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Short Communications

A simple and rapid method to simultaneously analyze ciclesonide and its impurities in a ciclesonide metered-dose inhaler using on-line supercritical fluid extraction/supercritical fluid chromatography/quadrupole time-of-flight mass spectrometry

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ABSTRACT

A simple and rapid on-line SFE/SFC/quadrupole TOF-MS method to simultaneously analyze active pharmaceutical ingredients and impurities from metered-dose inhalers (MDIs) was developed using ciclesonide MDI (CIC-MDI) as an example. CIC-MDI, as drug Alvesco®, has been approved for the treatment of bronchial asthma, and its major impurities are listed in the European Pharmacopoeia and in the supplementary package inserts of Alvesco® (called as "Pharmaceutical interview form" in Japan). In the developed method, CIC-MDI was manually sprayed only once on a glass disc prior to the SFE/SFC/quadrupole TOF-MS. In the SFE, CIC and its impurities and other impurities having various polarities and hydrophobicity, were extracted in 3.5 min and subsequently separated on a CHIRALPAK IE-3 column to be detected by quadrupole TOF-MS in 6.5 min. This method would be applicable to the analysis of other inhalable pharmaceutical products whose sample preparation requires complicated procedures, as well as to the analysis of general pharmaceutical products for profiling impurities.

1. Introduction

The efficacy and safety of pharmaceutical products are ensured by their quality. It is essential that the quality of drug substances and pharmaceutical products are confirmed by analyzing the impurities present in them. Although GC and HPLC have been widely used earlier for quality evaluation of drug substances and pharmaceutical products [1,2], specific detection methodologies in combination with MS are being used to analyze trace impurities, including carcinogens in the recent years [1–3].

Currently, SFC/MS is attracting attention as a novel analytical technology alternative to LC/MS and GC/MS. SFC demonstrates an outstanding isolation capacity for compounds with a wide range of polarities when a mixture of supercritical carbon dioxide (SC-CO_2) and organic solvents is used as the mobile phase [4–10]. In addition, SC-CO_2 is also used as an extraction solvent with some organic modifiers to extract non-polar as well as highly polar compounds. SFE allows rapid extraction under high-pressure and non-high-temperature conditions and is useful as a high-throughput method, because the process from extraction to detection can be automated by connecting on-line with SFC/MS [4–6]. Moreover, quadrupole TOF-MS (qTOF-MS) is suitable for non-target screening to detect unknown impurities because the chemical formula of the detected peaks can be tentatively identified only by obtaining an accurate mass. Although some reports on the analysis of pharmaceutical

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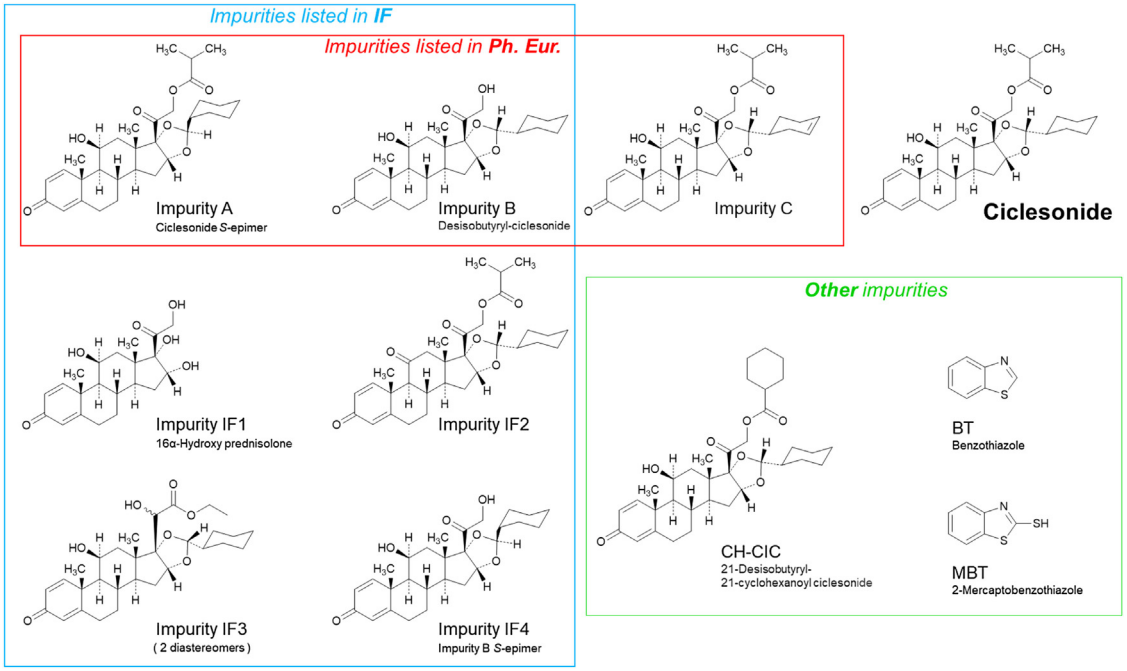

