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Critical review of reports on impurity and degradation product profiling in the last decade

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ABSTRACT

Drug impurity and degradation profiling mean the detection, structure elucidation and quantitative determination of impurities and degradation products in bulk drug materials and pharmaceutical formulations. This is today one of the most important fields of activities in pharmaceutical analysis. The reason for this is that unidentified, potentially toxic impurities are health hazards, and in order to increase the safety of drug therapy, impurities should be identified and determined by selective methods.

The aim of this review is to characterise the state-of-art in the field of impurity and degradation profiling of drugs based on papers published in the last decade. The separation and determination of impurities and degradants with a known structure are discussed, but emphasis is placed on the structure elucidation and determination of new (unknown) impurities and degradation products by off-line and on-line chromatographic–spectroscopic methods. The analytical aspects of enantiomeric purity of chiral drugs are also discussed.

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1. Introduction

The “International Council for Harmonisation and Technical Requirements for Pharmaceuticals for Human use (ICH)” presents the following definitions for impurities and impurity profile in new drug substances [1]. An impurity is “Any component of the new drug substance that is not the chemical entity defined as the new drug substance.” An impurity profile is “A description of the identified and unidentified impurities present in a new drug substance”. Impurity profiling is the common name of analytical activities for the detection, identification/structure elucidation and quantitative determination of organic and inorganic impurities as well as residual solvents in bulk drugs and pharmaceutical formulations [2].

The aim of this review paper is to give an overview on the state-of-art in impurity and degradation profiling of drugs based on papers published in the last decade. References to earlier publications on this topic can be found in the author's book [2] and in the author's review paper [3] (citing papers published up until 2000 and between 2000 and 2007, respectively). Only papers dealing with the identification and quantification of related organic impurities and degradation products are reviewed here: inorganic impurities are outside the scope of this paper. The classification of the chapters within the review is methodology-oriented. Both the classical approach, i.e. isolation of the impurity and off-line structure elucidation and the modern approach, i.e. using on-line hyphenated separation/spectroscopic methods are covered with emphasis on the latter. Chiral aspects, namely the determination of enantiomeric impurities in chiral drugs administered as pure enantiomers are also dealt with.

Impurity profiling is of great importance in synthetic drug research and production from the gramscale preparation of new compounds for pharmacological screening through the scaling up procedure and finally the production of bulk drugs. Even minor changes in the production technology, origin of starting materials, conditions of purification and storage can greatly influence the impurity profile. Its importance in the research and production of pharmaceutical formulations is also immense. The pharmaceutical technologist should have a clear picture of the impurity profile of the bulk-drug material used for the development of formulations in order to be able to differentiate between synthesis-related impurities and degradation products. This is of importance in developing stability-indicating analytical methods necessary in the course of the development of a drug formulation.

The importance of drug impurity/degradant profiling is that it affords data which can directly contribute to the safety of drug therapy by minimizing the impurity/degradant-related adverse effects of drug materials and drug preparations [2]. In the last

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decade the importance of assay methods for characterising the quality of bulk drug materials has decreased considerably [4–8]. Simultaneously with this, in the last twenty years the importance of impurity and degradation profiling has been continuously increasing. This can be illustrated by the publication of several books dealing solely with this issue [2,9–19] as well as book chapters [20–25] and reviews [26–43] published in the last decade.

2. Separation and determination of impurities and degradants with known structures

2.1. Introductory remarks

Impurity and degradation profiling begins with the detection and structure elucidation of impurities and degradants and is followed by the development of selective methods for their quantitative determination. If the structure of the impurities and degradants is known, moreover standards of these are available to the analytical chemist, the analytical task is reduced to developing chromatographic or related methods for the separation and quantification of the impurities and degradants of new drugs, or to improving the selectivity, accuracy and precision and decreasing the analysis time of the methods for old drugs as compared with those in earlier publications or in pharmacopoeias.

2.2. High-performance liquid chromatographic (HPLC) methods

2.2.1. Methods with UV-spectrophotometric detection

In the overwhelming majority of cases, the use of reversed phase (RP) HPLC conditions and UV detection has been reported for the solution of problems described in Section 2.1. Classical HPLC columns are still used. One of the several examples is the determination of degradants in azithromycin eye drops: Dikma Technologies Diamonsil C18 column, 5 μm, 150 mm × 4.6 mm was used. The separation and quantification were sufficient, but the run time was very long (25 min) [44]. Similarly long run time (20 min) was found when a Waters Xterra RP18 (5 μm, 250 mm × 4.6 mm) column was used for the determination of potential impurities in fampridine active pharmaceutical ingredient [45]. By carefully optimizing the chromatographic conditions, e.g. using ion-pair chromatography for the determination of impurities in L-asparagine [46], acceptable run times are available using 5 μm stationary phases. Another fairly successful application of the classical columns is the determination of impurities in ticagrelor [47].

Hydrophylic Interaction Chromatography (HILIC), in which the silica surface of the stationary phase is covered with cross-linked diol groups to increase the selectivity in the analysis of polar compounds [48], is often used in the separation and determination of impurities in drugs. This technique was successfully used for the separation and quantification of impurities, e.g. in prulifloxacin [49] metoprolol [50], iodixanol [51] and an antihistaminic compound [52]. The latter paper describes the comparison of HILIC and RP-HPLC. It is worth mentioning that the method can be used in protein analysis as demonstrated in a review paper dealing with the analysis monoclonal antibody-conjugates [53]. Another review deals with the use of four chromatographic techniques for the analysis of therapeutic proteins: RP-HPLC, size-exclusion chromatography, ion-exchange chromatography and HILIC [54].

The most important HPLC development in the last decade is that new stationary phases have been developed and widespread. These are sub-2 μm totally porous and sub-3 μm core–shell particles as the stationary phases of RP-HPLC, replacing step-by-step the 5 μm particles generally used for decades after the introduction of HPLC into pharmaceutical analysis. These changes improve the sensitivity and the resolution but the most important change is the possibility to drastically shorten the run time [55,56]. The techniques using these new stationary phases are named Ultra High Performance Liquid Chromatography (UHPLC), or UPLC when using patented Waters stationary phases and equipments. These techniques have great importance in drug impurity profiling: the majority of the methods developed in the last decade use these new stationary phases.

