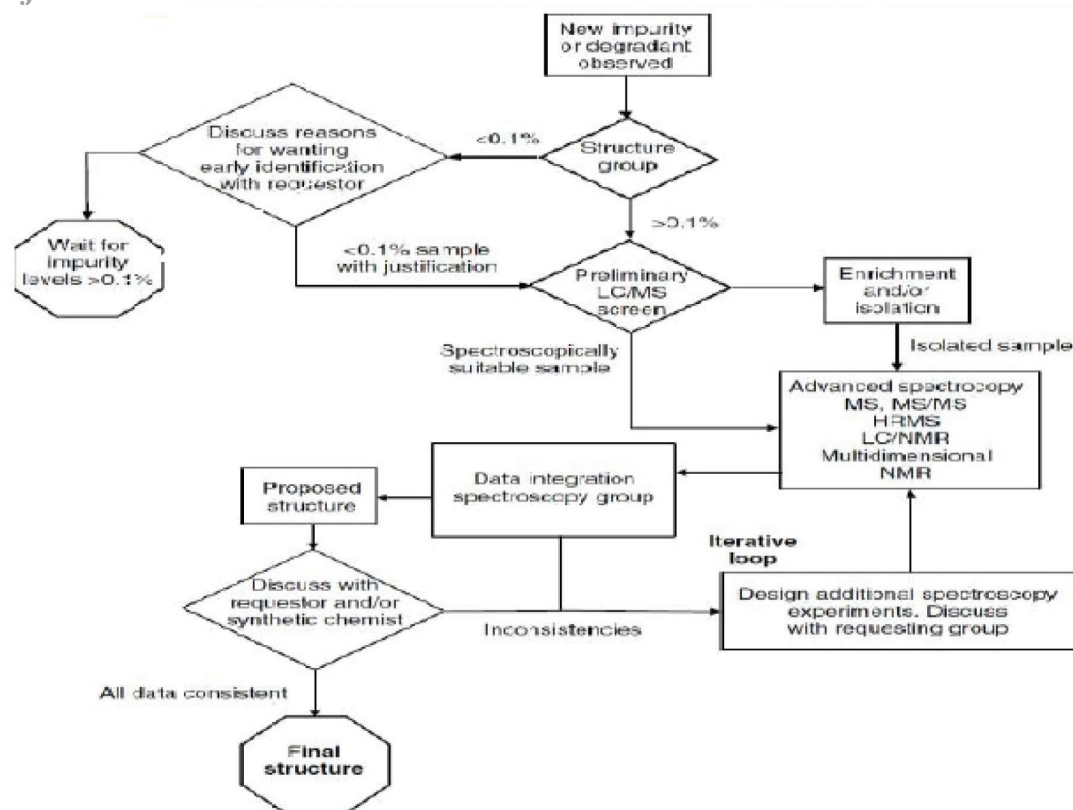| Maximum daily dose	Threshold
<10 mg	1.0% or 50 µg TDI, whichever is lower
10–100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg–2 g	0.2% or 3 mg TDI, whichever is lower
>2 g	0.15%

TDI = Therapeutic drug impurity

Figure 1: Schematic representation of scheme for impurity profiling of drugs[6]

understanding of drug substance and drug product stability, and to determine degradation pathways and degradation products. This study will help to generate the most stable formulation. The stability of drug product and drug substance is a critical parameter, which may affect purity, potency, and safety. Changes in drug stability can risk patient safety by formation of toxic degradation product or products or deliver lower dose than expected. Forced degradation study chart is shown in Figure 2. The ICH addresses the questions relating to stability as follows:

Q1A (R2): Stability testing of new drug substances and products
Q1B: Photostability testing of new drug substances and products
Q1C: Stability testing for new dosage form
Q1D: Bracketing and matrixing designs for stability testing of new drug substances and products
Q1E: Evaluation for stability data

Bioanalysis

Bioanalysis[16,17] is covering the identification and quantification of analytes in biological samples (blood, plasma, serum, saliva, urine, feces, hair, and organ tissue). Bioanalysis has an important role to perform toxicokinetic (TK), PK, and PD studies of new drugs. Bioanalytical method development is one of the bottlenecks for drug development, and validation is crucial for the quantitative determination of various types of

analytes in biological matrices. Bioanalysis is also established in clinical, preclinical, and forensic toxicology laboratories. It is an important discipline in many research areas such as development of new drug, forensic analysis, doping control, and identification of biomarker for the diagnosis of many diseases.

The bioanalysis procedure includes sampling, sample preparation, analysis, calibration, and data evaluation. Sample preparation has an important role in bioanalysis to get clean extract with high extraction efficiency. Regularly used sample preparation methods are protein precipitation, liquid–liquid extraction (LLE), solid phase extraction (SPE), supercritical fluid extraction, and matrix solid phase extraction (MSPE). Microextraction techniques are also there and these are solid phase microextraction (SPME), stir bar sorptive extraction (SBSE), and microextraction by packed sorbent. After sample preparation, separation and detection are performed with the help of different analytical techniques.

Gout

Gout is a common metabolic disorder caused by high uric acid levels and marked by episodic deposition of uric acid crystal in joints and other tissues such as the kidney. Gout affects around 1%–2% of the Western population at some point in their lifetime and is becoming more common. Some 5.8 million people were affected in 2013. Rates of gout approximately doubled between 1990 and 2010. This rise is believed to be due to increasing life expectancy, changes in diet, and an
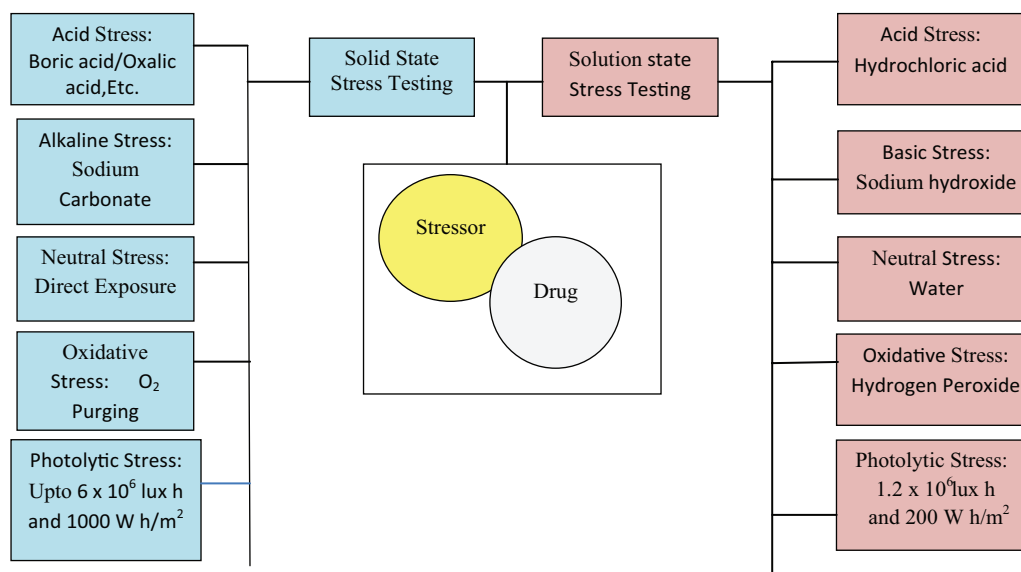
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Figure 2: Forced degradation study[15]

increase in diseases associated with gout such as metabolic syndrome and high blood pressure. These antigout agents have some major side effects such as headaches, dizziness, rashes, aggravation of asthma, heart and kidney problem, and increased blood pressure. These side effects are associated with drug substance, but these may be due to the presence of impurities or degradants.[18] Force degradation study provides very valuable information with respect to the stability of drug formulations during their life cycle.[15] So to avoid such side effects and to maintain quality and purity of both drug substance and drug product, impurity profiling, force degradation, and bioanalysis study of antigout drug are important and it was discussed and summarized in Tables 2 and 3.

Category-wise analytical perspectives of antigout drug

Various drugs from different classes of antigout drugs were studied for impurity profiling, force degradation, and bioanalysis. The study was based on the following analytical perspectives:

- Categories: Antigout drugs fall into variety of categories such as nonsteroidal anti-inflammatory drug (NSAID), steroids, microtubule inhibitor, uricosuric drug, and uric acid synthesis inhibitor. Impurity profile, force degradation study, and bioanalysis study are carried out on the drug belonging to these categories [Figure 3].
- Matrix: Maximum work is carried out on active pharmaceutical ingredient (API) followed by tablet and capsule. Other dosage forms such as suppository, ophthalmic, and topical preparation are used for impurity profiling and force degradation study [Figure 4].

For bioanalysis study, different species are used as shown in Figure 5. Plasma is widely used in bioanalytical method development. Other biological fluids such as urine, serum, aqueous humor, saliva, synovial fluid, and bile are also used [Figure 6].

- Column: Columns are one of the most important parts of chromatographic technique where separation of analyte is performed. Column dimensions, chemistry of column, nature of stationary phase filled in column, and particle size of stationary phase are important parameters for the separation of different components from a mixture. C_{18} columns are widely used column, whereas other C8, phenyl, cyano, and silica are used wherever they are suitable [Figure 7].
- Types of elution: Isocratic elution has used in greater amount as compared to isocratic elution [Figure 8].
- Detectors: Ultraviolet (UV) and mass detector are widely used. Photo diode array (PDA) and fluorescence detector are less used [Figure 9].

Force Degradation and Impurity Study

Acute gout

Nonsteroidal anti-inflammatory drug

Naproxen: Maher *et al.*[19] developed a simple and sensitive stability indicating HPLC-DAD method for determination of Diflunisal and naproxen. The response surface of diflunisal (DFL) and naproxen (NAP) was constructed by the artificial neural network model. No degradation was observed under the thermal conditions.

Habib *et al.*[20] developed two chromatographic methods for the determination of DFL and NAP in their binary mixture and in the presence of DFL toxic impurity, biphenyl-4-ol. First method was thin layer chromatography-densitometry and second was HPLC-DAD method. They were statistically compared with the reported method using Student's *t*-test and *f*-test; no significant difference was obtained.

Reddy *et al.*[21] reported a simple, rapid, gradient reverse-phase ultra-performance liquid chromatography (RP-UPLC)

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Table 2: Representative chromatographic analytical methods of impurity and forced degradation profiling of antigout drugs

Sr. no.	Name of drug	API/dosage form	Impurity/degradant	Stationary phase	Mobile phase	Detection	Year
I. Acute gout							
A. NSAID							
1	Naproxen						
	(i) Maher	Tablet		Eclipse XDB ss C18 (150 × 4.6 mm, 5 µm)	0.05 M sodium dihydrogen phosphate (pH 3.4):ACN (50:50 vol/vol)	DAD	2013
	(ii) Habib *et al.*	Tablet	1 Impurity	Zorbax Eclipse C18 (250 × 4.6 mm, 5 µm)	Methanol:water (pH 4 with OPA) (55:45 vol/vol)	DAD	2015
	(iii) Reddy *et al.*	Soft gelatin capsule	7 Impurities	Acquity BEH C18 column (100 × 2.1 mm, 1.7 µm)	0.1% OPA (pH 3):ACN (gradient)	UV 230 nm	2016
	(iv) Marwa *et al.*	Tablet	Naproxen-related impurity 1	Kromasil CelluCoat chiral column	Hexane:isopropanol:TFA (90:9:0.1 vol/vol/vol)	DAD	2017
2	Indomethacin						
	(i) Kwong *et al.*	Capsule suppository	2 Impurities in capsule and 2 impurities in suppository	C18 column (4.6 mm × 25 cm, 5 µm)	Methanol:water:acetonitrile:acetic acid (55:35:10:1 vol/vol/vol)	UV 234 nm	1981
	(ii) Nováková *et al.*	Gel	2 Degradants	Zorbax phenyl analytical column (75 × 4.6 mm, 3.5 µm) and Zorbax SB-CN (150 × 4.6 mm, 5 µm)	Acetonitrile:0.2% phosphoric acid (50:50 vol/vol)	UV 237 nm	2004
	(iii) Temussi *et al.*	API	7 Photoproducts	Sinergy Hydro RP 18 (250 × 4.6 mm, 4 µm)	Solvent A, Milli-Q water / Solvent B, Methanol:ACN (1:1 vol/vol)	PDA	2011
	(iv) Haq *et al.*	API	6 Degradants	Lichrosphere RP C18 (250 × 4.0 mm, 5 µm)	Ethyl acetate (100%)	UV 318 nm	2013
3	Piroxicam						
	(i) Bartsch *et al.*	API		Lichrosphere RP C18 (119 × 3 mm, 5 µm)	Methanol:0.4 M acetate buffer (pH 4.3) (45:55 vol/vol)	DAD	1999
4	Diclofenac						
	(i) Hajkova *et al.*	Topical emulgel	1 Degradant	SUPELCO C18 (125 × 4 mm, 5 µm)	Methanol:phosphate buffer (pH 2.5) (80:20 vol/vol)	UV 245 nm	2002
	(ii) Galmier *et al.*	Ophthalmic solution	3 Degradants	Kromasil C18 (5 µm)	Methanol:0.1% aqueous formic acid (pH 2.5) (80:20 vol/vol)	UV 254 nm	2005
5	Sulindac						
	(i) Krier *et al.*	API	3 Impurities	Alltima silica column (250 × 4.6 mm, 10 µm)	Acetic acid:ethanol:ethyl acetate:chloroform (1:4:100:400 vol/vol/vol/vol)	DAD 280 nm	2010

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Table 2: Continued

Sr. no.	Name of drug	API/dosage form	Impurity/degradant	Stationary phase	Mobile phase	Detection	Year
B. Steroids							
6	Corticosteroids						
	(i) Hymer	API	3 Impurities	Hypersil ODS (250 × 4.6 mm, 5 µm)	Solvent A, acetonitrile:water (15:85 vol/vol) Solvent B, acetonitrile:water (50:50 vol/vol) (gradient)	UV 245 nm	2004
	(ii) Lu *et al.*	API	32 Potential impurities	ACE C18 (150 × 4.6 mm, 3 µm)	Water:acetonitrile:acetic acid (70:30:1 vol/vol/vol)	DAD 254 nm	2010
7	Prednisolone						
	(i) Marley *et al.*	Ophthalmic suspension	8 Impurities	Agilent Poroshell C18 (100 × 4.6 mm, 2.7 µm)	Solvent A, acetonitrile:water (10:90 vol/vol) Solvent B, acetonitrile (gradient)	UV 254 nm	2014
8	Triamcinolone						
	(i) Matysovà *et al.*	Topical cream	1 Impurity	SUPELCO C18 (125 × 4 mm, 5 µm)	Acetonitrile:water (40:60 vol/vol)	240 nm	2003
II. Chronic gout							
A. Uric acid synthesis inhibitor							
9	Febuxostat						
	(i) Kadivar *et al.*	API	4 Impurities	Kromacil C18 (150 × 4.6 mm, 5 µm)	Solvent A, 0.01 M aqueous ammonium acetate (pH 3.5):trifluroacetic acid Solvent B, acetonitrile (gradient)	ESI–MS	2011