Fig. 1. Chemical structures of ciclesonide and its impurities.

Abbreviation: IF, supplement of package inserts for Alvesco®.

products using SFC/MS [3,11,12] and analysis of residual pesticides in agricultural products using on-line SFE/SFC/MS [13,14] have been published, there are no reports describing the application of on-line SFE/SFC/qTOF-MS in drug substances and pharmaceutical product analysis.

The aim of this study was to develop a simple and rapid method to simultaneously analyze active pharmaceutical ingredient (API) and its various impurities by on-line SFE/SFC/qTOF-MS, using ciclesonide metered-dose inhaler (CIC-MDI) as a model drug, to investigate the usefulness of on-line SFE/SFC/qTOF-MS. Because inhaled pharmaceutical products, such as CIC-MDI, possibly contain process-related impurities as well as contaminants leached from the pressurized container, analysis of the final pharmaceutical product is very important [15,16]. However, secure sample preparation for analysis requires complicated procedures because of the gas contained in pressurized MDI. On-line SFE/SFC/qTOF-MS does not require this procedure.

CIC-MDI has been approved for the treatment of bronchial asthma as Alvesco® and is used for the treatment of coronavirus disease 2019 (COVID-19) in Japan since early in the pandemic, based on the in vitro data demonstrating its robust activity against severe acute respiratory syndrome coronavirus 2 activity and potential anti-inflammatory effects [17–19]. Because it is highly possible that other pharmaceuticals delivered from MDI would be developed for the treatment of COVID-19 in the near future, appropriate and rapid quality evaluation methods are required. Therefore, we attempted to establish a simple and rapid method to analyze API and its impurities simultaneously from MDI using CIC-MDI as an example.

Ciclesonide is prescribed in the Ph. Eur. with the impurity test for three related substances of ciclesonide (impurities A, B, and C) (Fig. 1) [20]. The other four impurities of CIC-MDI (impurity IF1, IF2, IF3, IF4) are listed in the package inserts for Alvesco®, also known as “Pharmaceutical interview forms (IF)” in Japan (Fig. 1) [21]. However, there are no reports that simultaneously analyze all these impurities together with the API in the final product.

In this study, the final product, CIC-MDI, was analyzed by SFE/SFC/qTOF-MS to detect the main impurities and some other impurities, respectively.