Papers dealing with the comparison of classical and new-type columns and optimising the resolution of impurities and the run time using suitable software options are of special interest. For example, Kinetex columns of 1.3, 1.7, 2.6 and 5 μm with superficially porous packings (Phenomenex, Torrance, USA) were compared, and using the Drylab software optimal resolution and run time were predicted for other columns. As a result of this, the run time of 50 min of the European Pharmacopoeia method for loratidine related impurities was reduced to less than 4 min [57]. Fig. 1 shows the dependence of the run time on the particle size of the stationary phase. Using the Quality by Design (QdB) principles and the Drylab software the optimization of the separation and thorough reduction of the analysis time of impurities of amlodipine [58,59] and terazosin [60] are also described.

Some of the further several examples for the use of U(H)PLC in drug impurity profiling are the determination of impurities of taxane and degradants of atracurium besylate [61], impurities and degradants in retigabine [62], impurities in heroin [63], zolmitriptan [64] and impurities and degradants in ethinylestradiol [65].

An interesting application of impurity profiling is the estimation of the synthesis pathway of the drug on the basis of synthesis-related impurities and principal component analysis, demonstrated on the example of paracetamol [66].

2.2.2. Methods with aerosol-based detectors

A considerable proportion of pharmaceuticals lack UV-activity. In some cases some of the impurities of UV-active drugs are UV-inactive leading to incomplete impurity profiles. For the HPLC analysis of these compounds aerosol-based detectors are available [67,68]. The analytical signal produced by these detectors is based on the nebulisation of the effluent of HPLC, evaporation to dryness of the forming mini-droplets and measurement of the solid mini-particles of the analytes by different methods. The first method, often used in drug impurity profiling is ELSD (Evaporative Light Scattering Detector) based on the measurement of the light scattered by the mini-particles. This technique is sometimes used up to the present time, e.g. for the impurity profiling of a low molecular weight heparin [69]. However, a newer variant of the aerosol-based detectors, CAD (Charged Aerosol Detector) is much more frequently used even for drug impurity profiling [70]. In this technique the dry particles receive negative charge and the charged particles are measured with an electrometer. The advantageous characteristics of CAD are its high sensitivity and the more universe response to diverse sets of compounds, providing a better estimate of the total amount of material detected on average. Some of its applications are the impurity profiling of L-aspartic acid and L-alanine [71], streptomycin sulfate [72], carbocisteine [73], ibandronate sodium [74], gabapentin [75] and metoprolol [50].

2.2.3. Methods with other detectors

Electrochemical detection methods have little importance in the impurity profiling of drugs by HPLC. As examples the impurity profiling of pipecuronium bromide using coulometric electrode array detection [76], tobramycin with pulsed electrochemical detection [77] or integrated pulsed amperometric detection [78] are mentioned. *Refractive index (RI)* detector was among the standard detectors in the early phase of the development of HPLC. Due

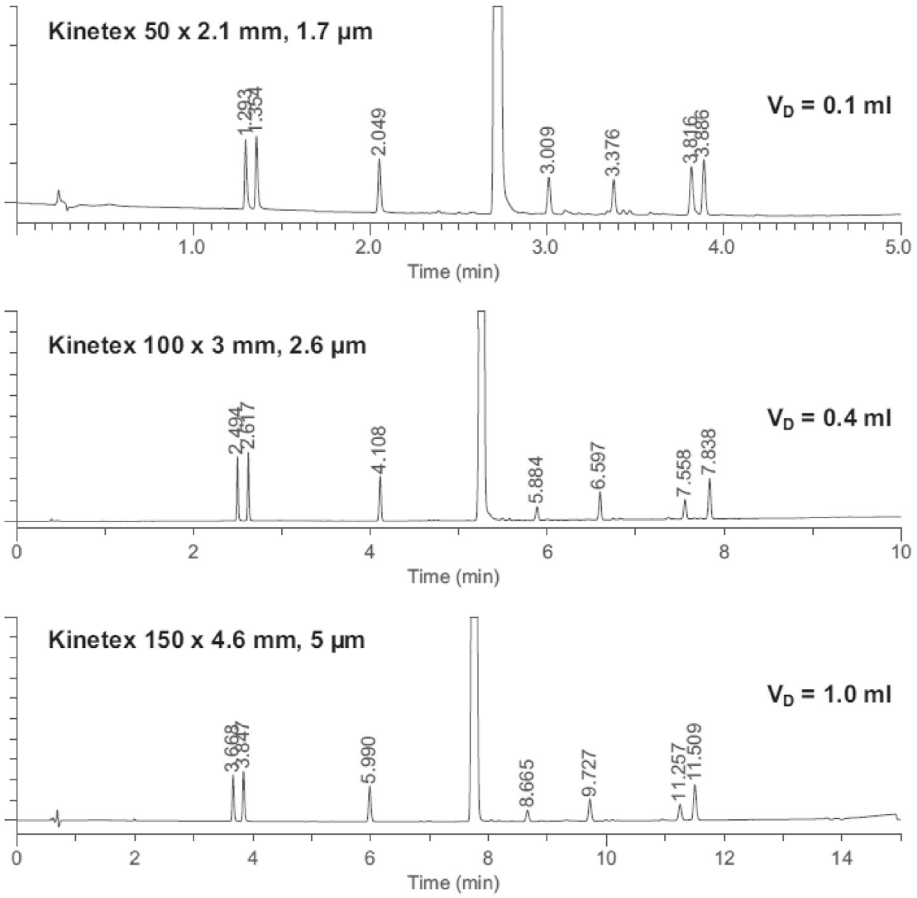


Fig. 1. Comparison of separations of loratadine and its seven related PhEur impurities performed on 50 mm × 2.1 mm, 1.7 µm, 100 mm × 3 mm, 2.6 µm and 150 mm × 4.6 mm, 5 µm Kinetex C18 columns. The flow rate is set to 0.5 ml/min, 1 ml/min and 2.4 ml/min on the 50 mm × 2.1 mm, 100 mm × 3 mm and 150 mm × 4.6 mm columns, respectively. The gradient times are set accordingly to 5, 10 and 15 min. Mobile phase A: 30 mM sodium dihydrogen phosphate buffer, mobile phase B: acetonitrile. From Ref. [57] with permission.