ACN = Acetonitrile; OPN = Ortho phosphoric acid

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141

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Table 3: Analytical methods of bioanalysis of antigout drugs

Sr. no.	Analyte	Matrix (species)	Stationary phase	Mobile phase	Detector	Year
I. Acute gout						
A. NSAID						
1	Naproxen					
	(i) Loenhout *et al.*	Plasma and urine (human)	Lichrosorb RP C8	Methanol:citrate buffer (pH 6.5) (50:50 vol/vol for plasma and 40:60 for urine). Flow rate 1.5 mL/min	UV 254nm, FLU Ex = 235 nm, Em = 350 nm	1982
	(ii) Wanwimolruk	Plasma (human)	Hypersil C18 (100 × 2 mm, 5 µm)	ACN:10mM phosphate buffer (pH 2.5) (40:60 vol/vol)	FLU Ex = 225 nm Em = 350 nm	2006
	(iii) Karidas *et al.*	Plasma and urine (human)	Spherisorb C18 (250 × 4.5 mm, 5 µm)	ACN: 0.1 m sodium acetate (pH 6.4 by glacial acetic acid) (35:15 vol/vol), flow rate 2.2 mL/min	UV 278 nm	2006
	(iv) Mikami *et al.*	Urine (human)	Wakosil C18 (150 × 4.6 mm, 5 µm)	ACN:water:triethylamine (pH 3 adjusted by phosphoric acid) (500:500:1 vol/vol/vol)	UV nm FLU Ex = 280 nm Em = 350 nm	2000
	(v) Elsinghorst *et al.*	Plasma (human)	Betasil C18 (50 × 4.6 mm, 5 µm)	0.02 M ammonium acetate buffer (pH 4):ACN (30:70 vol/vol) flow rate 1 mL/min	ESI–QqQ	2011
	(vi) Patel	Plasma (human)	Acquity BEH C18 (50 × 2.1 mm, 1.7 µm)	Methanol:acetonitrile:4.0 mM ammonium acetate	ESI–MS	2012
	(vii) Ahmadi and Bapirzadeh	Plasma (human)	Eurospher C18 (250 × 4 mm, 5 µm)	ACN:0.05 M phosphate buffer (pH 2.6) (65:35 vol/vol), flow rate 1 mL/min	UV 230 nm	2013
	(viii) Shi *et al.*	Plasma (rat)	Synergi fusion RP C18 (50 × 3 mm, 4 µm)	0.1% Formic acid aqueous solution:methanol (28:72 vol/vol), flow rate 0.5 mL/min	ESI–MS	2014
2	Indomethacin					
	(i) Terweij-Groen *et al.*	Serum and urine	Zorbaxx ODS (250 × 4.6 mm, 5 µm)	Ethanol:*n*-butanol:aqueous buffer (gradient)	UV 235 nm	1979
	(ii) Bernstein and Evans	Urine and plasma	C18 column (25 cm × 4.6 mm, 10 µm)	ACN:acetic acid (flow rate 1.5 mL/min for urine sample and 2 mL/min for plasma sample)	UV 285 nm FLU Ex = 288 nm Em = 390 nm	1981
	(iii) Shimek *et al.*	Plasma (human)	Zorbax ODS (25 cm × 4.6 mm)	Methanol:acetate buffer (gradient)	UV 254 nm	1982
	(iv) Greizerstein and Mclaughlin	Blood (rat)	Bondapak C18 (30 cm × 4 mm)	Methanol in water 66% vol/vol Flow rate 2 mL/min	UV	1982
	(v) Smith and Benet	Urine (human)	RP C8 (150 × 4 mm, 5 µm)	ACN:0.025 M sodium acetate (pH 4) (22:78 vol/vol) flow rate 2 mL/min	UV 254 nm FLU Ex = 305 nm Em = 370 nm	1983
	(vi) De Zeeuw *et al.*	Renal PST (rabbit)	µBondapak C18 (30 cm × 2 mm, 10 µm)	Methanol:water (52:48 vol/vol)	UV 254 nm FLU Ex = 295 nm Em = 376 nm	1986
	(vii) Sauvaire *et al.*	Plasma (Wistar rat and Beagle dogs)	Bondapak C18 (10 cm × 8 mm, 10 µm)	ACN:0.01 M acetic acid in water (70:30 vol/vol) flow rate 1.5 mL/min	UV 250 nm	1986

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Table 3: Continued

Sr. no.	Analyte	Matrix (species)	Stationary phase	Mobile phase	Detector	Year
	(viii) Stubbs *et al.*	Urine and plasma (human)	Sepralyte C18 (5 cm × 4.6 mm, 3 μm)	0.05 M Ammonium dihydrogen phosphate (pH 3.5 by 0.01 M phosphoric acid):methanol (42:58 vol/vol)	UV FLU Ex = 295 nm Em = 372 nm	1986
	(ix) Brown *et al.*	Serum (human)	Nova Radial-Pak C18 RP column	ACN:water:acetic acid (54.2:45.2:0.6)	UV detected 254 nm	1988
	(x) Kim *et al.*	Serum (Beagle dog)	RP-NOVA-PAK C18 (3.9 mm i.d. × 150 mm)	0.5 M Acetate buffer (pH 4):methanol (7:3 vol/vol)	FLU Ex = 278 nm Em = 358 nm	1988
	(xi) Avgerinos and Malamataris	Plasma and urine (human)	Spherisorb (25 cm × 45 mm, 5 μm)	ACN:0.1 M sodium acetate (35:65 vol/vol) flow rate 2.5 mL/min	UV 258 nm	1989
	(xii) Hubert *et al.*	Plasma	LichroCART C18 (125 × 4 mm)	Methanol:phosphate buffer (pH 7.4) (60:40 vol/vol) flow rate 0.7 mL/min	UV 254 nm	1989
	(xiii) Mawatari *et al.*	Serum (human)	Unisil C18 (150 × 4.6 mm, 5 μm)	0.07 M phosphate buffer (pH 6.6):ACN (65:35) flow rate 1 mL/min	FLU Ex = 358 nm Em = 462 nm	1989
	(xiv) Singh *et al.*	Plasma and urine (horse)	Supelcosil C8 (7.5 cm × 4.6 mm, 3 μm)	Phosphoric acid:ACN (55:45 vol/vol) flow rate 1 mL/min	DAD FLU Ex = 235 nm Em = 405 nm	1991
	(xv) Caturla and Cusido	Plasma (human and race horse)	Ultrasphere ODS (150 × 4.6 mm, 5 μm)	0.02 M ammonium sulfate:ACN (45:55 vol/vol)	UV 340 nm	1992
	(xvi) Kubo *et al.*	Serum	Inertsil ODS (150 × 4.6 mm, 5 μm)	30 mM H$_2$O$_2$	FLU Ex = 358 nm Em = 462 nm	1993
	(xvii) Vree *et al.*	Plasma and urine (human)	Spherisorb ODS (250 × 4.6 mm, 5 μm)	ACN:phosphoric acid (gradient)	UV 254 nm	1993
	(xviii) Niopas and Manzoridi	Plasma (human)	Vydacss analytical column (250 × 4.6 mm, 5 μm)	10 mM phosphoric acid:ACN (40:60 vol/vol) flow rate 0.9 mL/min	UV 280 nm	1994
	(xix) Sato *et al.*	Plasma (human)	Lichrosorb RP 18 (250 × 4, 7 μm)	6 mM phosphoric acid:ACN (50:50 vol/vol) flow rate 2 mL/min	UV 205 nm	1996
	(xx) Liu *et al.*	Plasma (rat)	Zorbax Eclipse C18 (250 × 4.6 mm)	Methanol:0.1% phosphoric acid (70:30 vol/vol) flow rate 1 mL/min	UV 254 nm	2001
	(xxi) Dawidowicz *et al.*	Plasma (human)	Prodigy C18 (150 × 4.6 mm, 5 μm)	ACN:water (63:37 vol/vol) flow rate 0.8 mL/min	UV	2009
	(xxii) Michail and Moneeb	Urine (human)	Zorbax C8 (250 × 4.6 mm, 5 μm)	10 mM Acetate buffer (pH 4):methanol (60:40 vol/vol) flow rate 1.5 mL/min	DAD	2011
	(xxiii) Liu *et al.*	Plasma, urine, and tissue (rabbit)	Diamonsil C18 (150 × 4.6 mm, 5 μm)	Methanol:ACN:water:formic acid (45:45:10:0.5 vol/vol/ vol/vol)	ESI–QqQ	2011
	(xxiv) Wang *et al.*	Plasma and urine (human)	Symmetry C18 (150 × 4.6 mm, 5 μm)	0.05% Formic acid aqueous solution:ACN (47:53 vol/ vol) flow rate 1 mL/min	ESI–MS	2013
3	Piroxicam					
	(i) Twomey *et al.*	Plasma (human)	Bondpack cyano column (300 × 3.9 mm, 10 μm)	ACN:water:acetic acid (25:70:5 vol/vol/vol) flow rate 1.2 mL/min	UV 365 nm	1980
	(ii) Dixon *et al.*	Plasma (human)	Lichrosorb RP C18 (150 × 3.2 mm, 5 μm)	ACN:water:0.1 M phosphate buffer (pH 5) (30:30:40 vol/vol/vol)	UV 361 nm	1984

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143

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Table 3: Continued

Sr. no.	Analyte	Matrix (species)	Stationary phase	Mobile phase	Detector	Year
	(iii) Richardson and Ross	Plasma and urine (human)	For plasma: µBondpack CN column (15 cm × 3.9 mm, 10 µm), and for urine: µBondpack C18 (30 cm × 3.9 mm, 10 µm)	For plasma: 50 mM $Na_2H_2Pb_4$ in acetonitrile:water (25:75 vol/vol) (pH 3.2) For urine sample: 5 mM sodium sulfonate buffer:tetrahydrofuran:glacial acetic acid (54:45:1 vol/vol/vol) flow rate 1.5 mL/min for both	UV 365 nm	1986
	(iv) Macek and Vacha	Plasma (human)	Separon CN (15 cm × 3.3 mm, 5 µm)	0.05 M pot. dihydrogen phosphate (pH 2.2):methanol (65:35 vol/vol) flow rate 0.5 mL/min	UV 360 nm	1987
	(v) Boudinot and Ibrahim	Plasma (human)	Econosphere ODS (25 cm × 4.6 mm, 5 µm)	0.04 M Phosphate buffer (pH 8):methanol (60:40 vol/vol) flow rate 1.2 mL/min	UV	1988
	(vi) Milligan	Plasma, urine, and bile (human)	Techsil C10 CN column (20 cm × 3.9 mm, 10 µm)	Acetonitrile:water (pH 3.5) (22:78 vol/vol)	UV 365 nm	1991
	(vii) Cerretani *et al.*	Plasma, muscle, and skin (rat)	Novapak C18 (15 cm × 3.9 mm, 3 µm)	THF:water (45:55 vol/vol) flow rate 0.7 mL/min	UV 313 nm	1992
	(viii) Avgerinos *et al.*	Plasma and urine (human)	Spherisorb C18 (25 cm × 4.5 mm, 5 µm)	ACN:0.1 M sodium acetate (pH 3.3 by glacial acetic acid) (33:67 vol/vol) flow rate 2.5 mL/min	UV 330 nm	1995
	(ix) Edno *et al.*	Plasma (human)	Spherisorb ODS (250 × 4.6 mm, 5 µm)	0.04 M disodium hydrogen phosphate (pH 8 by OPA):methanol (60:40 vol/vol) flow rate 1 mL/min	UV 360 nm	1995
	(x) Maya *et al.*	Plasma (human)	Lichrospher (250 × 4 mm, 5 µm)	Methanol:water:acetic acid	UV 340 nm	1995
	(xi) Amanlou and Dehpour	Plasma (rat)	µBondapak ODS C18 (300 × 3.9 mm, 10 µm)	Methanol:phosphate buffer pH 2 (45:55), flow rate 1.5 mL/min	UV 361 nm	1997
	(xii) Yritia *et al.*	Plasma (human)	Kromasil C18 (150 × 4 mm, 5 µm)	ACN:phosphate buffer 20 mM (pH 3.1) (50:50 vol/vol), flow rate 1 mL/min	UV 360 nm	1999
	(xiii) Dadashzadeh *et al.*	Plasma (human)	Novapak C18 (25 cm × 4.6 mm, 4 µm)	0.1 M sodium acetate:ACN:triethylamine (pH 4 by glacial acetic acid) (61:39:0.05 vol/vol), flow rate 1.5 mL/min	UV 330 nm	2001
	(xiv) Ji *et al.*	Plasma (human)	Sunfire column (100 × 2.1 mm, 5 µm)	Methaol:15 M ammonium formate (pH 3) (60:40 vol/vol) flow rate 0.2 mL/min	ESI-MS	2005
	(xv) Dowling and Malone	Plasma (bovine)	Agilent Eclipse Plus C18 (50 × 3 mm, 1.8 µm)	0.001 M acetic acid in water:ACN (gradient)	ESI-MS	2011
	(xvi) Calvo *et al.*	Plasma and saliva (human)	LichroCART C18 (205 × 4.6 mm, 5 µm)	Methanol:2% phosphoric acid (pH 2.7) (70:30 vol/vol), flow rate 1 mL/min	ESI-MS	2015
4	Diclofenac					
	(i) Godbillon *et al.*	Plasma and urine	Lichrosorb RP 8 (25 cm × 4 mm, 10 µm)	Methanol:phosphate buffer (pH 7) (60:40 vol/vol), flow rate 1.3 mL/min	UV 278 nm	1985
	(ii) Sioufi *et al.*	Plasma (human)	Novapak C18 (15 cm × 3.9 mm, 4 µm)	Methanol:phosphate buffer (pH 7.2) (56:44 vol/vol) flow rate 0.4 mL/min	UV 282 nm	1991
	(iii) Moncrieff	Serum (human)	Spherisorb ODS (250 × 4.6 mm)	Methanol:(pH 6.2) sodium phosphate buffer (43:57 vol/vol), flow rate 2 mL/min	FLU Ex = 282 nm Em = 365 nm	1992
	(iv) Blagbrough and Daykin	Plasma and synovial fluid	Spherisorb ODS (125 × 4.6 mm, 5 µm)	Methanol:water (pH 3.3) (63:37 vol/vol), flow rate 1 mL/min	UV 280 nm	1992
	(v) Miller	Plasma (human)	Nucleosil C18 (15 cm × 4.6 mm, 10 µm)	Sodium acetate (pH 7.1):ACN:methanol (52:23:25 vol/vol/vol), flow rate 1.5 mL/min	UV 280 nm	1993