2. Materials and methods

2.1. Materials

Alvesco® 200 μg Inhaler 56-puffs was purchased from Teijin Pharma Ltd. (Tokyo, Japan). All CRSs of Ph. Eur. grade (ciclesonide, ciclesonide containing impurity A, ciclesonide impurity B, and ciclesonide impurity C) were purchased from Merck (Darmstadt, Germany). 16α-Hydroxy prednisolone (impurity IF1) was purchased from Cayman Chemical Company (Ann Arbor, MI, USA). Benzothiazole (BT) and 2-mercaptobenzothiazole (MBT) were purchased from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan). Ethanol (99.5 %, HPLC grade), and methanol (LC/MS grade) were purchased from FUJIFILM Wako Pure Chemical Corporation. Ammonium formate was purchased from Nacalai Tesque Inc. (Kyoto, Japan). Carbon dioxide (industrial grade, 99.9 % purity) was purchased from Iwatani Corporation (Osaka, Japan).

2.2. Sample preparation

A glass disc was cut to fit the CIC-MDI. The disc was attached to the inlet port of the inhaler and sprayed once. The disc was cut out with a puncher and then placed into an extraction vessel S (0.2 mL) for SFE-30A (Shimadzu). Approximately 1.00 mg of each compound (ciclesonide, impurity A, impurity B, impurity C, impurity IF1, and MBT) and approximately 10 mg of BT were weighed. Each compound was dissolved in 10 mL of ethanol. Seven standard solutions were mixed in equal amounts, and then 1 μL was injected into another extraction vessel. In addition, 1 μL of the mixed standard solution was injected into the SFC/qTOF-MS system for column scouting.

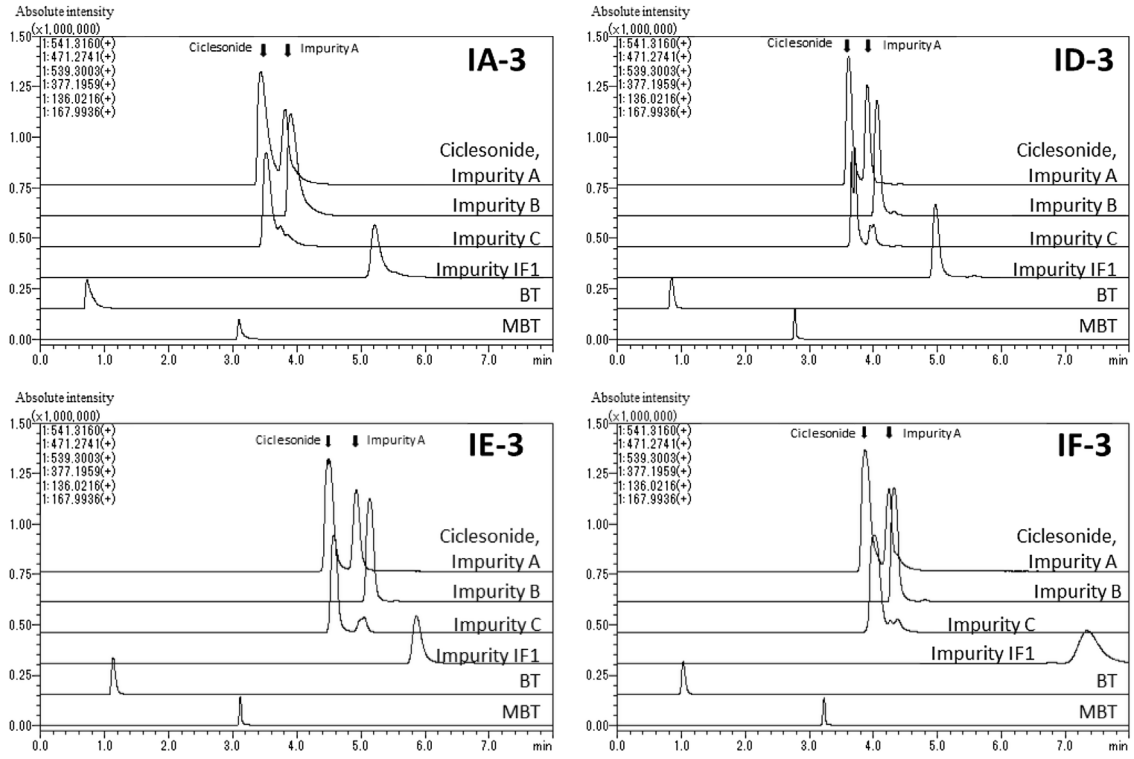

Fig. 2. Comparison of the separation effects of extracted ion chromatogram of SFC/quadrupole TOF-MS among the four different SFC columns.
XICs using the other SFC columns are shown in Fig. S1.
Abbreviations: BT, Benzothiazole; MBT, 2-mercaptobenzothiazole.