to its low sensitivity this technique is not frequently used for drug impurity profiling. In contrast to this, mass spectrometry coupled to HPLC (*(HP)LC–MS*) is the most developed and generally used method in this field. Since in the majority of these cases MS is also used for the identification/structure elucidation of the impurities, the use of this technique will be discussed in Chapter 3. *Fluorimetric detection* had great importance before the spreading of LC–MS methods due to its higher sensitivity than that of the UV-detector. Since usually pre-column derivatization was necessary to achieve the high sensitivity and many impurities are not readily derivatized, the importance of this technique has greatly decreased.

2.3. Gas chromatography (GC)

Since the possibilities of the use GC are restricted to relatively small molecules and less polar, volatile compounds the application of this technique for impurity profiling is incomparably lower than that of HPLC. In the majority of applications GC is coupled to MS and due to this reason the examples for this are discussed in Chapter 3 restricting ourselves here to applications with flame ionization detector (FID).

The most generally used GC method for impurity profiling of drugs is the determination of solvent residues in the headspace mode [79,80].

Decades ago, when GC was the main method for impurity profiling, the possibilities of its use were extended by derivatizing the polar functional groups of the analytes. Derivatization (alkylsilylation) is still a useful method prior to the GC–FID determination and impurity profiling of illicit drugs [81]. GC–FID is still an important method for the determination and impurity profiling of amphetamines, e.g. methamphetamine [82] in forensic analysis. Another application field of this method is the analysis of low molecular weight intermediates (e.g. 5-chlorovaleroyl chloride [83]) of the syntheses of pharmaceuticals.

2.4. Supercritical fluid chromatography (SFC)

The introduction of the new stationary phases (see Section 2.2.1) and new instruments specifically designed for SFC, and the good properties of this technique (low viscosity of the mobile phases, short analysis time, low fraction of polar organic modifier – usually methanol – to be added to CO_2) resulted in the increasing number of publications describing new applications in pharmaceutical analysis, among others in drug impurity profiling. SFC is a good complementary technique to RP-HPLC enabling in many cases the detection of impurities not detectable by HPLC. The separation of impurities of a great number of drugs in dissimilar stationary phases is described in Ref. [84]. Of the several examples described in the literature the application of SFC to the impurity profiling of mometasone furoate [85], vitamin D3 [86] and salbutamol sulfate [87] are mentioned.

Especially interesting are the papers where the comparison of the impurity profiles of lamivudine, BMS-986001 and efavirenz in a tablet formulation [88] and agomelatine [89] obtained with SFC and UHPLC is described. The performance of the SFC method was found to be at least equivalent to that of the UHPLC method.

2.5. Thin-layer chromatography (TLC)

Thin-layer chromatography (TLC) is a widely used separation technique because of its ease of use, cost-effectiveness, good sensitivity, speed of separation, as well as its capacity to analyse multiple samples simultaneously. TLC plays an essential role in the early stage of drug development when knowledge about the impurities and degradants in a drug substance and drug product is limited. As a consequence of the development in the field of TLC plates (introduction of high-performance thin-layer chromatography – HPTLC) and the instrumentation (versatile densitometers), TLC plays an important role in the quantitative analytical aspects of drug impurity profiling: it is a complementary technique to HPLC, since in the majority of cases it is a normal phase while the latter is a reversed phase technique.

TLC is not used in pharmacopoeias for the assay of bulk drug materials and formulations. At the same time it is an important method for the identification of drugs [90,91] and is used for the impurity profiling in about 25% of the monographs in the main pharmacopoeias [92].

In some of the recently published papers on the determination of impurities by TLC-densitometry the investigation of glimepiride [93], paracetamol and chlorzoxazone [94], moxonidine [95], sulfasalazine [96] and ziprasidone [97] merit mentioning.

Overpressured-Layer Chromatography [98,99] is a branch of TLC with high speed and high selectivity. This method was successfully used for the impurity profiling of several drugs [100].

2.6. Capillary electromigration methods (electrophoretic and related methods)

Due to their advantageous properties capillary electrophoresis and related methods can be successfully used in pharmaceutical analysis among others in drug impurity profiling. However, since HPLC is the preferred method of pharmacopoeias and regulatory agencies for this purpose, the use of these methods is of moderate importance here. The results in this field are the subjects of a book [101] and review papers summarizing the early [102] and new [103–105] aspects.

2.6.1. Capillary electrophoresis (CE)

The results in drug impurity profiling by CE published before 2008 are summarized in a review [106]. Of the later applications of the method the advantages of non-aqueous CE are emphasized in Ref. [107]. CE played an important role in solving the problem of the toxicity of some batches of heparin by the separation and quantification of its toxic impurity oversulfated chondroitin sulfate and also dermatan sulfate [108]. In the impurity profiling of dexamphetamine sulfate by CE, enantiomeric impurities were separated by adding sulfobutylether-β-cyclodextrin and sulfated β-cyclodextrin to the background electrolyte [109]. CE was successfully applied for the impurity profiling of ramipril [110] and for the determination of potentially genotoxic alkylation compounds in drugs [111]. In the latter case preliminary derivatization with 4-dimethylaminopyridine or butyl 1-(pyridinyl- 4yl) piperidine 4-carboxylate was necessary to enable the use of CE and MS detection was used to achieve high sensitivity.

CE and related techniques are important tools for the characterisation of protein-type drugs including their purity control as shown in recently published reviews [112,113].