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Table 3: Continued

Sr. no.	Analyte	Matrix (species)	Stationary phase	Mobile phase	Detector	Year
(vi)	Avgerinos et al.	Plasma and urine (human)	Spherisorb RP C18 (25 cm × 4.5 mm, 5 μm)	ACN:0.1 M sodium acetate (pH 6.3) (35:65 vol/vol), flow rate 1 mL/min	UV 210 nm	1993
(vii)	Mohamed et al.	Plasma (Beagle dog)	Novapak C18 (150 × 3.9 mm)	ACN:water (pH 3.5 by glacial acetic acid) (50:50 vol/vol), flow rate 1.5 mL/min	UV 278 nm	1994
(viii)	Mason and Hobbs	Plasma (human)	Nucleosil C18 (25 cm × 4.6 mm, 5 μm)	ACN:water (pH 2.8 by OPA) (35:65 vol/vol), flow rate 1.5 mL/min	UV 280 nm	1995
(ix)	Li et al.	Plasma (human)	Spherisorb ODS (200 × 4.6 mm, 10 μm)	Methanol:sodium acetate buffer (pH 4.2) (68:32 vol/vol), flow rate 1.4 mL/min	UV 274 nm	1995
(x)	Kuhlmann et al.	Aqueous humor (human)	Regis SPS 100RP C8 (150 × 4.6 mm, 5 μm)	ACN:30 mM sodium acetate (pH 3 with phosphoric acid) (40:60 vol/vol or 50:50 vol/vol), flow rate 1.3 mL/min	Electrochemical detector	1997
(xi)	Giagoudakis and Markantonis	Plasma (human)	Spherisorb C18 (25 cm × 4.6 mm, 5 μm)	ACN: 0.1 M sodium acetate (pH 6.3) (35:65 vol/vol), flow rate 1 mL/min	UV 278 nm	1998
(xii)	Bakkali et al.	Urine (human)	Novapack C18 (15 cm × 3.9 mm, 4 μm)	10 mM acetate buffer (pH 4):ACN (58:42 vol/vol), flow rate 1 mL/min	UV 210 nm	1999
(xiii)	Lee et al.	Plasma (human)	Luno phenyl–hexyl column (100 × 2 mm, 3 μm)	ACN:0.02 M potassium phosphate (pH 7) (33:67 vol/vol), flow rate 0.2 mL/min	UV 278 nm	2000
(xiv)	Arcelloni et al.	Plasma (human)	RP C18 (250 × 4.6 mm, 5 μm)	25 mM dihydrogen potassium salt (pH 3.5):ACN (30:70 vol/vol), flow rate 1 mL/min	UV 280 nm	2001
(xv)	Liu and Tsai	Bile (rat)	Microbore RP C18 (150 × 1 mm, 5 μm)	100 mM sodium dihydrogen phosphate (pH 3.1):ACN (30:70 vol/vol), flow rate 0.05 mL/min	UV 280 nm	2002
(xvi)	Dorado et al.	Urine (human)	Hypersil ODS (250 × 4.6 mm, 5 μm)	ACN:methanol:THF:water (20:10:3:65 vol/vol/vol/vol), flow rate 0.8 mL/min	UV 282 nm	2003
(xvii)	Roskar and Kmetec	Synovial fluid (human)	Kromasil C18 (150 × 4.6 mm, 5 μm)	0.05 M KH_2PO_4 (pH 7 by NaOH):methanol:ACN (58:21:21 vol/vol/vol), flow rate 1 mL/min	UV 205 nm	2003
(xviii)	Malliou et al.	Urine (human)	Rosil C18 (150 × 4.6 mm, 5 μm) and Lichrosorb RP 18 (250 × 4.6 mm, 5 μm)	Ammonium acetate:methanol:ACN (40:30:30 vol/vol/vol), flow rate 0.6 mL/min	UV 258 nm	2004
(xix)	Kaphalia et al.	Serum (rat)	RP C18 analytical column (250 × 4.6 mm, 5 μm)	ACN:sodium acetate buffer (pH 5 with acetic acid) (2:1.5 vol/vol) flow rate 0.5 mL/min	UV 280 nm	2005
(xx)	Sparidans et al.	Plasma (mouse)	Altantis C18 column (100 × 2.1 mm, 3 μm)	Solvent A, 8.5 mM ammonium acetate:0.0075% vol/vol formic acid in water; Solvent B, Methanol (gradient)	ESI–QqQ	2008
(xxi)	Nasir et al.	Plasma and aqueous humor (bovine)	Hypersil C18 (250 × 4.6 mm, 5 μm)	0.2% Triethylamine:ACN (pH 2.75 by 85% phosphoric acid) (40:60 vol/vol), flow rate 1 mL/min	UV 284 nm	2011
(xxii)	Aguiar et al.	Plasma (rabbit)	LichroCART RP C18 (125 × 4.6 mm, 5 μm)	0.7 M acetic acid (pH 2.5 by NaOH):ACN (1:1 vol/vol), flow rate 1 mL/min	DAD 282 nm	2011
(xxiii)	Emara et al.	Plasma (human)	Symmetry C18 (390 mm ×)	ACN:water (pH 4) (55:45 vol/vol), flow rate 1 mL/min	UV 282 nm	2012
	Phenylbutazone					
(i)	Pound and Sears	Plasma (human)	(100)	0.002% Acetic acid:23% THF in *n*-hexane (flow rate 1 mL/min)	UV 254 nm	1975
(ii)	Marunaka et al.	Plasma and urine (rat)	Bondapak C18 (30 cm × 4 mm, 8–10 μm)	Methanol:0.01 M sodium acetate buffer (pH 4) (gradient)	UV 254 nm	1980

5

www.SID.ir

145

Archive of SID

Table 3: Continued

Sr. no.	Analyte	Matrix (species)	Stationary phase	Mobile phase	Detector	Year
	(iii) Hardee *et al.*	Plasma (horse)	Spherisorb ODS (5 µm)	Methanol:ACN:1% acetate buffer (pH 3.0) (30:20:50 vol/vol/vol), flow rate 1.2 mL/min	UV 254 nm	1982
	(iv) Taylor and Westwood	Plasma (equine)	Hypersil C18 (100 × 4.6 mm, 5 µm)	Methanol:0.1 M acetic acid with heptane sulfonic acid (0.01%) (60:40 vol/vol), flow rate 1.5 mL/min	PDA 240 nm	1995
	(v) Neto *et al.*	Plasma and urine (horse)	Lichrospher C18 (125 × 4 mm, 5 µm)	0.01 M acetic acid:methanol (45:55 vol/vol), flow rate 1 mL/min	UV 254 nm	1996
	(vi) Haque and Stewart	Serum	SPS C18 (15 cm × 4.6 mm)	ACN:0.05 M phosphate buffer (pH 7.5) (15:85 vol/vol), flow rate 1 mL/min	UV 265 nm	1997
	(vii) Grippa *et al.*	Serum (equine)	C18 (250 × 4.6 mm, 5 µm)	ACN:water (51:49 vol/vol), containing 0.1% TFA, flow rate 1 mL/min	UV 254 nm	2000
	(viii) Asea *et al.*	Muscle tissue (bovine, equine, and porcine)	C8 (150 × 3.9 mm, 5 µm)	0.05 M ammonium acetate solution (pH 5):methanol:ACN (53:35:12 vol/vol/vol), flow rate 1 mL/min	UV 270 nm	2004
	(ix) Igualada and Moragues	Urine (porcine, bovine, equine, ovine, and coprine)	Zorbax Eclipse C18 (250 × 3 mm, 5 µm)	Formic acid:10 mM (50:50 vol/vol), flow rate 1 mL/min	ESI–MS	2005
6	Oxyphenbutazone Sioufi *et al.*	Plasma (human)	Lichrosorb RP 18 (25 cm × 4.7 mm, 10 µm)	Methanol:phosphate buffer (pH 4) (63:37 vol/vol), flow rate 1.5 mL/min	UV 254 nm	1983
7	Sulindac					
	(i) Shimek *et al.*	Plasma (human)	Zorbax ODS (25 cm × 4.6 mm)	Sodium acetate buffer (pH 4 and 5):acetic acid (gradient)	UV 254 nm	1981
	(ii) Swanson and Boppana	Plasma and urine (human)	Spherisorb ODS column (10 µm)	Methanol:0.4 N sodium acetate buffer (pH 4) (63:37 vol/ vol), flow rate 1.2 mL/min	UV 254 nm	1981
	(iii) Grgurinovich	Plasma (human)	Waters Phenyl RP column (300 × 3.9 mm, 10 µm)	ACN:GAA:10 mM sodium acetate buffer (pH 4.2) (42:1:57 vol/vol), flow rate 2 mL/min	UV 315 nm	1987
	(iv) Ray *et al.*	Plasma, urine, and feces (human)	Octyl (150 × 4.6 mm, 5 µm)	ACN:acetic acid:water (37.5:1:61.5 vol/vol/vol), flow rate 2 mL/min	UV 329 nm	1995
B.	Steroids					
8	Corticosteroids					
	(i) Fluri *et al.*	Urine (human)	Inertsil 3 ODS (150 × 3 mm, 3 µm)	1 mM ammonium acetate:ACN (60:40 vol/vol) (gradient)	ESI–Q	2001
	(ii) Sangiorgi *et al.*	Urine (bovine)	Symmetry C18 (150 × 4.6 mm, 5 µm)	Water:ACN (gradient), flow rate 1 mL/min	APCI–QqQ	2003
	(iii) Rönquist-Nii and Edlund	Tissue of liver and adipose	Symmetry C8 (150 × 2.1 mm, 5 µm)	0.02% TFA in Milli-Q water:0.02% TFA in methanol, flow rate 0.3 mL/min (gradient)	ESI–MS	2005
		Adipose tissue (mouse)	Luna C8 (150 × 2 mm, 5 µm)	0.02% TFA in Milli-Q water:0.02% TFA in ACN (gradient)		
	(iv) Leung *et al.*	Urine (horse)	Supelcosil C8 (3.3 cm × 2.1 mm, 3 µm)	5 mM acetic acid:ammonium formate (pH 3.8):ACN, flow rate 0.2 mL/min (gradient)	ESI–QqQ	2005
	(v) Spyridaki *et al.*	Urine (human)	Zorbax C8 (150 × 2.1 mm, 5 µm)	0.1% Acetic acid in water:0.1% acetic acid in ACN (gradient)	ESI–IT	2006

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Archive of SID

Table 3: Continued

Sr. no.	Analyte	Matrix (species)	Stationary phase	Mobile phase	Detector	Year
	(vi) Ho *et al.*	Urine (horse)	Supelcosil LC 8 DB (3.3 cm × 2.1 mm, 3 µm)	5 mM acetic acid:ammonium formate (pH 3.8):methanol (gradient)	ESI–QqQ	2006
	(vii) Cho *et al.*	Urine (human)	Hypersil Gold C18 (50 × 2.1 mm, 1.9 µm)	0.1% Acetic acid in 5% ACN:0.06% acetic acid in 95% ACN (gradient)	ESI–QqQ	2008
	(viii) Andersen *et al.*	Urine (porcine and bovine)	Zorbax Eclipse (100 × 2.1 mm, 1.8 µm) and Hypercarb (100 × 2.1 mm, 5 µm)	ACN:0.1% formic acid (3:7)	ESI–MS	2008
	(ix) Gao *et al.*	Tissue (mice)	ODS–AQ column (100 × 2 mm, 3 µm)	0.1% Formic acid in water:0.1% formic acid in methanol	ESI–QqQ	2009
	(x) Croes *et al.*	Liver (bovine)	Hypercarb (100 × 2.1 mm, 5 µm)	Water:ACN (20:80), flow rate 300 µL/min	ESI–MS	2009
	(xi) Dusi *et al.*	Liver (bovine)	XTerra C18 (150 × 2.1 mm, 3.5 µm)	0.1% Aqueous acetic acid solution:ACN (gradient)	ESI–QqQ	2010
	(xii) Deceuninck *et al.*	Liver (animal)	Acquity BEH C18 (100 × 2.1 mm, 1.7 µm)	0.5% Acetic acid in water:0.5% acetic acid in ACN, flow rate 0.6 mL/min (gradient)	ESI–MS	2011
	(xiii) Pavlovic *et al.*	Urine (bovine)	Restek Ultra II Allure Biphenyl (100 × 2.1 mm, 3 µm)	0.05% Formic acid in water:0.05% formic acid in methanol (45:55), flow rate 200 µL/min	ESI–Q	2012
	(xiv) Marcos *et al.*	Urine (human)	Acquity BEH C18 (100 × 2.1 mm, 1.7 µm)	0.01% Formic acid in water:methanol with 0.01% formic acid	ESI–QqQ	2014
	(xv) Rey-Salgueiro *et al.*	Saliva (pig)	Kinetex C18 (100 × 2.1 mm, 2.6 µm)	Water:methanol:10% HCOOH in water (gradient), flow rate 0.25 mL/min	ESI–QqQ	2015
9	Prednisolone					
	(i) Loo *et al.*	Plasma (human)	Lichrosorb (250 × 3.2 mm, 5 µm)	0.2% GAA:6% methanol:30% methylene chloride in *n*-hexane (vol/vol), flow rate 120 mL/h	UV 254 nm	1977
	(ii) Frey and Frey	Urine (Human)	(250 × 3.2 mm, 5 µm)	Hexane:diethylether:ethanol:THF:GAA (59.9:31.2:3:6.5:0.3 vol/vol), flow rate 1.8 mL/min	UV 254 nm	1982
	(iii) Ui *et al.*	Serum (human)	Zorbax–SIL (25 cm × 4.6 mm, 5 µm)	Dichloromethane:methanol (92.5:7.5 vol/vol), flow rate 1 mL/min	UV 254 nm	1982
	(iv) Prasad *et al.*	Plasma (swine)	Lichrosorb Si–60 (25 cm × 4.6 mm)	Methylene chloride:water:saturated methylene chloride:THF:methanol:glacial acetic acid (664.5:300:10:25:0.5), flow rate 0.8 mL/min	UV 254 nm	1986
	(v) Carlin *et al.*	Plasma (swine)	Zorbax C18 (25 × 0.46 cm, 5–6 µm)	THF:water (25:75 vol/vol), flow rate 1 mL/min	UV 240–242 nm	1988
	(vi) Yamaguchi *et al.*	Plasma (human)	TSK–gel ODS (250 × 4.6 mm, 5 µm)	Methanol:ACN:1 M ammonium acetate (38:25:45 vol/vol/vol), flow rate 1 mL/min	FLU Ex = 350 nm Em = 390 nm	1991
	(vii) Musson *et al.*	Aqueous humor (rabbit)	Chemcosorb 5 ODS (150 × 4 mm, 5 µm)	Isopropanol:water with 2 mL of H_3PO_4, pH 3 adjusted by 1 M NaOH (250:750 vol/vol)	UV 245 nm	1991
	(viii) Garg and Jusko	Urine (human)	Zorbax C18 (250 × 4.6 mm, 5–6 µm)	Methylene chloride:glacial acetic acid:methanol (91.3:7.5:1.2 vol/vol/vol), flow rate 2 mL/min	UV 254 nm	1991
	(ix) Jusko *et al.*	Plasma (human)	Zorbax SIL (250 × 4.6 mm, 5–6 µm)	Methylene chloride:heptane:glacial acetic acid:ethanol (600:350:10:35 vol/vol/vol/vol)	UV 254 nm	1994
	(x) Hirata *et al.*	Serum (human)	Hypersil ODS (25 × 0.46 cm)	Solvent A, Isopropanol:0.05 M acetate buffer pH 4.5 (10:90 vol/vol) Solvent B, Isopropanol:0.05 M acetate buffer pH 4.5 (gradient)	UV 254 nm	1994