2.3. Instruments and analytical conditions

Twenty different SFC columns (Shim-pack UC Diol, RP, Sil, NH2, CN, phenyl, amide, GIS II (4.6 mm I.D. × 250 mm, 5 μm, Shimadzu GLC Ltd., Tokyo, Japan)) and (CHIRALPAK: AD-3, OX-3, AY-3, OD-3, OJ-3, OZ-3, IA-3, IB-3, IC-3, ID-3, IE-3, IF-3 (3.0 mm I.D. × 100 mm, 3 μm, Daicel Corporation, Osaka, Japan)) were prepared for column scouting. The Nexera UC system was used for the on-line SFE/SFC/qTOF-MS analysis and consisted of an SFE-30A auto extractor, an SFC-30A backpressure regulator, an LC-30AD$_{SF}$ pump, two LC-30AD pumps, a DGU-20A$_{5R}$ degasser, a CTO-30AC column oven, an SIL-30AC auto sampler, and an LCMS-9030 quadrupole time-of-flight mass spectrometer (Shimadzu). The SFE analytical conditions were as follows: extraction solvent, liquid carbon dioxide (A)-methanol containing 10 mM ammonium formate (B) (90/10, v/v); flow rate, 3 mL/min; and vessel temperature, 60 °C. The pressure of the pre and post column backpressure regulator was set to 40 MPa and 10 MPa, respectively. Static extraction was performed for 0.5 min and dynamic extraction was continued for 3 min. After a total extraction time of 3.5 min, the valve was switched to SFC analysis mode. The SFC analytical conditions were as follows: mobile phase, liquid carbon dioxide (A), and methanol containing 10 mM ammonium formate (B); flow rate, 3 mL/min; column oven temperature, 40 °C. The pressure of the pre and post column backpressure regulator was set to 40 MPa and 10 MPa, respectively. The gradient elution was as follows: 2% B (0–1 min) and 2%–40 % B (1–5 min), 40 % B (5–6 min), 40–2% B (6–6.1 min), 2% B (6.1–8 min) for column scouting by SFC/qTOF-MS; 0.5 % B (3.5–4 min), 0.5–25 % B (4–4.1 min), 25–40 % B (4.1–6 min), 40 % B (6–8 min), 40–100 % B (8–8.1 min), 100 % B (8.1–9.5 min), 100–0.5 % B (9.5–10 min) for sample analysis by SFE/SFC/qTOF-MS. Pure methanol was selected as the make-up solvent and delivered at 0.2 mL/min. MS was measured in positive-ion electrospray mode. Nitrogen was used as the desolvation gas and the experimental conditions were as follows: neutralizer gas flow rate, 3.0 L/min; heating and drying gas flow rate, 10.0 L/min; interface temperature, 300 °C; desolvation line temperature, 250 °C; heat block temperature, 400 °C. Data were collected over the *m/z* range of 100–1000 with a resolution of 30,000 Full Width at Half Maximum at *m/z* 1,972.