2.6.2. Electrophoresis-related chromatographic techniques

CE is suitable for the investigation of only ionic compounds (acids in alkaline, bases in acidic medium.) This limitation of CE in the separation and determination of impurities in drugs can be overcome by using electrophoresis-related chromatographic techniques such as micellar electrokinetic chromatography (MEKC), microemulsion electrokinetic chromatography (MEEKC) and capillary electrochromatography (CEC). Several papers deal with the application of these techniques for the separation and determination of impurities in drugs. It is worth mentioning that due to the good characteristics of these methods, some of these are applied to ionisable drugs as well. In spite of these good characteristics the importance of these methods in this field is not comparable with that of HPLC.

2.6.2.1. Micellar electrokinetic chromatography (MEKC). A review of the applications of this method was published in 2012 [114]. Some of its applications are the evaluation of the stability of gentamicin in different carriers [115], impurity profiling of ertapenem [116], budesonide [117], ritonavir [118], the determination of guanine impurity in valacyclovir and acyclovir [119], determination of the degradation products of cyclosporine A [120], stability-indicating assay of gliclazide and its impurities [121] and impurity profiling of goserelin [122].

2.6.2.2. Microemulsion electrokinetic chromatography (MEEKC). The early literature of the application of MEEKC is summarized in a review published in 2007 [123]. In one of the later publications [124] (2-hydroxypropyl)-β-cyclodextrin was added to the background electrolyte to improve the performance of the impurity profiling of oxybutynin. Two cyclodextrin derivatives [methyl-β-cyclodextrin and heptakis (2,6-di-*O*-methyl)-β-cyclodextrin] were used in the case of impurity profiling of clemastine [125]. Similarly to the above mentioned cases, chemometric methods were used also in the case of the determination of almotriptan and its impurities [126] using the principles of QbD. The MEEKC method was used for the determination of impurities and degradants of five fluoroquinolone antibiotics [127]. In the QbD method for the determination of the impurities of diclofenac, methyl-β-cyclodextrin was added to the background electrolyte [128].

2.6.2.3. Capillary electrochromatography (CEC). Several review papers summarize the achievements of CEC usually together with those of other electromigration and micro-chromatographic methods with relatively few applications for drug impurity profiling. Some of these are [129] (only CEC), [130–133] (peptides)]. Monolithic columns are used for the separation of acetylsalicylic acid [134] and pramipexole [135] and their impurities.

2.7. Methods not requiring separation

2.7.1. Spectroscopic methods

Although spectroscopic methods (mainly MS, NMR and UV) are used in drug impurity profiling either in the off-line mode (recording spectra of individual impurities after their separation) or in the on-line mode (using hyphenated separation-spectroscopic methods), recording the spectra of the contaminated sample of drugs directly can be very useful in certain cases [136,137]. The NMR aspects of this possibility are discussed in a book [138] a book chapter [139] and a review [140]. This method is successfully used to detect falsification of drugs as shown in the example of the detection and determination of toxic oversulfated chondroitin sulfate and dermatan sulfate in heparin [141–143] (see also Sections 2.6.1 and 2.7.2).

Mass spectrometry without the separation of the impurity from the drug is frequently used mainly in the forensic analysis aiming the detection of the falsification of drugs [144].

The new possibilities of NMR spectroscopy in the field of proteins were recently reviewed [145].

2.7.2. Electroanalytical methods

Electroanalytical methods have never played an important role in drug impurity profiling. However, due to the recent progress in sensors [146] some interesting possibilities have become available for solving certain problems. For example potentiometric sensor is suitable for purity evaluation of recombinant protein A [147]. Another electrochemical sensor, a reversible pulsed chronopotentiometric polyanion-selective membrane electrode offers a good alternative to the chromatographic and electrophoretic methods for the determination of the toxic impurity oversulfated chondroitin sulfate in heparin [148].

3. Simultaneous application of chromatographic and spectroscopic methods for the structure elucidation of impurities

Before beginning to present examples of the off-line and on-line use of separation by chromatographic and related techniques and spectroscopy, mainly NMR and mass spectrometry for the identification/structure elucidation of impurities and degradants in drugs, it has to be noted that this field is extremely wide. The number of hits at Scopus between 2009 and 2017 with the keywords “drug, impurity, determination” and “drug, impurity, identification” was 1624 and 728, respectively. This means that in this review paper the author is able to make reference only to a small proportion of the published papers.

3.1. Off-line use of chromatographic and spectroscopic methods for the structure elucidation of impurities and degradants

A very simple, useful and still widely used method for the structure elucidation of impurities and degradants in bulk drug materials and their formulations is the off-line method, i.e. the isolation of the impurities followed by spectroscopic studies. The source of the impurities/degradants to be separated are the drug (formulation) itself, or the reaction mixture, mother liquor of the synthesis or samples exposed to forced degradation conditions.

In the majority of cases preparative HPLC using C18 and C8 columns is used for the isolation of the impurities, but in a recent paper the advantages of countercurrent chromatography is described [149].

NMR spectroscopy plays an important role in the off-line structure elucidation of impurities. In many cases after on-line HPLC–MS investigation some of the impurities are separated deliberately for NMR investigation. Two reviews deal with the NMR aspects including the evaluation of spectra after separation, with the direct coupled HPLC–NMR applications and investigation of the samples without separation [150,151]. An example where NMR spectroscopy played a predominant role in the structure elucidation of impurities is the case of dapoxetine [152].

On the basis of using current MS and NMR technologies for the characterisation of bis-indole alkaloids [153] several impurities were isolated and identified in vinblastine and vincristine, solving serious structure elucidation problems [154]. Some further examples of the use of off-line chromatography–spectroscopy are the impurity profiling of rivastigmine tartrate [155] and the degradation profile of ezetimibe [156], olanzapine [157], pemetrexed disodium [158], lamivudine and tenofovir disoproxil fumarate [159] and abacavir [160].