www.SID.ir

147

Archive of SID

Table 3: Continued

Sr. no.	Analyte	Matrix (species)	Stationary phase	Mobile phase	Detector	Year
	(xi) Döppenschmitt et al.	Serum (human)	Lichrosorb (250 × 4 mm, 5 μm)	n-hexane:dichloromethane:methanol:acetic acid (266:120:26:0.8 vol/vol/vol/vol), flow rate 2 mL/min	UV 242 nm	1995
	(xii) AbuRuz et al.	Plasma and urine (human)	ThermoHypersil (250 × 4.6 mm, 5 μm)	Dichloromethane:water saturated DCM:methanol:THF:GAA (66.45:30:2.5:1% vol/vol/vol/vol), flow rate 2 mL/min	UV 240 nm	2003
	(xiii) Frerichs and Tornatore	Serum (human)	Symmetry C18 (30 × 2.1 mm, 3.5 μm)	Methanol:5 mM acetate buffer pH 3.25 (gradient), flow rate 400 μL/min	ESI–MS	2004
	(xiv) Difrancesco et al.	Plasma (human)	Symmetry C18 (30 × 2.1 mm, 3.5 μm)	5 mM ammonium acetate pH 3.5:methanol (gradient), flow rate 400 μL/min	ESI–QqQ	2007
	(xv) Ding et al.	Adipose tissue (human)	Luna C18 (50 × 2 mm, 5 μm)	0.02% Formic acid in water:0.02% formic acid in methanol (gradient), flow rate 0.35 mL/min	ESI–QqQ	2009
	(xvi) Chen et al.	Plasma (human)	Genesis C18 (50 × 4.6 mm, 3 μm)	0.1% Formic acid in water:0.1% formic acid in ACN (gradient), flow rate 1 mL/min	ESI–QqQ	2009
	(xvii) Ionita et al.	Plasma (human)	Zorbax–SB Phenyl (100 × 2.1 mm, 1.8 μm)	ACN:water:formic acid (32:68:0.1 vol/vol/vol), flow rate 0.140 mL/min	ESI–MS	2009
	(xviii) Mcwhinney et al.	Plasma, urine, and saliva (human)	Acquity UPLC BEH C18 (50 × 2.1 mm, 1.7 μm)	Solvent A, 2 mmol/L ammonium acetate in water with 0.1% formic acid Solvent B, 2 mmol/L ammonium acetate in methanol with 0.1% formic acid, flow rate 0.4 mL/min	ESI–MS	2010
	(xix) Fung et al.	Plasma (human)	Zorbax C18 (50 × 2.1 mm, 3.5 μm)	Solvent A, 10 mM ammonium formate:0.1% formic acid in water Solvent B, 10 mM ammonium formate:0.1% formic acid in 80% methanol:20% ACN (gradient), flow rate 0.3 mL/min	QTOF	2011
	(xx) Li et al.	Milk (bovine)	Acquity UPLC BEH C18 (50 × 2.1 mm, 1.7 μm)	0.1% Formic acid in water:0.1% formic acid in ACN (gradient), flow rate 0.3 mL/min	ESI–QqQ	2012
	(xxi) Pavlovic et al.	Urine (bovine)	Restek Ultra (100 × 2.1 mm, 3 μm)	0.05% Formic acid in water:0.05% formic acid (45:55 vol/vol), flow rate 200 μL/min	Q–MS	2012
	(xxii) Liu et al.	Milk (cow)	Acquity UPLC BEH C18 (50 × 2.1 mm, 1.7 μm)	Solvent A, 0.1% formic acid in water Solvent B, 0.1% formic acid in ACN, flow rate 0.3 mL/min	ESI–QqQ	2016
	(xxiii) Huang et al.	Serum and urine (rat)	BEH C18 (100 × 2.1 mm, 1.7 μm)	0.1% Formic aid in water:0.1% formic acid in ACN (gradient)	ESI–MS	2016
10	Triamcinolone					
	(i) Döppenschmitt et al.	Plasma (human)	Lichrosher RP 18 (250 × 4 mm, 5 μm)	Methanol:water:THF (vol/vol/vol), flow rate 1 mL/min	UV 252 nm	1996
	(ii) Główka et al.	Plasma (human)	Lichrospher RP 18 (125 × 4.6 mm, 5 μm)	ACN:0.3 mM OPA (pH 4.6) (470:530 vol/vol), flow rate 2 mL/min	FLU Ex = 360 nm Em = 460 nm	2006
	(iii) Vieira et al.	Plasma (rat)	Kromasil C18 (250 × 4.6 mm, 5 μm)	Methanol:water (72:28 vol/vol), flow rate 0.8 mL/min	UV 254 nm	2010
C. Microtubule inhibitor						
11	Colchicine					
	(i) Jiang et al.	Plasma (human)	Zorbax C18 (150 × 4.6 mm, 5 μm)	Formic acid:10 mM ammonium acetate:methanol (1:49:75 vol/vol/vol)	ESI–MS	2007

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Table 3: Continued

Sr. no.	Analyte	Matrix (species)	Stationary phase	Mobile phase	Detector	Year
	(ii) Chen *et al.*	Plasma (mouse)	Diamonsil C18 (250 × 4.6 mm, 5 µm)	ACN:phosphoric acid solution (27:73 vol/vol), flow rate 1 mL/min	UV 350 nm	2007
	(iii) Bourgogne *et al.*	Plasma (human)	Hypersil C18 (50 × 2 mm, 3 µm)	0.1% Formic acid in water:0.1% formic acid in methanol (gradient)	ESI–QqQ	2013
	(iv) Kovvasu *et al.*	Plasma (human)	Synergy (75 × 4.6 mm, 4 µm)	10 mM ammonium formate (pH 3.5):methanol (20:80 vol/vol)	ESI–QqQ	2018
II. Chronic gout						
A. Uricosuric drug						
12 Sulfinpyrazone						
	(i) Inaba *et al.*	Serum (dog)	Micro-Pak (25 cm × 2.2 mm, 10 µm)	Dioxane:methanol (65:35 vol/vol), flow rate 0.7 mL/min	UV 254 nm	1975
	(ii) Wong *et al.*	Plasma and urine (Male albino Wistar rat and rabbit)	Lichrosorb (250 × 2.8 mm, 10 µm)	0.1 M ammonium acetate in ACN:water (pH 5 adjusted with acetic acid) 30:70 or 35:75 vol/vol, flow rate 0.5 mL/min	UV 275 nm	1978
	(iii) Bjornsson *et al.*	Plasma and urine (human)	µBondapak C18 (30 cm × 0.39 cm, 10 µm)	0.1 M ammonium acetate in ACN:water (30:70 vol/vol), flow rate 1 mL/min	UV 270 nm	1980
	(iv) Jakobsen and Pedersen	Plasma (human)	Spherisorb ODS (250 × 4.6 mm, 5 µm)	Methanol:0.02 M phosphate buffer pH 7 (40:60 vol/vol)	UV 254 nm	1981
	(v) Godbillon *et al.*	Plasma (human)	Lichrosorb RP 8 (25 cm × 4.6 mm, 10 µm)	2.2 mM OPA:ACN:ethanol (50:35:15 vol/vol/vol), flow rate 3 mL/min	UV 254 nm	1982
	(vi) de Vries *et al.*	Plasma and urine (human)	µBondapak C18 (300 × 3.9 mm, 10 µm)	Solvent A, 0.1 M ammonium acetate:ACN (780:220 vol/vol); Solvent B, ACN (gradient)	UV 254 nm	1983
	(vii) Tam *et al.*	Plasma (human)	Radial Pak C 18 (11.5 cm × 8 mm, 5 µm)	ACN:0.02 M phosphate buffer pH 7.0, flow rate 2 mL/min	UV 254 nm	1984
13 Benzbromarone						
	(i) Vergin and Bishop	Serum (human)	µBondapak C18, (30 cm × 4 mm, 10 µm)	Methanol:water:ACN:ethyl acetate:acetic acid (72:23:3:1.1)	UV 254 nm	1980
	(ii) Arnold *et al.*	Plasma and urine (human)	Nucleosil C8 (125 × 4.6 mm, 5 µm)	ACN:5 mM sodium dihydrogen phosphate (pH 3.5 adjusted with phosphoric acid) (60:40 vol/vol), flow rate 0.5 mL/min	UV 280 nm	1991
	(iii) Wu *et al.*	Plasma, urine, feces, and bile (rat)	RP C18 (75 × 4.6 mm, 3.5 µm)	0.2% Formic acid in ACN:0.2% formic acid in water (gradient)	UV 235 nm	2012
B. Uric acid synthesis inhibitors						
14 Febuxostat						
	(i) Wang *et al.*	Plasma (human)	Capcell Pak C18 (100 × 4.6 mm, 5 µm)	ACN:5 mM ammonium acetate:formic acid (85:15:0.015), flow rate 0.6 mL/min	ESI–QqQ	2012
	(ii) Vaka *et al.*	Plasma (human)	Zorbax SB–C18 (75 × 4.6 mm, 3.5 µm)	ACN:5 mM ammonium formate (60:40 vol/vol), flow rate 0.5 mL/min	ESI–QqQ	2013
	(iii) Chandu *et al.*	Plasma (human)	Ascentis Express C18 (50 × 4.6 mm, 3.5 µm)	10 mM ammonium formate:ACN (20:80 vol/vol), flow rate 0.8 mL/min	ESI–QqQ	2013

www.SID.ir

149

Kachave, *et al.*: A review on analytical methods of antigout agents

Table 3: Continued

Sr. no.	Analyte	Matrix (species)	Stationary phase	Mobile phase	Detector	Year
	(iv) Xie *et al.*	Plasma (human)	XTerra MS C8 (150 × 2.1 mm, 5 μm)	0.1% Formic acid in ACN:0.1% formic acid in water (gradient)	ESI–MS	2014
	(v) Choudhury *et al.*	Plasma (human)	Zorbax SB–CN (50 × 4.6 mm, 3.5 μm)	0.2% Formic acid solution in water:methanol (10:90 vol/vol), flow rate 0.5 mL/min	ESI–QqQ	2014
	(vi) Wu *et al.*	Plasma (human)	Zorbax SB C18 (50 × 4.6 mm, 5 μm)	0.2% Formic acid in water:ACN (gradient)	ESI–QqQ	2015
15	Allopurinol					
	(i) Reinders *et al.*	Serum (human)	Lichrospher100 RP18 (250 × 4 mm, 5 μm)	0.02 M sodium acetate with acetic acid 30%, pH 4.5, flow rate 1 mL/min	UV 254 nm	2007
	(ii) Kasawar *et al.*	Plasma (human)	Symmetry Shield RP18 (150 × 3.9 mm, 5 μm)	0.01% Formic acid in water and ACN (95:5 vol/vol)	ESI–MS	2011
	(iii) Liu *et al.*	Plasma and urine	Agilent Eclipse C18 (150 × 4.6 mm, 3.5 μm)	Solvent A, 5 mM ammonium formate:0.1% formic acid (95:5 vol/vol) Solvent B, methanol:5 mM ammonium formate (95:5 vol/vol)	ESI–MS	2013
	(iv) Rathod *et al.*	Plasma (human)	Hypersil Gold (150 × 4.6 mm, 5 μm)	0.1% formic acid in water:ACN (98:2 vol/vol) flow rate 0.5 mL/min	ESI–MS	2016

APCI–MS = atmospheric pressure chemical ionization–mass spectrometry, DCM = Dichloromethane, TFA = Trifluroacetic acid, GAA = Glacial acetic acid, OPA = Ortho phosphoric acid, ESI-IT = Electrospray ionization- ion trap, QqQ = Triple Quadrupole, FLU = Fluorescence, THF = Tetrahydrofuran
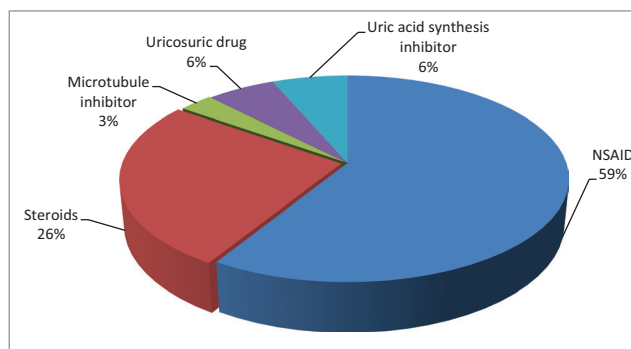
Figure 3: Categories of antigout drugs on which impurity profiling, forced degradation, and bioanalytical study are studied
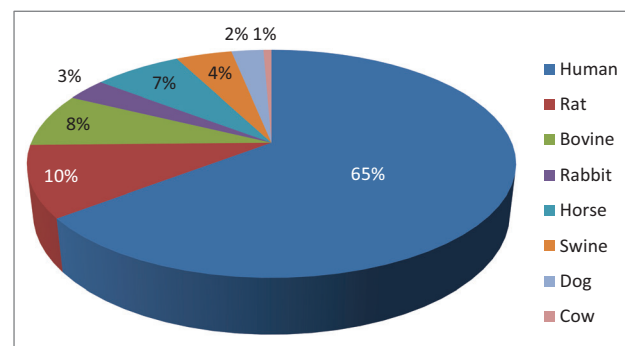
Figure 4: Different matrices used for impurity and forced degradation profiling of antigout drugs
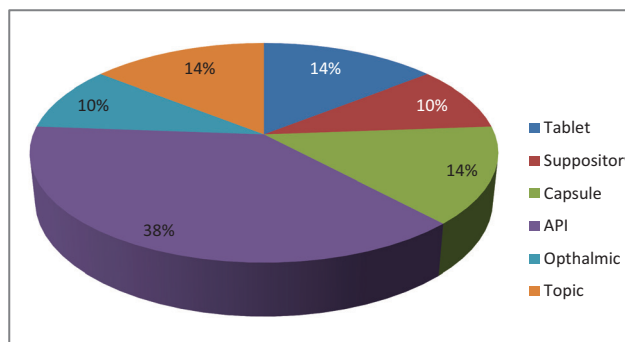
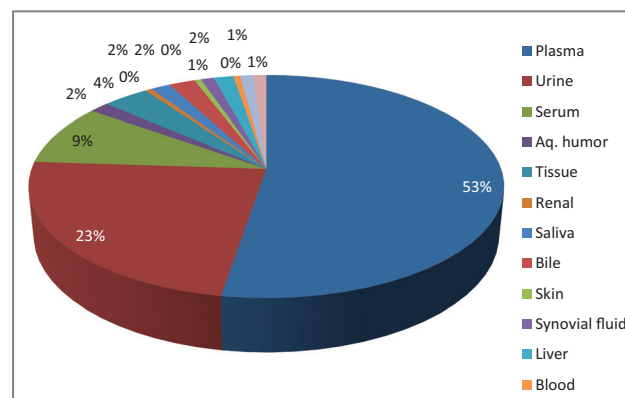Figure 5: Different species used for bioanalytical method of antigout drugs