3. Results and discussion

3.1. Column scouting

Firstly, column was scouted to select the best column prior to SFE/SFC/qTOF-MS analysis of CIC-MDI. SFC columns with different stationary phases exhibited significant differences in both selectivity and polarity. To simultaneously detect ciclesonide and its impurities as narrow and symmetrical peaks, 20 different SFC columns (Shim-pack UC Diol, RP, Sil, NH2, CN, phenyl, amide, GIS II, CHIRALPAK AD-3, OX-3, AY-3, OD-3, OJ-3, OZ-3, IA-3, IB-3, IC-3, ID-3, IE-3, IF-3) were tested with mixed standard solution by SFC/qTOF-MS (Figs. 2 and S1). As shown in Fig. 2, the IE-3 column presented the better resolution of ciclesonide and its possible impurities, with all the peaks exhibiting satisfactory separation effects and peak shapes. The elution order observed was BT, MBT, ciclesonide, impurities C, A, B, and impurity IF1. Thus, the CHIRALPAK IE-3 column was selected for the simultaneous detection of ciclesonide and its impurities in SFE/SFC/qTOF-MS.

3.2. On-line analysis of CIC-MDI

Secondly, the mixed standard solution was analyzed using an on-line SFE/SFC/qTOF-MS method, with extraction solvents consisting of liquid carbon dioxide/methanol containing 10 mM ammonium formate (90:10), under static extraction conditions for 0.5 min and dynamic extraction conditions for 3 min at 60 °C. The

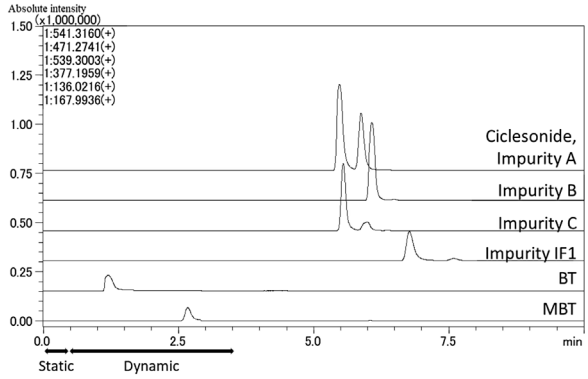

Fig. 3. Extracted ion chromatograms of SFE/SFC/quadrupole TOF-MS of ciclesonide and its impurities.
Abbreviations: BT, benzothiazole; MBT, 2-mercaptobenzothiazole.

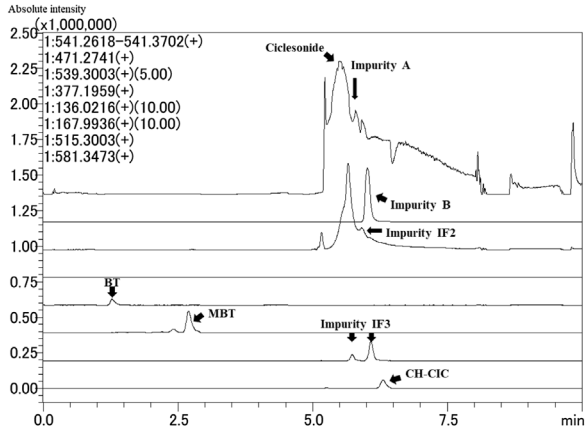

Fig. 4. Extracted ion chromatograms (XICs) of SFE/SFC/quadrupole TOF-MS of ciclesonide metered-dose inhaler.
XIC of *m/z* 539.30 was drawn as five-fold intensity, and XICs of *m/z* 136.02 and *m/z* 167.99 were drawn as 10-fold intensity.
Abbreviations: BT, benzothiazole; CH-CIC, 21-desisobutyl-21-cyclohexanoyl ciclesonide; MBT, 2-mercaptobenzothiazole.

compounds were extracted well in 3.5 min and were separated using SFC/MS by modifying the condition of gradient elution (Fig. 3).