Although IR spectroscopy and X-ray diffraction methods do not play an important role in drug impurity profiling, it is worth mentioning that these methods are sometimes used to confirm the structure elucidation of impurities isolated for NMR analysis.

The use of off-line HPLC–MS is not restricted to small molecules: it is a useful tool also for the structure elucidation of impurities of monoclonal antibodies, e.g. for those in an anti-*Clostridium difficile* IgG1 mAb drug substance [161].

An interesting aspect of drug impurity profiling is that the impurity “fingerprint” of a drug substance can be diagnostic of the synthetic route by which it was obtained, especially if the stable isotope ratio method is used. For example, by the selective extraction of the impurities followed by GC–MS analysis the “route specific” impurities of methamphetamine could be identified [162]. Investigations and results like this can be of great importance from the point of view of criminal investigations and, specifically, on tracking down drug trafficking routes, sources of supply, and relationships between seizures.

To finish this section, an interesting case is presented on the separation and identification of a virtual impurity in ulipristal acetate (ULIPA) [163]. In the course of the impurity profiling of the drug by HPLC–UV using one of the most up-to-date stationary phases (see Section 2.2.1 – Kinetex XB-C18 column (150 mm × 4.6 mm, 2.6 μm core–shell particles), Phenomenex, USA) an “impurity” of 0.07% was found at a relative retention time of 0.98. LC–MS showed a molecular mass with a single mass unit higher than that of ULIPA. After enrichment of the “impurity” by semi-preparative HPLC, MS and NMR investigations have shown that it was a mono-deuterium isotopologue of natural origin of ULIPA. For the structures and the chromatogram see Figs. 2 and 3. It is worth mentioning that before the publication of this paper the isolation and identification of such a virtual impurity was unprecedented in this molecular mass range.

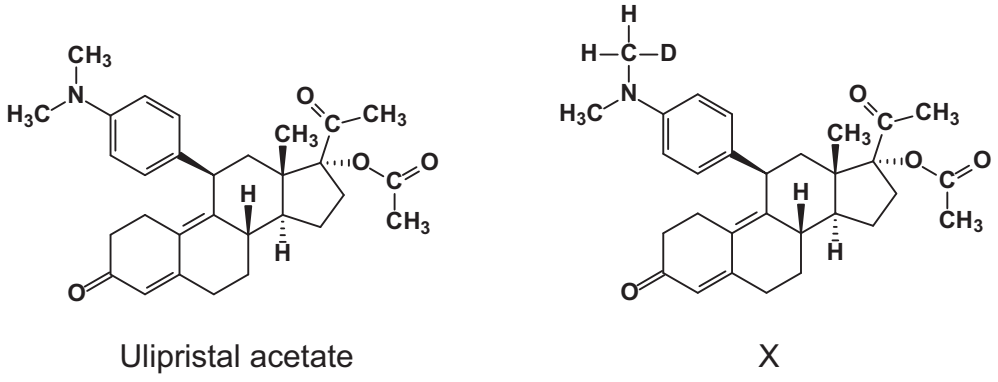


Fig. 2. Structures of ulipristal acetate and its monodeuterated isotopologue (X).

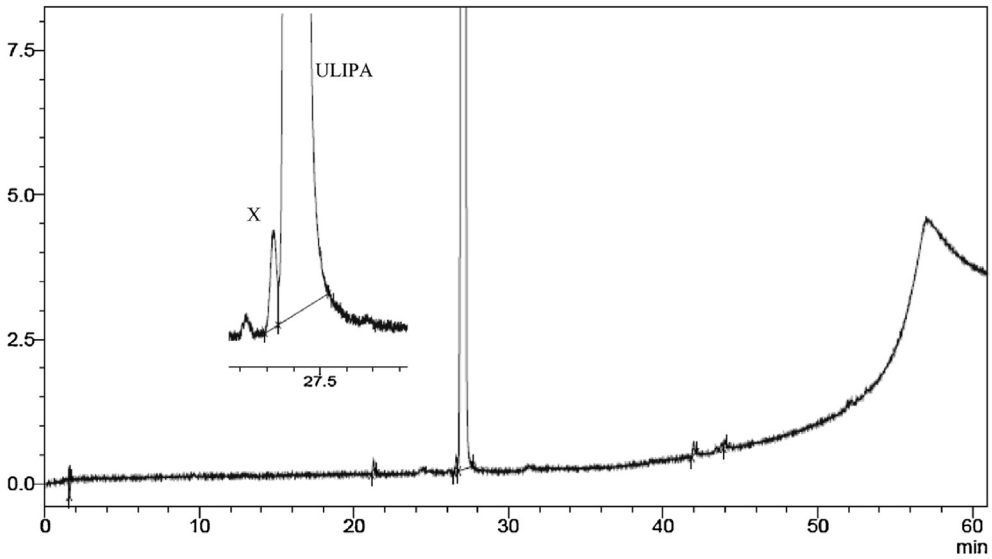


Fig. 3. HPLC chromatogram of ulipristal acetate (ULIPA). Kinetex XB-C18 column (150 mm × 4.6 mm, 2.6 μm, Phenomenex, USA); UV detector: 305 nm. Mobile phase A: 990 ml of water + 10 ml of 1 M triethyl ammonium phosphate (TEAP) solution; mobile phase B: 900 ml of acetonitrile + 90 ml of water + 10 ml of TEAP. Gradient program: the ratio of mobile phase B was 25% (0 min), 60% (35 min), 100% (55 min), 100% (60 min). From Ref. [163] with permission.

3.2. On-line use of chromatographic and related methods coupled to various spectroscopic methods for the structure elucidation of impurities and degradants

3.2.1. HPLC–UV

In almost all cases where HPLC is coupled with high-performance spectroscopic techniques, the UV spectra of the impurities are also available at the end of the chromatographic run if diode-array UV detector is used in the system. Of course the information content of these is not comparable with those of MS and NMR. For this reason chromatographers usually neglect them and UV spectra only very seldom appear in the modern publications dealing with drug impurity profiling. In the author's opinion in some cases at least moderate information is obtainable from the UV spectra taken with the aid of diode-array UV detectors to contribute to the structure elucidation of the impurities. Good examples of this are the structure elucidation of degradants of glimepiride [164] and of nifedipine formed due to the catalysis by atenolol in a dual formulation [165]. Some (mainly old) examples are summarized in [2a].