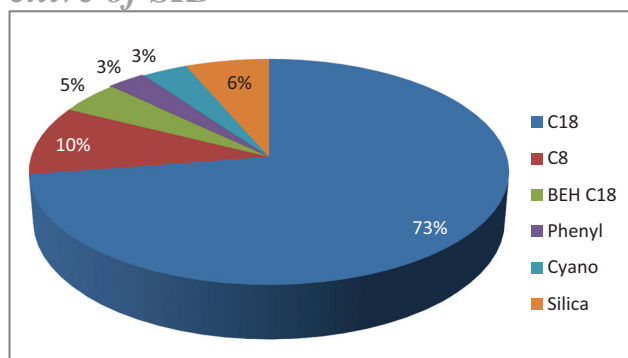Figure 6: Different matrices used for bioanalytical method of antigout drugs

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Figure 7: Different columns used for of impurity profiling, forced degradation, and bioanalytical method of antigout drugs

Figure 8: Types of elution performed in analysis for impurity, forced degradation profiling, and bioanalysis of antigout drugs
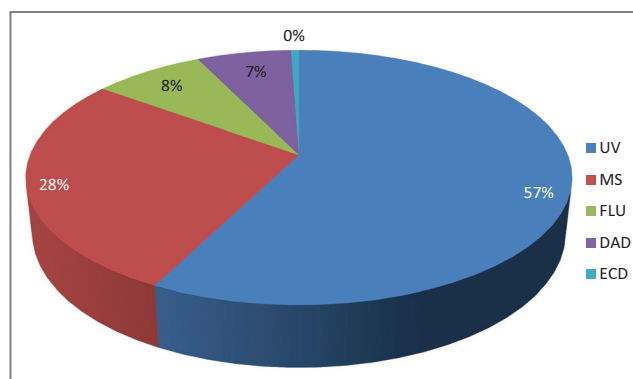

Figure 9: Different detectors used for impurity profile, forced degradation, and bioanalytical method of antigout drugs, Fluorescence, Electron capture detector
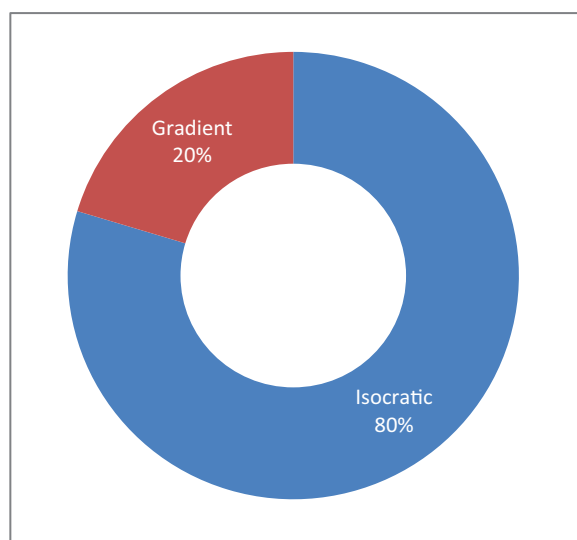
to Zorbax phenyl analytical column for the separation of IDM and its two degradation products, 4-chloro-benzoic acid and 5-methoxy-2-methylindoleacetic acid.

Temussi *et al.*[25] developed method for the determination of photostability and photodegradation products of IDM in aqueous media. The drug was photochemically degraded affording eight photoproducts. All photoproducts were isolated by preparative HPLC and characterized by nuclear magnetic resonance (NMR) techniques (correlation spectroscopy [COSY], heteronuclear single quantum coherence spectroscopy [HSQC], heteronuclear multiple bond coherence [HMBC], and nuclear Overhauser effect spectroscopy [NOESY]) and liquid chromatography–mass spectrometry (LC–MS) experiments.

Haq *et al.*[26] developed an environmentally benign approach for rapid analysis of IDM using stability indicating RP-HPLC method. The stability study of IDM was carried out, which revealed six degradant products, of which two were acid hydrolysis, one was base hydrolysis, two were oxidative hydrolysis, and one was thermal hydrolysis product.

Piroxicam: Bartsch *et al.*[27] developed three methods of stability indicating assays for the determination of piroxicam. First method was HPLC, whereas second was High performance thin layer chromatography and third is capillary electrophoresis (CE) method. The aim of the study was mainly selective determination of piroxicam, no separation of all degradation products was necessary. The relative standard deviation (RSD) for the three methods at each concentration gave the best results for quantitation using HPLC.

Diclofenac: Hajkova *et al.*[28] developed reverse-phase chromatographic method with UV spectrometric detection for the simultaneous determination of methylparaben, propylparaben, and sodium diclofenac and its degradation product in a topical emulgel. Degradation product of diclofenac was 1-(2,6-dichlorophenyl)-indolin-2-ome occurring in a formulation after long-term stability tests.

Galmier *et al.*[29] developed the LC–MS method on degradation products of diclofenac in aqueous dosage form in accelerated storage conditions. Electrospray ionization – mass spectrometry

method for determination of NAP in the presence of its impurities. Study revealed total seven impurities, which are characterized on the basis of stress degradation studies. No considerable degradation was observed in photolytic degradation.

Marwa *et al.*[22] developed HPLC-DAD for separation and analysis of NAP and esomeprazole in the presence of their chiral impurities and enantiomeric purity determination in tablets. This method separates the four isomers of the two drugs simultaneously. The chiral impurities (R-isomers of NAP and omeprazole) detected at 1% level.

Indomethacin: Kwong *et al.*[23] reported HPLC method for efficient separation of indomethacin (IDM) and its impurities. Study revealed total four impurities. This method was found to be sensitive, linear, and showed good repeatability.

Novakova *et al.*[24] reported simple, sensitive, and validated method for determination and quantitation of IDM and its degradant product by RP-HPLC using UV as detector. Faster separation was obtained with analytical column Zorbax SB CN (Agilent technologies, Prague, Czech Republic) as compared

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(ESI-MS) spectra were used to study diclofenac fragmentation and to characterize the structures of degradation products. The study revealed the presence of three degradation products.

Sulindac: Krier *et al.*[30] developed HPLC method for quantification of sulindac and its related impurities. This method was optimized using design of experiment methodology and the diclofenac sodium (DS) concept. The impurity study of sulindac was carried out, which revealed its three related impurities.

Steroids

Corticosteroids: Hymer[31] developed simple, accurate, and reproducible HPLC method for the determination of three known major impurities present in corticosteroids (CRS). This method used gradient elution method by using UV detector.

Lu *et al.*[32] reported a sensitive rugged and robust HPLC method, which was suitable for the identification assay of betamethasone sodium phosphate and betamethasone acetate, and for the identification and estimation of their impurities/degradants. This method could separate a total of B2 potential impurities and degradation products from the two APIs and also from each other.

Prednisolone: Marley *et al.*[33] developed RP-HPLC method for the determination of prednisolone acetate (PA) and impurities in an ophthalmic suspension. This method was simple, accurate, precise, and specific, which was carried out according to the ICH guidelines, and all eight known impurities were separated.

Triamcinolone: Matysová *et al.*[34] developed a novel RP-HPLC method for the determination of active component triamcinolone (TMC) acetonide, its degradation product TMC, occurring in formulation after long-term stability tests. The main impurity TMC was found in cream formulation.

Chronic gout

Uric acid inhibitor

Febuxostat: Kadivar *et al.*[35] studied impurity profile of febuxostat API and carryover impurity from the intermediate stage and raw materials using LC–MS quadrupole time-of-flight instrument and were characterized after they were synthesized by infrared and NMR. Four impurities were identified as amide, sec-butyl, des-cyano, and des-acid in febuxostat drug analog.

Bioanalytical Method

Acute gout

Nonsteroidal anti-inflammatory drug

Naproxen: Loenhout *et al.*[36] developed HPLC method for the quantitative analysis of NAP and its major metabolite des-methyl-NAP in biological fluid samples (plasma and urine). Two methods of detection were compared, that is, UV spectrophotometry and spectrophotofluorometry. The

sensitivity of the fluorimetric detection was higher than that of the UV detection.

Wanwimolruk[37] reported a simple, rapid, and sensitive method for the determination of NAP in human plasma. The sensitivity of the method was improved with the help of microbore column. This method is suitable for its use in clinical studies.

Karidas *et al.*[38] developed extractionless HPLC method for the determination of NAP in human plasma and urine with UV detection at 278 nm. The method was sufficiently sensitive for biopharmaceutical studies, after the oral administration of a single sustained release dose.

Mikami *et al.*[39] developed HPLC method for the simultaneous determination of NAP, nabumetone, and its major metabolite 6-methoxy-2-naphthylacetic acid. The procedure described is rapid, simple, selective, and suitable for routine analysis of pharmaceuticals and PK studies in human urine samples.

Elsinghorst *et al.*[40] developed a sensitive, precise, and accurate quantitative liquid chromatography tandem mass spectrometry (LC–MS/MS) method for the measurement of NAP in human plasma and completely validated according to the current Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines. The maximum concentration (C_{max}) value was found to be 8.61%.

Patel *et al.*[41] developed UPLC–MS/MS method for the simultaneous determination of sumatriptan (SUM) and NAP in human plasma of 28 healthy subjects. This method was validated as per the US FDA guidelines. The C_{max}, time taken to achieve maximum concentration (T_{max}), and half-life ($t_{1/2}$) values for SUM and NAP were 78.04 ± 6.50 and 60.36 ± 3.12 µg/mL, 0.88 ± 0.14 and 3.98 ± 0.35 h, and 2.24 ± 0.22 and 14.07 ± 0.83 h, respectively.

Ahmadi and Bapirzadeh[42] reported a simple, rapid, partial selective and sensitive HPLC method for the analysis of NAP. This method used in-tube SPME–liquid liquid liquid extraction, an ideal sample preparation technique, because of fast operation and low expense. This method is a useful tool for the screening and determination of acidic drugs in clinical control and forensic analysis.

Shi *et al.*[43] developed a novel LC–MS method to simultaneously determine the concentration of naproxcinod and its active metabolite in rat plasma. The C_{max}, T_{max}, and $t_{1/2}$ values for naproxcinod and NAP were 23.4 ± 7.1 and 3610 ± 1620 ng/mL, 8 ± 1.8 and 8 ± 2.1 h, 11.7 ± 3.2 and 5.5 ± 1.8 h, respectively.

Indomethacin: Terweij-Groen *et al.*[44] developed a HPLC method for the quantitative analysis of IDM and salicylic acid in blood serum and urine. The recovery was found to be 88% and 77% for IDM and salicylic acid, respectively. The results of this study do not solve the clinical issue of a possible interaction of IDM and salicylic acid.

Bernstein and Evans[45] developed a rapid and sensitive HPLC-fluorescence method for the quantitative analysis of IDM and

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its metabolite in urine. This is used in laboratory for the analysis of I and II metabolites in biological fluids.

Shimek *et al.*[46] developed a rapid, specific method for the quantitation of tolmetin, IDM, and sulindac and their respective metabolites in plasma. The method described here can be recommended for routine patient monitoring or for PK studies.

Greizerstein and Mclaughlin[47] developed the method to determine the concentration of IDM in blood of rats by HPLC–UV method. The simple extraction and the short time required for analyses of blood samples make this method very economical and fast for the analyses of samples.

Smith and Benet[48] developed an HPLC method for the determination of IDM and its two primary metabolites in urine. Inter- and intraday precisions were smaller than 10% for IDM, desmethyl (DMI), and deschlorobenzoyl (DBI). This method has been used successfully for bioavailability studies.

De Zeeuw *et al.*[49] developed a highly sensitive HPLC method combined with post-column alkaline hydrolysis of IDM. The utility of this method in measuring IDM concentrations in small sample volumes was collected from microperfusion of an isolated segment of renal proximal tubule. The lower limit of detection was reported to be approximately 0.02 µg/mL for IDM.

Sauvaire *et al.*[50] developed a liquid chromatographic method for determination of IDM and its prodrug apyramide in plasma. In this method, experimental design approach was used. A PK study in dogs and rats provided information about the biological disposition of the ester prodrug.

Stubbs *et al.*[51] developed an improved method for the determination of IDM in plasma and urine by RP-HPLC. The results were in good agreement with their target values and showed relative standard deviation of 3.6% and 2.7% for plasma and 3.9% and 3.1% for urine for low and high values, respectively. It has been successfully used to assay many clinical samples and has been proved to be very rugged.

Brown *et al.*[52] developed an HPLC method for the determination of IDM serum concentrations. Recovery ranged from 0.1 to 4 µg/mL. Their approach was to adjust each IDM concentrations and clinical response until PDA closure was achieved.

Kim *et al.*[53] developed quantification of IDM in serum by HPLC using fluorescence detection. This method could be used for PK and bioavailability studies of IDM in man, and tissue distribution in small laboratory animals. The highest recovery (102%) was obtained with a buffer of pH 6.6.

Avgerinos and Malamataris[54] developed a similar simple, rapid, and sensitive method for the determination of IDM in both human plasma and urine. The %RSD < 4 indicated that the method was sufficiently precise. The method is currently being used for a PK and bioequivalence investigation of controlled release formulations.

Hubert *et al.*[55] developed a fully automated RP-HPLC method for the determination of IDM in plasma. The absolute recovery of the drug is 70%. The method is also applicable to the bioavailability studies of IDM not only after oral administration but also after external application to the skin as a spray solution.

Mawatari *et al.*[56] developed an HPLC method involving post-column photochemical reaction and fluorimetric detection for the determination of IDM in serum. The mean recovery was found 94.3%. This method is sensitive and specific enough to estimate IDM in human serum and is expected to be useful in therapeutic drug monitoring.

Singh *et al.*[57] developed a simple and reproducible HPLC and gas chromatography–mass spectrometry (GC–MS) method for the simultaneous analysis of several acidic drugs in horse plasma and urine. The recovery of each drug from plasma was calculated as 95%, and the assay showed good precision. The capillary GC–MS column provided better separation of the drugs than the reversed phase C18 HPLC column. This study indicated that the sensitivities of different acidic drugs were comparable when determined by the GC–MS method.

Caturla and Cusido[58] developed a sensitive, specific, and selective HPLC method for the determination of IDM, suxibuzone, phenylbutazone, and oxyphenbutazone in plasma. The recovery of suxibuzone, phenylbutazone, and oxyphenbutazone was 92.8%–99.0%, 90.8%–99.5%, and 96.4%–101.5%, respectively. SPE method is less time-consuming and prevents degradation of the compounds than the LLE. It is useful for PK studies, drug monitoring, or doping control of these substances in plasma.

Kubo *et al.*[59] developed a sensitive and specific fluorimetric method for the determination of IDM in serum by HPLC using in-line oxidation with hydrogen peroxide. The recovery of IDM was found to be 95%. This method can be used for routine therapeutic monitoring and also for the determination of other compounds that are oxidized with hydrogen peroxide.

Vree *et al.*[60] developed an HPLC method for the determination of IDM, its metabolites, and their glucuronides in human plasma and urine. The C_{max}, T_{max}, and $t_{1/2}$ values for IDM were 5.4 µg/mL, 1.0 h, and 0.84 h, respectively. In urine, the parent drug (IDM) as well as the metabolite and conjugate (DMI and DBI) were present. The possible metabolite DBI was not detected in urine. In this method, the effect of probenecid was studied, which inhibits the formation of both the ether and the acyl glucuronide of DMI.

Niopas and Mamzoridi[61] developed a simple, rapid, relatively inexpensive, precise, accurate, and sensitive HPLC method for the determination of IDM and mefenamic acid in plasma. The accuracy was found to be nearly 100% for both drugs. This method is useful for routine clinical monitoring of IDM and mefenamic acid in small volumes of plasma and particularly use for pediatric use.

Sato *et al.*[62] developed a simple, rapid, and sensitive method for the determination of IDM in plasma by HPLC with UV

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detection. The recoveries of the drug were found to be nearly 100%. This method is very suitable for the therapeutic drug monitoring of IDM in premature infants with symptomatic PDA and also in patients undergoing conventional IDM therapy.

Liu *et al.*[63] developed a rapid, accurate, and sensitive automated analytical method for the determination of IDM in animal plasma using an on-line column switching HPLC technique. The accuracy of IDM ranged from –0.62% to 3.22%. The method has been successfully used to provide PK data in a large number of diverse pharmaceutical studies.

Dawidowicz *et al.*[64] developed a simple and sensitive method of free IDM analysis in plasma samples using HPLC-UV detection. The method is characterized by high yield (recovery approximately 97%) and detection limit (3 ng/mL), which is so far one of the lowest values reported for HPLC method.

Michail and Moneeb[65] designed an HPLC-DAD assay, combining SPE with pre-column derivatization to determine methotrexate (MTX) and IDM in human urine. The stability was tested under the conditions recommended by the FDA, which are freeze and thaw stability, short-term temperature stability, long-term stability, processed samples stability, and stock solution stability. They were hoped that further studies concerning the urinary levels of MTX and NSAID in cancer.

Liu *et al.*[66] developed a LC–MS/MS for measuring plasma and uterine tissue levels of IDM in rabbits treated with IDM-mediated Copper Intrauterine devices (Cu-IUDs). The mean recoveries of IDM at low, medium, and high concentration levels were 90.8% ± 4.6%, 88.5% ± 4.4%, and 89.0% ± 9.1%. This method was successfully applied to investigate the absorption and uterine distribution of IDM in rabbits after insertion of IDM-mediated Cu-IUDs.

Wang *et al.*[67] developed LC-ESI-MS for quantitative determination of IDM in maternal plasma and urine of pregnant patients. The relative standard deviation of this method was less than 8%, and the accuracy found was between the range 90% and 108%. This method is suitable for determining the PK parameters of IDM during pregnancy.

Piroxicam: Twomey *et al.*[68] reported an HPLC method for the analysis of piroxicam in plasma. The recovery of piroxicam was 73.6%. This method was reproducible and accurate and did not require chemical modification of drug.

Dixon *et al.*[69] developed a rapid, sensitive, and reproducible method for the quantitative analysis of tenoxicam and piroxicam in plasma. Mean recovery of piroxicam and tenoxicam was found to be 81 ± 3.0% and 81 ± 7.9%, respectively. The mean plasma half-life of piroxicam was 46.7 h.

Richardson and Ross[70] developed an HPLC method for the analysis of piroxicam and its metabolite 5-hydroxypiroxicam in human plasma and urine. Recoveries of piroxicam and 5-hydroxypiroxicam ranged between approximately 80% and

90%. The method was routinely used in laboratories for the analysis of human plasma and urine in clinical studies.

Macek and Vacha[71] developed a rapid, sensitive, and selective method for the determination of piroxicam in human plasma by HPLC. The %RSD was 2.9% and was sufficient for PK studies.

Boudinot and Ibrahim[72] reported a precise, specific, and sensitive HPLC method for the assay of piroxicam in human plasma. The mean recovery of piroxicam was found to be 91% ± 6%.

Milligan[73] developed an HPLC method for the determination of piroxicam and its major metabolites in plasma, urine, and bile. The %RSD of piroxicam and 5-hydroxypiroxicam in plasma, urine, and bile was found to be <2.9% and <8.0%, < 4.9% and < 4.5%, and < 3.9%, respectively.

Cerretani *et al.*[74] developed a rapid, precise, and sensitive HPLC method for the determination of piroxicam in rat plasma, muscle, and skin. The C_{max}, T_{max}, and $t_{1/2}$ (distribution) and $t_{1/2}$ (elimination) values for piroxicam in plasma, muscle, and skin were 58.3, 23.2, and 257.4 µg/mL; 4, 1, and 2 h; 11.6, 0.4, and 1.2 h; and 10.9, 185, and 29.5 h. The method was adopted for a PK study in rats.

Avgerinos *et al.*[75] reported a simple, rapid, and sensitive extractionless HPLC method for the simultaneous determination of piroxicam and 5-hydroxypiroxicam in human plasma. The %RSD was found to be <4.6% and the detection limit was 0.05 µg/mL. It is useful in the determination of PK parameter for drug formulation studies.

Edno *et al.*[76] developed a reproducible, rapid, and sensitive HPLC assay method for the quantitation of piroxicam in plasma. The mean recovery was found to be 95 ± 3%. The method was validated according to good laboratory practices guidelines and was applied to check the compliance of treatment for patient with rheumatological disorders.

Maya *et al.*[77] developed a rapid and sensitive method for the determination of piroxicam in plasma. The mean relative recovery was found between the range 94% and 108% ± 3.67%. This method is also used in bioavailability study.

Amanlou and Dehpour[78] developed a simple, sensitive, and rapid HPLC method to measure plasma concentration of piroxicam in rat. The mean extraction recovery for piroxicam was found to be 82% ± 6%.

Yritia *et al.*[79] described a fully automated method for the determination of piroxicam in human plasma using an on-line SPE, and this was compared with the same chromatographic method using off-line SPE. The validation of the method showed good recoveries (over 90%). Two methods are suitable to quantify drug level in PK studies, but the online method saves a lot of time and needs less manipulation.

Dadashzadeh *et al.*[80] reported a simple, reliable, accurate, and precise HPLC method for the determination of piroxicam in

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plasma. A mean recovery of 100.09% ± 6.52% was observed in the concentration range of 0.1–3 µg/mL. This method is also used in the bioavailability study.

Ji *et al.*[81] developed a rapid, sensitive, and reliable LC–MS/MS method for the determination of piroxicam, meloxicam, and tenoxicam in human plasma, The C_{max} and T_{max} values of piroxicam were 6.1 ± 1.4 ng/mL and 33 h, respectively. This method was successfully applied to a PK study of piroxicam after application of transdermal piroxicam patches to humans.

Dowling and Malone[82] developed a fast, simple, sensitive, and selective LC–MS/MS method for the determination of firocoxib, propyphenazone, romifenazone, and piroxicam in bovine plasma. Accuracy of the methods in plasma was between 93% and 102%.

Calvo *et al.*[83] developed a rapid, sensitive, and selective LC–MS/MS method for the simultaneous determination of piroxicam and 5'-hydroxypiroxicam in saliva and human plasma. The C_{max}, T_{max}, and $t_{1/2}$ values for piroxicam and 5'-hydroxypiroxicam in plasma and saliva were 2275.9 ± 367.7 and 133 ± 47.2 ng/mL; 50.9 ± 24.8 and 5.9 ± 2–8 ng/mL; 4.0 ± 1.2 and 53.6 ± 14.7 h; 4.7 ± 2.4 and 54.9 ± 14.2 h; 50.7 ± 8.8 and 4167.6 ± 1318.2 h, respectively. The stabilities in plasma were evaluated at different conditions including short-term stability, post-processing stability, freezing, and thawing.

Diclofenac: Godbillon *et al.*[84] developed a sensitive and selective HPLC method for the determination of diclofenac and its monohydroxy-related metabolites in plasma and urine. The mean recovery of DS, 4'OH, and 5'OH was found in the range of 97%–109%, 93%–97%, and 100%–101%. The dihydroxy-related metabolite could not be assayed because of interference.

Sioufi *et al.*[85] determined diclofenac in plasma using a fully automated analytical system combining liquid–solid extraction with liquid chromatography. The overall accuracy was ranging from 95% to 101% and the %RSD was 1.0%–9.3%. The automated determination of drugs in biological fluids increases the sample throughput.

Moncrieff[86] developed an RP-HPLC method with fluorimetric detection of DS in serum. The relative recovery was 98.2%–102%. This method is sufficiently sensitive to follow the PK of all dosing routes for diclofenac other than topical application.

Blagbrough and Daykin[87] reported an HPLC assay method to determine the levels of NAP, ibuprofen, and diclofenac in plasma and synovial fluid. The mean recovery from plasma extracts ranged within 89.5%–95.1% at a concentration between 100 and 1000 ng/mL. This method was used in clinical studies of the three drugs in a patient with osteoarthritis and rheumatoid arthritis.

Miller[88] developed an HPLC method to determine diclofenac in human plasma using automated column switching. The C_{max}, T_{max}, and $t_{1/2}$ values were found to be 1400 ng/mL, 2.6 h, and 0.9 h, respectively. The mean absolute recovery was 90.5%.

Avgerinos *et al.*[89] developed an extractionless HPLC method for the determination of diclofenac in human plasma and urine. The %RSD was found to be <4 in plasma and <5 in urine. The method was also applicable in hospitalized patients.

Mohamed *et al.*[90] developed an improved HPLC method for the quantitation of diclofenac in dog plasma. The C_{max} and T_{max} values were found to be 78.2 ± 12.5 µg/mL and 0.4 ± 0.19 h, respectively, and the mean recovery was 98% ± 5.5%. The method was applied for the determination of the PK parameters of diclofenac given by oral and intravenous (IV) bolus administration to dogs.

Mason and Hobbs[91] reported a simple, rapid HPLC method for the determination of diclofenac in human plasma. The recovery was found to be 82%–97%. This method could be used for clinical research.

Li *et al.*[92] developed an RP-LC method for the determination of DS in human plasma. The mean percentage recoveries of DS were 91.3% ± 10.1% and 93.2% ± 3.9% for the low (0.20 µg/mL) and high (1.20 µg/mL) concentrations, respectively. This method was successfully applied in clinical trials.

Kuhlmann *et al.*[93] developed an RP-HPLC method for the simultaneous bioanalysis of diclofenac and oxybuprocaine in human aqueous humor. The detection limits were 0.5 ng/mL for diclofenac and 50 ng/mL for oxybuprocaine. This method has improved sensitivity and selectivity that enable kinetic studies at very low concentration.

Giagoudakis and Markantonis[94] reported an HPLC method to determine the diclofenac and flurbiprofen in plasma. The average accuracy was 98.8% for diclofenac. The assay was applied in an ongoing PK and PD study of NSAIDs.

Bakkali *et al.*[95] developed an HPLC method for the analysis of DS, IDM, and phenylbutazone in human urine. Absolute recoveries were approximately 50% for phenylbutazone and 85% for DS and IDM.

Lee *et al.*[96] reported an automated narrow bore HPLC method using column switching for the simultaneous determination of aceclofenac and diclofenac from human plasma. The C_{max}, T_{max}, and $t_{1/2}$ values for aceclofenac and diclofenac were 6.6 ± 1.1 and 3.0 ± 0.7 µg/mL; 1.5 and 1.3 ± 0.4 h; and 2.3 ± 0.04 and 2.1 ± 0.1 h, respectively.

Arcelloni *et al.*[97] developed an HPLC method to quantify the diclofenac in human. The significant differences between treatments were evaluated by Student's *t*-test. The results were obtained after rectal administration; T_{max} was 1.0 ± 0.5 h with a C_{max} of 1650 ± 600 ng/mL, which was significantly higher than after the slow release oral one where C_{max} was 630 ± 390 ng/mL and T_{max} was 6.0 ± 2.0 h. The method was statistically significant at $P < 0.05$.

Liu and Tsai[98] described a rapid and sensitive method for the determination of diclofenac in rat bile using *in vivo* microdialysis by HPLC. The C_{max} and $t_{1/2}$ values of diclofenac without cyclosporine A and with cyclosporine A were found

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to be 798 ± 110 and 1187 ± 146 ng/mL and 31 ± 4 and 35 ± 4 min, respectively. The C_{max} increased by adding cyclosporine A. This method has good clinical evidence, showing the value of diclofenac for the treatment of biliary colic.

Dorado *et al.*[99] developed an HPLC method to measure simultaneously diclofenac and its metabolites in human urine. The mean accuracy was greater than 99% for diclofenac and 98%, 99%, and 97% for 3'–OH, 4'–OH, and 5'–OH metabolites, respectively, over 4–12 mg/L range.

Roskar and Kmetec[100] reported an HPLC method to determine diclofenac in the synovial fluid. The recovery of diclofenac was above 87% with a mean value of 91%, and the standard deviation (SD) was less than 5.0%. This method is reliable and suitable for monitoring diclofenac levels after oral or cutaneous administration of the drug to patient with inflammatory and degenerative joint diseases.