3.2.2. HPLC–MS

This is the most generally used method of drug impurity profiling. The successful use of this technique for the structure elucidation of all impurities and degradants (without the use of NMR spectroscopy) requires the use of up-to-date HPLC techniques and MS detectors and last but not least a high level of analysts' expertise in drawing conclusions from the degradation profile of the separated peaks as shown in a recently published review [166]. The group of the main author of this review published a series of papers dealing with the structure elucidation of degradants and describing the degradation pathway of several drugs using HPLC coupled with time-of-flight mass spectrometer (LC–TOF–MS) and MS^n mass spectrometer. The investigated materials included glimepiride [164], nifedipine [165], ingredients of various polypills [167], atenolol, lisinopril, aspirin [168], enalapril maleate [169], atenolol [170], lamivudine [171], rifampicin [172], candesartan cilexetil [173], clopidogrel bisulphate [174], lornoxicam [175], furosemide [176], fosinopril [177], emtricitabine and tenofovir disoproxil fumarate [178], comparison of the degradation of tenofovir alafenamide fumarate with tenofovir disoproxil fumarate [179], torasemide [180] and lamivudine and emtricitabine [181]. To increase the information obtainable from the MS fragmentation data, the on-line H/D exchange technique [182] was successfully used in some of the above listed cases [174,175,177,178,180].

A few of the several further examples where the HPLC–MS technique was successfully used for impurity and degradation profiling are listed here: atomoxetine hydrochloride [183], palonosetron hydrochloride [184], bitespiramycin [185], eslicarbazepine acetate [186], thyroxine [187], griseofulvin [188], (Z)-endoxifen [189], monoclonal antibodies [190,191], nevirapine [192], azilsartan [193], trelagliptin succinate [194], bleomycin sulfate, tyrothricin, vancomycin HCl, bacitracin [195] and vonoprazan fumarate [196].

In many cases the HPLC–MS analysis is supplemented by the use of off-line NMR spectroscopy to identify some of the impurities or to confirm the structures obtained by mass spectrometry; (see Section 3.1). The complex mechanism of the oxidative degradation of estradiol was elucidated in this rate [197]. Further examples are the structure elucidation of impurities and degradants in for omeprazole [198], vortioxetine [199], acrivastine [200] and cilostazol [201].

3.2.3. HPLC–NMR

The commercial availability of coupled HPLC–NMR instruments offers a third possibility for the use of NMR spectroscopy in drug impurity profiling. In addition to using NMR without separation of the impurity (see Section 2.7.1) and in the off-line mode after the separation of the impurity by (semi)preparative HPLC (see Sections 3.1 and 3.2.2), coupled HPLC–NMR offers an on-line possibility to record the NMR spectrum of the impurity and the degradant usually complementing the information obtained by HPLC–MS.

The first example here is the detection and determination of toxic impurities in heparin [202] already mentioned (using other methods) in Sections 2.6.1, 2.7.1 and 2.7.2. In this method both the continuous-flow and stopped-flow variant of HPLC–NMR were used. The latter variant was also used when this technique was applied for the structure elucidation of an impurity in icofungipen [203].

A group of authors in the previous section [167–181] used LC–NMR (sample loop technique) in some of their papers parallel

with the LC–MS studies. These papers deal with the degradation profile of telmisartan [204], irbesartan [205], oseltamivir phosphate [206], benazepril [207], cilazapril [208] and a formulation containing amlodipine besylate and losartan potassium [209]. The mechanism of the degradation of irbesartan obtained by the LC–MS and LC–NMR study is shown in Fig. 4 [205].

3.2.4. GC–MS

As described in Section 2.3, the possibilities of gas chromatography in drug analysis are very limited due to the low volatility and high polarity of the majority of drugs. The application of GC–MS is modestly possible [15,210] and was an important method in the early times but LC–MS has now practically displaced it in drug impurity profiling.

3.2.5. TLC–MS

Although on-line coupling of thin-layer chromatography and mass spectrometry is commercially available [211], this technique does not play an important role in drug impurity profiling.

3.2.6. CE–MS and related techniques

Of the separation methods capillary electrophoresis coupled to mass spectrometry (CE–MS) is definitely in the second place behind LC–MS in drug impurity profiling [212,213]. Usually electrospray ionisation is used but other ionisation modes such as atmospheric pressure chemical ionization (APCI), atmospheric pressure photoionization (APPI) and thermospray ionization (TSI) are also available. The performance of these was investigated using the impurities in carbachol, lidocaine and proguanil as examples [214]. Some further examples of the application of CE–MS for impurity profiling of drugs are dendrimeric contrast agent Gadomer [215], heroin [216], tetracosactide [217], anti-cancer drugs [218], the therapeutic peptide aviptadil [219], methamphetamine [220], potentially genotoxic alkylation compounds [111] and lactic acid [221].

CE–MS is especially suitable for the analysis of protein pharmaceuticals. The book dealing with this [222] contains, among others, the identification and determination of host cell impurities in monoclonal antibody drugs. As examples of the application of CE–MS impurity profiling publications describing the identification and determination of impurities in lysozyme are mentioned [223,224].

The coupling of the techniques related to CE (MEKC, MEEKC, CEC – see Section 2.6.2) is available [223,224] but these methods do not play an important role in the impurity profiling of drugs.

4. Separation and determination of enantiomeric impurities

Due to the great importance of chiral aspects in drug biochemistry and pharmacology, enantiomeric analysis is among the hot topics in contemporary pharmaceutical analysis as shown among others by books [225–227] a book chapter [228] and a special issue of the Journal of Pharmaceutical and Biomedical Analysis [229] published in the last decade.

Of the great number of papers published on this subject in the last decade, in this short section only some of those will be referred to which deal with the determination of enantiomeric purity of chiral drugs administered as the pure enantiomer, i.e. the determination of the unwanted enantiomers as impurities in enantiomeric drugs and drug products. These are really considered as ordinary impurities in drugs with similar requirements as for their permitted quantity.

There are three general methods for the simultaneous determination of enantiomers [230]:

1. Indirect methods based on the transformation of the enantiomers by homochiral derivatizing agents to a pair of covalently bound diastereomeric derivatives followed by their separation by chromatographic, mainly HPLC methods using achiral stationary phases.
2. Methods based on the transformation of the enantiomers by homochiral mobile-phase additives to a pair of diastereomeric adducts and separation of the latter by achiral stationary phases, mainly HPLC.
3. Direct separation on chiral HPLC, CEC, GC, SFC, or TLC stationary phases or chiral micellar electrokinetic chromatography (MEKC) and microemulsion electrokinetic chromatography (MEEKC) quasistationary phases.

In the practice of drug impurity profiling, in the last decade mainly general method 3 was used. This will be the subject of this Section.

The standard method for this purpose is HPLC with homochiral additives coated-bonded to silica as the stationary phase [231–242]. This method is almost exclusively used in pharmacopoeias. The most frequently used homochiral additives are tris(phenylcarbamoyl)-cellulose [234–236,238,239,241] or amylose [233,240,242] derivatives. The enantioresolution of the columns can be increased by using chlorophenylcarbamoyl derivatives [234–236,238,239,242]. Other homochiral additives among the above examples are γ-cyclodextrin [231], vancomycin [232] and Pirkle-type additives [237]. It is worth mentioning that in one of the above cases the CEC variant of the method is also described [238].

The determination of the enantiomeric purity of the following compounds was described using the above listed stationary phases: sertraline [231], atenolol [232], esomeprazol Mg [233], S-amlodipine [234], alaptide [235], ropivacaine [236], S-naproxen, laevokalim and S-flurbiprofen [237], amlodipine [238], oxaliplatin [239], ondansetron [240], S-naproxen, esomeprazole [241] and R-besifloxacin [242].

Capillary electrophoresis (CE) is eminently suitable for the determination of the enantiomeric purity of various drugs due to its high resolution power, low reagents and sample consumption, and due the possibility to easily modify the migration of the analytes by the chiral selector (a great variety of cyclodextrin derivatives) added to the buffer solution [243]. Strategies in method development to quantify enantiometric impurities using CE are described in Ref. [244]. Examples of the application of CE for the determination of enantiomeric purity by CE are dexamphetamine sulfate [245], primaquine, tafenoquine, mefloquine, chloroquine, quinacrine [246], chloroquine [247], nicotine butyric acid [248], escitalopram [249], esomeprazol [250], duloxetine [251], levosulpiride [252], tapentadol [253], vildagliptin [254] and colchicine [255].

Among the related methods, micellar electrokinetic chromatography (MEKC) was also applied for the determination of the enantiomeric purity of palonosetron hydrochloride [256], montelukast [257] and ambrisentan [258]. The use of supercritical fluid chromatography (SFC) using a chiral column is also described for the enantioseparation of timolol [259].

5. Miscellaneous

5.1. Proposals to ICH guidelines

As described in the introduction of this paper the ICH Guidelines contain, among others, requirements for controlling the purity of drugs and drug products to be accepted and followed by the drug industry. These guidelines should follow in