Malliou *et al.*[101] developed a sensitive and efficient method for the simultaneous determination of clobutinol, diclofenac, meloxicam, and nimesulide in urine. The intra- and inter-day accuracy and precision at low, medium, and high concentrations were in the range 1.76%–5.06% of %RSD. This method can be applicable for PK study.

Kaphalia *et al.*[102] developed a simple and rapid method to determine diclofenac and its major 4'–hydroxy metabolite in serum. Recovery for the 4'–hydroxy metabolite in serum was found to consistently average from 0.10% to 12%, whereas recovery of diclofenac in serum declined from 0.45% to 0.37%. This method is suitable for the measurement of a major diclofenac metabolite in experimental studies.

Sparidans *et al.*[103] reported a validated LC–MS/MS assay for quantitative analysis of diclofenac and three primary metabolites (i.e., DF–G, 4'–H–DF, and 5'–H–DF) in plasma. The accuracies were found in the range of 90%–108%, within day precisions were <10%, and between day precisions were <13%. The assay will be valuable tool in mouse PK studies. For studies in men, partial revalidation will be required.

Nasir *et al.*[104] developed HPLC–UV method for the simultaneous determination of timolol maleate, rosuvastatin calcium, and DS in pharmaceuticals and physiological fluids. The recoveries in human plasma were 98.72%, 96.04%, and 95.14% for timolol maleate, rosuvastatin, and DS, respectively, whereas in aqueous humor, they were 94.99% and 98.23% for timolol maleate and DS, respectively. This method can also be applied for routine laboratory practice.

Aguiar *et al.*[105] reported an HPLC method for the determination of DS in rabbit plasma and the characterization of its crystalline forms (i.e., anhydrous and hydrate) on the antipyretic effect. The C_{max} and T_{max} values for DS were found to be 2.998 µg/mL and 1.529 h, respectively. The results showed that hydrate and anhydrous forms of DS have a similar PK and PD profile at least in reducing fever in rabbits.

Emara *et al.*[106] developed a bioanalytical HPLC method for monitoring DS in human plasma. The C_{max} and T_{max} values in modified release products (Retard and sustained release) were 765.21 and 722.12 ng/mL and 6.0 and 3.0 h, respectively. This method was validated according to the US FDA guidelines.

Phenylbutazone: Pound and Sears[107] reported a rapid, sensitive, and precise method for the simultaneous determination of phenylbutazone and oxyphenbutazone in plasma by high-speed liquid chromatography. The mean recovery values of 99.44% ± 1.17% and 99.28% ± 1.26% were obtained for phenylbutazone and oxyphenbutazone, respectively. It can be used for the analysis of phenylbutazone and oxyphenbutazone in multiple dose as well as single dose PK studies.

Marunaka *et al.*[108] reported a precise and sensitive HPLC method for the determination of phenylbutazone and its metabolites in plasma and urine. The detection limit for phenylbutazone, oxyphenbutazone, and for γ-hydroxyphenylbutazone was 0.05 µg/mL. The overall recoveries of phenylbutazone, oxyphenbutazone, and γ-hydroxyphenylbutazone were 96.7% ± 1.7%, 93.1% ± 3.7%, and 81.7% ± 4.2%, respectively. The present assay method was then applied to the plasma and urine of other animals and men to which phenylbutazone and its metabolites were added.

Hardee *et al.*[109] developed an HPLC method for the simultaneous determination of flunixin, phenylbutazone, oxyphenbutazone, and γ-hydroxyphenylbutazone in equine plasma. Absolute recoveries found were 99% ± 2% for oxyphenbutazone, 96% ± 3% for NAP, 97% ± 4% for flunixin, 96% ± 3% for phenylbutazone, and 98% ± 2% for the γ-OH. This study also presented results for clinical cases of intestinal ischemia treated with non-steroidal anti-inflammatories.

Taylor and Westwood[110] developed an HPLC method for the quantitation of phenylbutazone and oxyphenbutazone in equine plasma. Confirmatory analysis was achieved by GC–MS with on-column derivatization (methylation) of back extracted residues from the HPLC method. The accuracy ranges found were 53.5%–63.1% for phenylbutazone (PB) and 43.3%–47.2% for oxyphenbutazone (OPB).

Neto *et al.*[111] described a method for the qualitative and quantitative determination of phenylbutazone and oxyphenbutazone in horse urine and plasma samples by HPLC and GC–MS method. The limit of detection was 0.5 µg/mL and the limit of quantitation was 1.0 µg/mL for both drugs. The recoveries were found to be 83% and 105% for PB and OPB, respectively. This method gives enough sensitivity to be used in the anti-doping control of racehorses.

Haque and Stewart[112] reported a direct injection method for the determination of phenylbutazone and its active metabolite oxyphenbutazone in serum by using the semipermeable surface (SPS) column. Recoveries of phenylbutazone and oxyphenbutazone on the SPS column were determined to be

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79.7% ± 2.7% and 94.2% ± 4.5%, respectively. This method is useful for PK and TK studies of both analytes.

Grippa *et al.*[113] described an RP-HPLC method for the simultaneous analysis of selected steroidal and NSAIDs in equine serum suitable for anti-doping control. The overall recoveries were found to be 89.0% ± 7.8% for hydrocortisone, 88.2% ± 0.4% for dexamethasone, 37.9% ± 0.9% for oxyphenbutazone, 6.5% ± 0.9% for probenecid, 78.1% ± 5.5% for IDM, and 51.5% ± 2.7% for phenylbutazone.

Asea *et al.*[114] developed a sensitive liquid chromatographic method for the analysis of phenylbutazone drug residues in bovine, equine, and porcine muscle tissues. The mean recovery of phenylbutazone from bovine muscle tissues was found to be 58%.

Igualada and Moragues[115] developed an ion-trap LC–MS method to determine oxyphenbutazone and phenylbutazone residues in the urine of several animal species. The method was validated according to the requirements of the 2002/657/EC European decision, and the calculated decision limit (CCα) and detection capability (CCβ) were 2 and 3 ng/mL, respectively.

Oxyphenbutazone: Sioufi *et al.*[116] described a simple and rapid HPLC method for the determination of oxyphenbutazone in human plasma. The mean recovery was found 98.4% ± 7.1%. It is useful to determine OPB in small volumes of plasma when the drug is administered to children.

Sulindac: Shimek *et al.*[46] described a rapid, specific HPLC method for the determination of IDM, sulindac, and tolmetin by isocratic and gradient elution to determine these drugs and metabolites. The recoveries were found to be 66.41% ± 0.71% for IDM, 69.04% ± 1.13% for sulindac, and 73.06% ± 2.65% for tolmetin. This method can be recommended for routine patient monitoring or PK studies.

Swanson and Boppana[117] developed sensitive HPLC method for the measurement of sulindac and its metabolites in human plasma and urine. The recovery was found to be 89% for sulindac from both plasma and urine. This method can be applied to studies on the bioavailability, metabolism, and clearance of sulindac in human.

Grgurinovich[118] reported a sensitive HPLC of sulindac and its sulfone and sulfide metabolites in plasma. The recovery was found to be 95.1% ± 5.24% for sulindac. This method does not require solvent programming to achieve suitable separation and elution times.

Ray *et al.*[119] developed an HPLC method for the determination of (Sulindac sulfone) derivative of sulindac-1 in human plasma, urine, and feces. The extraction efficiency of FGN-1 was approximately 75% from plasma, 90% from urine, and 97% from feces.

Steroids

Corticosteroids: Fluri *et al.*[120] reported the development of a method for the confirmation of synthetic CRS in doping urine samples by LC-ESI-MS. Detection limits were determined as ≤1 ng/mL, the limit of confirmation was at 1–5 ng/mL. This method is selective and sensitive, which assures the exclusion of false positive results obtained by corticosteroid group enzyme-linked immunosorbent assay screening tests.

Sangiorgi *et al.*[121] described an LC–MS method for the determination of CRS in bovine urine. The recoveries were found at two different levels (i.e., 5 μg/kg % relative coefficient of variation (RCV) and 1 μg/kg % RCV), 55.6% (11.2%) and 45.8% (12.4%) for TMC, 68.7% (10.1%) and 97.0% (8.8%) for prednisone (PN), 72.8% (9.6%) and 103.7% (9.5%) for PN, 87.5% (9.1%) and 106.4% (8.1%) for dexamethasone, 91.4% (8.2%) and 113.2% (4.2%) for betamethasone, 70.7% (9.0%) and 87.6% (9.5%) for flumethasone, 71.9% (5.6%) and 95.5% (7.2%) for TMC acetonide, respectively. Neutral loss mode is suitable for the detection of all the CRS for their simultaneous determination with a limit of detection of 1 μg/kg. The method fully meets the European Union (EU) legislation requirement for the determination of the banned drugs.

Rönquist-Nii and Edlund[122] developed an LC–MS/MS method for the determination of corticosterone and 11-dehydrocortisone (11-DHC) levels in mouse liver and adipose tissue and hydrocortisone and cortisone levels in human adipose tissue. The absolute recoveries from spiked mouse liver homogenate were 96% for corticosterone and 100% for 11-DHC. The recoveries from spiked mouse adipose homogenate were 99% for corticosterone and 93% for 11-DHC. The recoveries from human adipose tissue homogenate were 100%, 92%, and 89% for hydrocortisone and 95%, 88%, and 86% for cortisone.

Leung *et al.*[123] described LC–MS/MS methods for the screening of CRS and basic drugs in horse urine. For CRS, the precision ranged from 2% to 11%, and the relative retention times ranged from 0% to 0.49%. For basic drugs, the precision ranged from 5% to 17%, and the relative retention times ranged from 0.65% to 1.83%. This method is useful for the screening of CRS and basic drugs in equine sports at low ppb (parts per billion) levels in horse urine.

Spyridaki *et al.*[124] developed an LC-ESI-MS ion trap method for the determination of CRS and the quantification of ephedrine, salbutamol, and morphine in urine. The recovery was found to be from 74% to 113%, and 100% recovery was observed only for prednisolone (PO). This method is useful in Olympic Games Athens for doping control analysis.

Ho *et al.*[125] reported an LC–MS method for the screening of anabolic steroids, CRS, and acidic drugs in horse urine. The recoveries found for anabolic steroids ranged from 31% to 81%, and for CRS, they ranged from 4% to 87%, and for acidic drugs, they ranged from 7% to 97%. The purpose of the study is for doping control in equine sports.

Cho *et al.*[126] developed a method to measure the levels of the 21 endogenous CRS in urine samples obtained from the patients with prostate cancer and Benign prostatic hyperplasia

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by LC–MS/MS. The recoveries were found in the range of 85%–106%, with the limit of quantitation in the range from 0.5 to 2 ng/mL and accuracy (%bias) of the assay at 95.1%–105.4%. This method has a sufficient sensitivity to allow the profiling of both gluco- and minerolo-CRS at a time.

Andersen *et al.*[127] developed a method for the quantitative determination of CRS in urine by LC–MS. This method was validated according to EU regulations. The relative and absolute recoveries were found to be 96%–103% and 81%–89%, respectively.

Gao *et al.*[128] developed a novel SPE-LC-MS/MS method for the quantitative determination of six CRS in *ex vivo* samples. The linearity range was 0.4–30,000 fmol. This method is developed to assess the effect of pharmacological inhibitors of 11B- Hydroxysteroid dehydrogenase-1.

Croes *et al.*[129] developed an LC/Tandem mass spectrometry method for the determination of 12 CRS in bovine liver, which has been optimized and validated in accordance with the European Commission decision 2002/657 EC. The mean recoveries were between 91% and 109%, repeatability and reproducibility coefficients of maximum were 13.7% and 18.0%, respectively.

Dusi *et al.*[130] developed an LC–MS/MS method for the simultaneous determination of nine corticosteroid residues in bovine liver samples. The recoveries were above 62% for all analytes. Repeatability and reproducibility for all analytes were below 7.65% and 15.5%, respectively. This method applied to the confirmation of corticosteroid treatments within Italian National Residue Control Program.

Deceuninck *et al.*[131] developed an ultra-high performance liquid chromatography (UHPLC) method for the determination of maximum residual limit (MRL)–regulated CRS in liver from various species. This method was validated according to the 2002/657/EC requirements. The decision limit (CCα) values were 2.31, 2.35, 11.93, and 11.88 µg/kg, whereas the detection capability (CCβ) values were 2.57, 2.63, 13.60, and 14.02 µg/kg for dexamethasone, betamethasone, PO, and methylprednisolone, respectively. The method was developed in order to obtain an efficient separation of stereoisomers.

Pavlovic *et al.*[132] developed a quantitative LC–ESI single quadrupole MS method for the determination of cortisol (CRL), cortisone, PO, and PN in bovine urine. RSDs were found to be 4.9% for PN, 6.8% for cortisone, 10.5% for CRL, and 15.6% for PO. This method might be used in the screening of glucocorticoid abuse.

Marcos *et al.*[133] developed an LC–MS method for accurate and precise measurement of endogenous corticosteroid profiles in human urine. Recoveries were higher than 80% and intra-assay precisions were below 20% at three concentration levels. In this article, they studied 47 steroids in healthy individuals. This method is useful for clinical purposes due to satisfactory

quantitative results, short analysis time, low sample volume, and simple sample preparation.

Rey-Salgueiro *et al.*[134] developed an LC-MS method for the simultaneous determination of five CRS in pig saliva. The analyte recoveries were in the range of 60 to 90%. There was a significant correlation detected between CRL and CRS, and they hypothesized that CRL and CRS could be used both as biomarkers of non-stress in the saliva of pigs.

Prednisolone: Loo *et al.*[135] described a sensitive, specific HPLC method for the determination of PO in human plasma. The mean recovery was found to be 98.6%. This method is also useful for assessing the specificity and accuracy of a radioimmunological assay for PO.

Frey and Frey[136] developed an HPLC method for the simultaneous measurement of PN, PO, and 6β-hydroxyprednisolone in human urine. The analytical recovery for 6β-hydroxyprednisolone and for [³H] prednisolone was 70% ± 2% and 85% ± 3%, respectively.

Ui *et al.*[137] described a reliable and rapid method for the determination of PN and PO in human serum by HPLC. The recovery was observed 83.4% for each of the steroids. This method has good applicability, which shows that conversion of PN into PO is impaired in patients with liver cirrhosis.

Prasad *et al.*[138] described an HPLC method for the simultaneous determination of PA, PO, PN, cortisone, and hydrocortisone in swine plasma. The average recovery of PA, PO, and PN at 20 ng/mL was between 70% and 90%.

Carlin *et al.*[139] developed an RP-HPLC method for the analysis of PA and related corticoids in swine plasma. The recoveries were found to be 87% ± 13%.