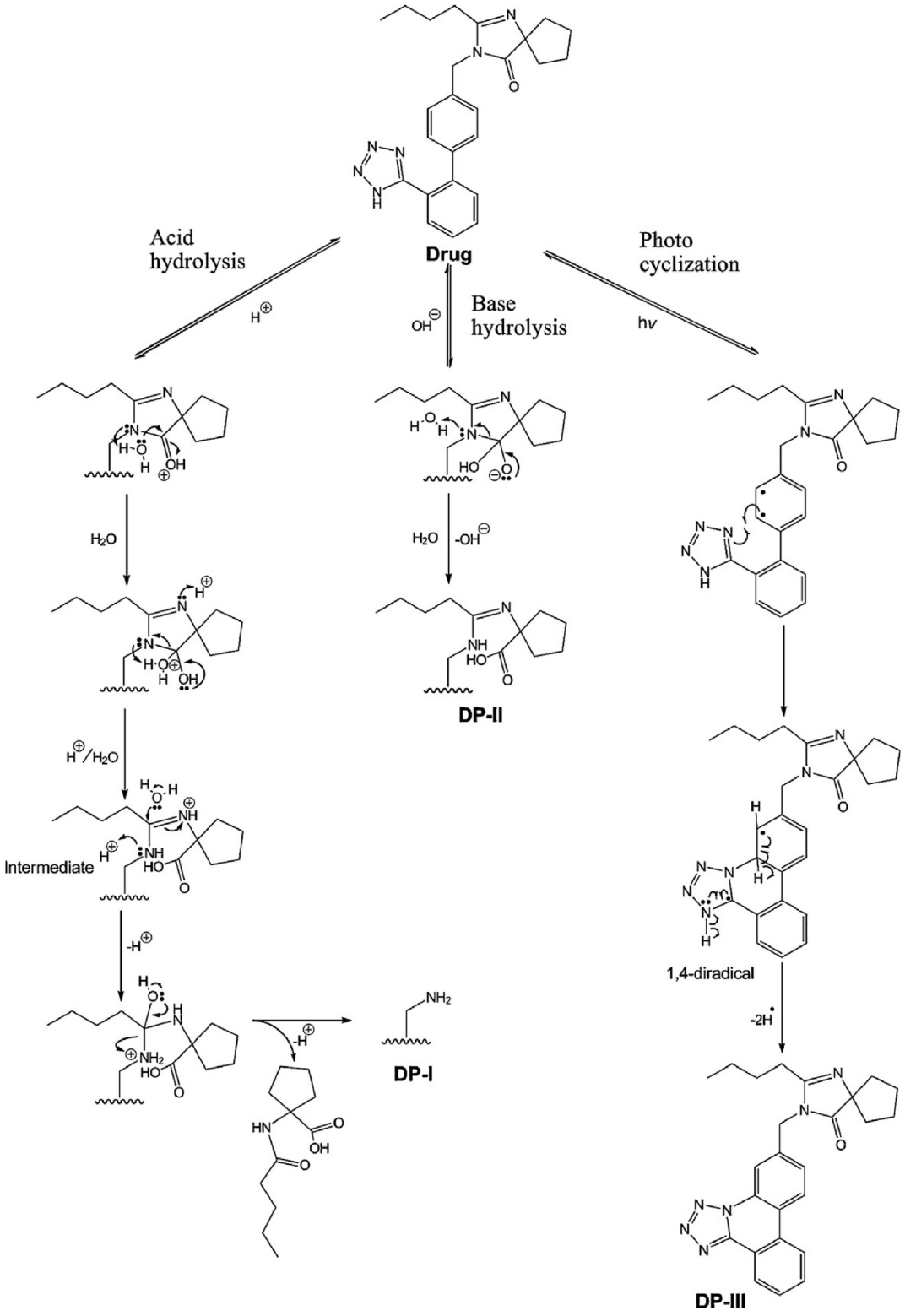


Fig. 4. Mechanism of the degradation of irbesartan. From Ref. [205] with permission.

their new editions the developments in the particular fields. Comments and proposals published in the literature are very useful from this point of view. As examples, commentaries on drug photostability testing [260–262] and genotoxic impurities [263] are mentioned.

5.2. Genotoxic impurities

The special requirements necessitating the use of special, highly sensitive methods to control genotoxic impurities [264] belong to the hot topics of contemporary pharmaceutical analysis. Without

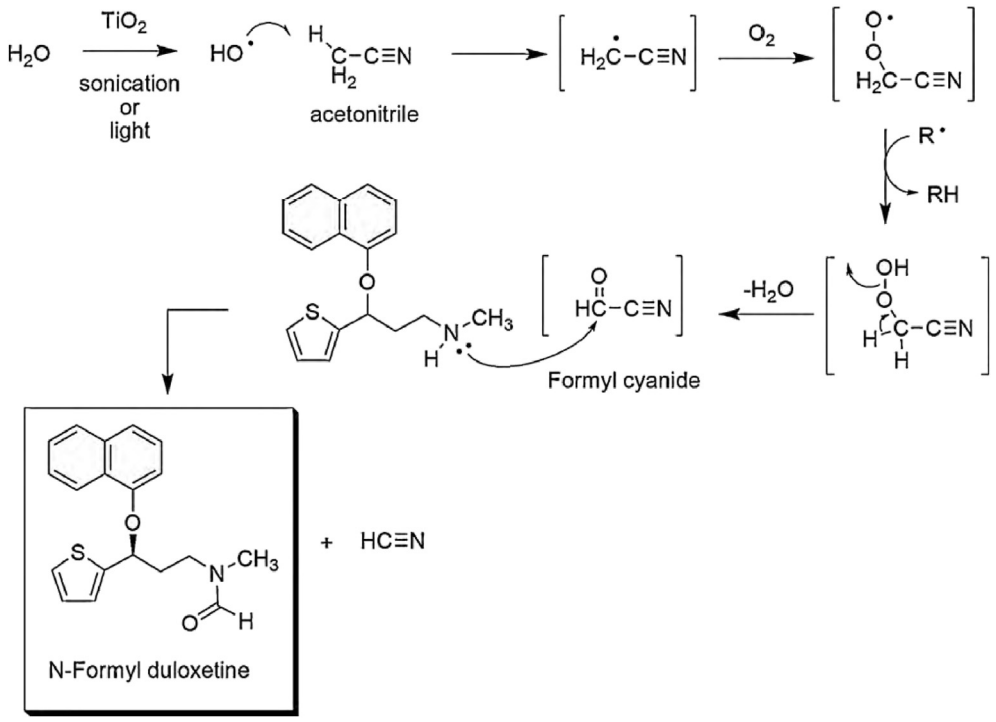


Fig. 5. Proposed mechanism for the artifactual formation of N-formyl duloxetine during sample preparation. From Ref. [271] with permission.

going into details, two books [265,266], two reviews [267,268] and some references in the present review [35,111,263] are mentioned.

5.3. Counterfeit products

The use of analytical methods to fight against counterfeit products is outside the scope of this review. However, some drugs or drug-like compounds may be present illegally at low concentration level in herbal dietary supplements. The analytical problem of detecting, identifying and determining them is similar to the problem of detecting, identifying and measuring impurities in drug materials or drug products [269]. As for details of this problem a recently published review and the references in it are recommended [270].

5.4. Artifacts in drug impurity profiling

Artifacts which look like real impurities can sometimes form during the sample preparation or the analytical procedure. For example, N-formyl duloxetine was found as an impurity in the course of the impurity profiling of duloxetine. However, it was found that this “impurity” is an artifact. The formylating agent is formed from the solvent acetonitrile via a radical initiated mechanism catalysed by the excipient TiO_2, light and sonication, as shown in Fig. 5 [271,272].

6. Conclusions

Although the use of several techniques has been described in the last decade for drug impurity and degradation profiling, the most generally used techniques have remained HPLC-UV for the determination of impurities and degradants with known structures and HPLC–MS with on-line or off-line HPLC–NMR or using NMR spectroscopy without separation for the identification/structure elucidation of unknown impurities and degradants. In the field of HPLC the most important development was the spreading of low particle size core–shell and totally porous stationary phases. These together with the use of new or developed software for the optimization of the chromatographic conditions have greatly increased the sensitivity and selectivity of the method and have dramatically shortened the time necessary for reliable impurity or degradation profiling.

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