Yamaguchi *et al.*[140] developed an LC method for the determination of PO and PN in plasma. The recoveries of PO and PN were 86.4% ± 3.3% and 88.3% ± 3.5%, respectively. This method may be useful for the determination of TMC and methylprednisolone in biological materials.

Musson *et al.*[141] developed an RP-HPLC assay method for PO, PA, and prednisolone sodium phosphate in rabbit aqueous humor and ocular physiological solution. The coefficient variation was found in between 3.99% and 9.11% for pred-P, pred-A, and PO.

Garg and Jusko[142] developed an HPLC method for the simultaneous determination of PN, PO, and their major hydroxylated metabolites in human urine. The extraction recovery of PO was approximately 75%, whereas for the other steroids, including PN, the recoveries averaged to approximately 65%. This method is also useful for routine clinical studies.

Jusko *et al.*[143] developed a precise, reproducible, and specific HPLC assay method for the simultaneous determination of PN, CRL, and PO in human plasma. The mean recoveries were found in the range from 72% to 78%.

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Hirata *et al.*[144] developed an HPLC method for the simultaneous determination of deflazacort metabolites II and III, CRL, cortisone, PO, and PN in human serum. The recoveries were found in the range between 82.7% and 102.7%.

Döppenschmitt *et al.*[145] developed an HPLC method for the simultaneous determination of PO, PA, and hydrocortisone in human serum. The absolute recoveries were found for three analytes in the range between 72.6% ± 2.1% and 89% ± 4.3%. This method is useful to estimate the side effect of the exogenous glucocorticoids on the serum levels of the physiological glucocorticoid hydrocortisone.

AbuRuz *et al.*[146] developed a simple, rapid HPLC method for the simultaneous determination of PO and CRL in plasma and urine. The recovery of CRL from plasma range between 87.0% and 93.1%, and from urine, it was between 85.4% and 101.3%. The recovery of PO from plasma ranged between 82.2% and 89.8%, and from urine, it was between 82.0% and 102.2%.

Frerichs and Tornatore[147] developed an LC–MS/MS method for the determination of the glucocorticoids, PN, PO, dexamethasone, and CRL in human serum. The relative standard deviation was between 2.41% and 7.11% for the between and within day measurements. This method is useful to support clinical pharmacology studies of these glucocorticoids in post-renal transplant patients of varying health status.

Difrancesco *et al.*[148] developed an LC–MS/MS method for the simultaneous analysis of several glucocorticoids, mycophenolic acid (MPA), and MPA glucuronide in human plasma. The %RSD for intraday and inter-day variation was between 0.76% and 9.57% for all analytes. This assay provides a clinical tool for therapeutic drug monitoring.

Ding *et al.*[149] developed an LC–MS/MS method for the determination of PO to the estimation of 11β-hydroxysteroid dehydrogenase activity in human adipose tissue. The percentage recovery of PO was found ranged between 96.6% and 103%.

Chen *et al.*[150] developed an accurate, sensitive, and robust LC–MS/MS method for the simultaneous quantitation of PO and dipyridamole in human plasma. The mean extraction recoveries were in the range of 92.2%–104%. This method is applicable to a PK study and provide efficient and timely support for further clinical studies.

Ionita *et al.*[151] developed a highly sensitive, selective, and robust LC–MS/MS method for the simultaneous quantification of CRL, cortisone, PO, and PN in human plasma. Recovery was found to be within 98%–105% for each of the four compounds. This method is successfully used to analyze over 500 incurred samples obtained from kidney transplant recipients who were treated with PN as well as with up to 21 other medications.

McWhinney *et al.*[152] described an UHPLC–MS/MS method for a routine laboratory to determine CRL, cortisone, PO, dexamethasone, and 11-deoxycortisol in plasma, plasma ultrafiltrate, urine, and saliva. The average recovery was found

to be 108%. This method should be suitable for use in a high-volume routine laboratory.

Fung *et al.*[153] reported an LC–high resolution mass spectrometry method for quantifying PN and PO in human plasma. The extraction recovery was 68%–69% for both analytes. The assay accuracy was in between 98.4% and 106.3%.

Li *et al.*[154] developed an UPLC–MS/MS method for the simultaneous quantification of amoxicillin (AMOX) and PO in bovine milk. The mean recoveries were 89.2%–92.3% for AMOX and 98.7%–102.8% for PO. The method is validated according to European Commission requirements.

Pavlovic *et al.*[132] developed an LC–ESI method for the determination of CRL, cortisone, PO, and PN in bovine urine. Intraday and intermediate precision were estimated where RSD < 17%. This method is considered as a possible biomarker of illegal treatment.

Liu *et al.*[155] developed a reliable UPLC–MS/MS method for the simultaneous measurement of AMOX, clavunic acid (CLAV), and Prednisolone (PSL) in cow's milk. The recoveries of three analytes were found within 84.2% to 101.45%. This method is applicable to study the comparative kinetic behavior of AMOX, CLAV, and PSL after intermammary infusing in healthy mastitis cows.

Huang *et al.*[156] developed a metabonomic method based on UPLC–MS to profile the metabolic alternations of PO-induced osteoporosis. The %RSD for urine and serum were found in between 3.6%–9.0% and 1.1%–5.2%, respectively. The work also showed that the metabonomic method is a promising tool in the research of traditional Chinese compound medicine.

Triamcinolone: Döppenschmitt *et al.*[157] developed an HPLC method for the simultaneous determination of TMC acetonide and hydrocortisone in human plasma. The absolute recoveries of two analytes were found in the range 89.5% ± 4.5% to 100.1% ± 2.3%.

Główka *et al.*[158] described a sensitive and specific RP-HPLC method for the determination of small quantities of TMC in plasma in the presence of endogenous steroids. The recovery of TMC ranged from 76% to 83%. This method is useful for PK and bioavailability studies of TMC, administered in small doses.

Vieira *et al.*[159] reported a specific and reliable HPLC method for the simultaneous quantitative determination of TMC acetonide and budesonide in microdialysate and rat plasma. The mean absolute recovery at low, medium, and high quality control samples was 109%, 103%, and 99.6%. This method is applicable for the bioanalysis of TMC in clinical studies using free drug monitoring via microdialysis.

Microtubule inhibitor

Colchicine: Jiang *et al.*[160] developed a rapid and sensitive method to determine colchicine in human plasma by LC–MS/

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MS. The mean recoveries of colchicine were found to be 95.6%–105.3%. This method was applied to a PK study of colchicine in healthy volunteers given an oral dose of 2.0 mg.

Chen *et al.*[161] described a simple and sensitive HPLC method for the determination of colchicine in mouse plasma. The mean recoveries of colchicine from mouse plasma at the concentration of 3, 120, and 900 ng/mL were 92.8%, 94.6%, and 96.0%. This method is used in the study of PK of colchicine after IV injection and intraperitoneal injection.

Bourgogne *et al.*[162] developed an automated LC–MS/MS method for the determination of colchicine in human plasma using Turbulent flow chromatography-LC-MS/MS. The accuracy was found to be 84.4%–110%. This method is suitable for monitoring intoxication in patients undergoing chronic treatment and is routinely applied to toxicological samples.

Kovvasu *et al.*[163] described a simple, reliable, and rapid LC–MS/MS method for the determination of colchicine in human plasma. The mean recovery was found to be 97.3% ± 1.30%. This method was fully validated as per the US FDA guidelines, and well suitable for PK or bioavailability/bioequivalence application.

Chronic gout

Uricosuric drugs

Sulfinpyrazone: Inaba *et al.*[164] described HPLC method for determination of sulfinpyrazone (SO) in serum. The percentage recovery was found to be 80%–94%. This method is specific enough and useful when a patient is on multiple medications.

Wong *et al.*[165] described a simple, rapid RP-HPLC method for micro-determination of SO in biological fluids. The average recovery of SO was 78.52% ± 4.04%. This method is also allowed for the direct analysis of urine samples containing a sufficiently high concentration of the drug.

Bjornsson *et al.*[166] described a simple, specific, sensitive, and accurate HPLC assay for the simultaneous analysis of SO and two of its metabolites in plasma and urine. The total recoveries by two different extraction procedures were found to be between the range of 50%–65% and 70%–80%.

Jakobsen and Pedersen[167] described HPLC method for the simultaneous determination of SO and four of its metabolites. The percentage recovery of SO and its metabolites (SO$_2$, S, SOOH, and SOH) was 85% and 85%, 88%, 16% and 99%, respectively.

Godbillon *et al.*[168] described an HPLC method for the analysis of the sulfide metabolite of SO in plasma. The mean recovery was found to be 95%–102%. This method is useful for the assay of sulfide in plasma.

de Vries *et al.*[169] developed an HPLC method for the analysis of SO and its metabolites in human plasma and urine. The recoveries were found to be 90%–100%. The method is useful

in human PK studies, in the drug level monitoring of patients, and in animal experimentation.

Tam *et al.*[170] described a simple and rapid HPLC method for the analysis of SO and four of its metabolites in human plasma. The recovery was found to be higher than 99%. The applicability of this method was shown by measuring SO and its metabolites in human plasma after different routes of administration.

Benzbromarone: Vergin and Bishop[171] described a specific, sensitive, and rapid procedure for the simultaneous determination of benzbromarone and benzarone in serum concentration using HPLC method. The recovery was found to be 80% ± 1.45% for benzbromarone over a range of 1.29–10.30 µg/mL. This method is also suitable for measuring or determining urine levels and plays a subordinate role in benzbromarone therapy.

Arnold *et al.*[172] developed an LC–MS method using a thermospray interface where seven benzbromarone metabolites in human plasma and urine were identified. In this work, they used electron impact ionization for off-line technique and thermospray for on-line interfacing; by comparing these techniques, they concluded that EI is suitable for identification of major metabolites, which requires relatively large amounts of analytes.

Wu *et al.*[173] developed an HPLC-quadrupole time of flight-MS method for the investigation of benzbromarone metabolites in rat plasma, urine, feces, and bile samples. Among the 17 metabolites, the deoxidized phase-I metabolites and an array of phase-II metabolites–surface conjugates were detected in the biological samples.

Uric acid synthesis inhibitors

Febuxostat: Wang *et al.*[174] developed an LC–MS/MS method for the determination of febuxostat in human plasma. The mean recovery of febuxostat and internal standard (IS) was found to be 96.16% and 98.6%, respectively. The intra- and inter-day precision were less than 7.9% and 7.2%, respectively. Instability of analyte in human plasma was not observed when stored at –20°C for 31 days.

Vaka *et al.*[175] reported a sensitive LC–MS/MS method for the quantification of febuxostat in human plasma. The mean recovery of febuxostat and IS was found to be 82.7% ± 3.64% and 88.5% ± 0.75%, respectively. The C_{max} in plasma was 5.21 ± 0.80 µg/mL attained at 0.91 ± 0.27 h (T_{max}). The area under curve (AUC)$_{0-t}$ and AUC from zero to infinity were 15.1 ± 3.56 and 15.1 ± 3.57 µg·h/mL, respectively. The $t_{1/2}$ was found to be 4.23 ± 0.69 h.

Chandu *et al.*[176] developed an LC–MS/MS method for quantification of febuxostat in human plasma. The overall average recovery of febuxostat and Febuxostat D7 (i.e., IS) was found to be 81.59% and 89.28%, respectively. The C_{max} value for test and reference product of febuxostat was found to be 3065.46 and 3726.09 ng·h/mL, and T_{max} was 1 h for both. The

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test and the reference product had similar $t_{1/2}$ (approximately 6.5 h). The analysis of variance study showed that period, sequence, and treatment had no significant effect on C_{max}, T_{max}, AUC_{0-t}, and AUC from zero to infinity.

Xie *et al.*[177] developed an HPLC–MS/MS method for the simultaneous determination of active metabolite of febuxostat (67M-1, 67M-2, and 67M-4) in human plasma. The recovery was greater than 90.13% for all analytes in plasma sample. The method was statistically significant because of no difference in $t_{1/2}$ ($P > 0.05$, paired sample *t*-test) and T_{max} (Wilcoxon signed-rank test) between two dosing groups.

Choudhury *et al.*[178] developed and validated a simple, novel, and sensitive assay method for the estimation of febuxostat in human plasma using HPLC–MS/MS. The mean recovery was found to be 93.16% ± 2.873%, whereas recovery of IS was reported to be 91.60% ± 3.815%. The AUC_{0-t} and C_{max} value for febuxostat were found to be 31.401 ± 5.949 µg·h/mL and 4.936 ± 0.440 µg/mL at the time 2 ± 0.426 h (T_{max}). The method will be widely applicable in preclinical PK, regulatory TK, clinical kinetic study, and bioequivalence study.

Wu *et al.*[179] described an LC–MS/MS method for the simultaneous determination of febuxostat and its three active metabolites in human plasma. The extraction recoveries of the analyte from human plasma ranged from 87.1% to 98.6% with maximum RSD of 13.7% and IS recovery of 89.4% ± 3.8%.

Allopurinol: Reinders *et al.*[180] developed and validated a simple quantitative assay using RP-HPLC method for allopurinol and oxypurinol in human serum. Intra- and inter-day precision showed coefficient of variation < 15% over the complete concentration range; accuracy was within 5% for allopurinol and oxypurinol. This method was proven to be valid for samples of patients with gout who were frequently using concomitant medications.

Kasawar *et al.*[181] reported a rapid and highly sensitive LC–MS/MS method for the determination of allopurinol and oxypurinol in human plasma. The CV for assay precision was found to be <6.94%, and the accuracy was found to be >96.03.

Liu *et al.*[182] developed a sensitive and reliable LC–MS/MS method to determine the concentration of allopurinol and its active metabolite oxypurinol in human plasma and urine. The extraction recoveries of allopurinol from plasma and urine were 51.1%, 55.8%, and 53.0%; and 79.3%, 80.1%, and 83.8%, respectively. The extraction recoveries of oxypurinol from plasma and urine were 72.4%, 75.6%, and 76.7%; and 75.0%, 75.4%, and 78.0%, respectively. This method is useful for preclinical experiment and clinical trials.

Rathod *et al.*[183] described a simple, reliable, and reproducible LC–MS/MS method for the simultaneous determination of allopurinol and its active metabolite oxypurinol in human plasma for a PK/bioequivalence study. The accuracy for analytes varied from 94.74% to 97.03% and from 94.10% to 98.88%, respectively, for both analytes. The method was

successfully applied for a clinical study involving healthy subjects.

Conclusion

This systematic review was able to gather all records present in the scientific literature about validated impurity profile, force degradation, and bioanalytical methods for the quantitation of antigout agent. This review provides information of earlier research work on antigout agent with a view to help the analyst to know about which research work was carried out.

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Conflicts of interest

There are no conflicts of interest.

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