Finally, an on-line SFE/SFC/qTOF-MS method was established for CIC-MDI analysis. A once-pushed sample on the glass filter was successfully extracted, and nine compounds were detected within 10 min, including the extraction time (Fig. 4). Ciclesonide (RT = 5.46 min, *m/z* 541.31 for $[M+H]^+$), impurity A (RT = 5.90 min, *m/z* 541.31 for $[M+H]^+$), impurity B (RT = 6.08 min, *m/z* 471.27 for $[M+H]^+$), BT (RT = 1.19 min, *m/z* 136.02 for $[M+H]^+$) and MBT (RT = 2.68 min, *m/z* 167.99 for $[M+H]^+$) were identified by comparing with their respective standards. The peaks at 5.73 min and 6.12 min were tentatively identified to be two diastereomers of impurity IF3 (*m/z* 515.30 ($[M+H]^+ = C_{30}H_{42}O_7$)) and the peaks at 5.96 min and 6.33 min were tentatively identified to be impurity IF2 (*m/z* 539.30 ($[M+H]^+ = C_{32}H_{43}O_7$)) and 21-desisobutyl-21-cyclohexanoyl ciclesonide (CH-CIC) (*m/z* 581.35 ($[M+H]^+ = C_{35}H_{49}O_7$)), respectively (Table 1). Among the detected compounds, BT and MBT are considered to be impurities derived from the container of CIC-MDI, and not from ciclesonide, the API of CIC-MDI. Extractables and leachables of inhaled pharmaceutical products are commonly evaluated using GC/MS [22,23]. Using the established on-line SFE/SFC/qTOF-MS method, both compounds that are not suitable (ciclesonide) or suitable (BT and MBT) to be analyzed by GC/MS, were detected simultaneously. To characterize this method, additional analyses using the conventional methods (HPLC, LC/MS, GC/MS) were performed, and the details are shown in Supplementary data. These data affirm the advantages, such as the convenience of sample preparation of on-line SFE/SFC/qTOF-MS method. Using the method developed in this study, non-polar as well as polar compounds were able to be detected simultaneously by only one spray of CIC-MDI on the glass disc. Furthermore, it was automatically analyzed in only 10 min after spraying CIC-MDI. This method can be applied as a high-throughput analytical method for profiling impurities in other inhaled or general pharmaceutical products. However, this method is not sufficient for quantitative analysis of impurities as compared to off-line conventional methods. Using triple quadrupole MS with SRM mode as a detector and an appropriate internal standard in addition to SFE may allow higher accuracy and precision in quantitative analysis. We are currently investigating the use of on-line SFE/SFC/triple quadrupole MS for quantitative analysis. Nevertheless, this on-line SFE/SFC/qTOF-MS method can be useful for identifying unexpected unknown impurities arising during the manufacturing processes at the in-process control as well as end product stage of both drug substances and products [24,25].

4. Conclusions

This is the first study on a simple, rapid, and simultaneous analysis method using on-line SFE/SFC/qTOF-MS for detecting both known and unknown impurities in CIC-MDI. This developed

Table 1
The detected compounds by on-line SFE/SFC/qTOF-MS analysis.

Compound	Formula and *m/z* $[M+H]^+$	Listed in		Detected from CIC-MDI
		Ph. Eur.	IF	
Ciclesonide	$C_{32}H_{44}O_7$, *m/z* 541.31	√	√	√
Impurity A	$C_{32}H_{44}O_7$, *m/z* 541.31	√	√	√
Impurity B	$C_{28}H_{36}O_6$, *m/z* 471.27	√	√	√
Impurity C	$C_{32}H_{42}O_7$, *m/z* 539.30	√		Trace
Impurity IF1	$C_{21}H_{28}O_6$, *m/z* 377.20		√	N.D.
Impurity IF2	$C_{32}H_{42}O_7$, *m/z* 539.30		√	*√
Impurity IF3 (2 diastereomers)	$C_{30}H_{42}O_7$, *m/z* 515.30		√	√
			√	√
Impurity IF4	$C_{28}H_{36}O_6$, *m/z* 471.27		√	N.D.
CH-CIC	$C_{35}H_{48}O_7$, *m/z* 581.34			√
BT	C_7H_5NS, *m/z* 136.02			√
MBT	$C_7H_5NS_2$, *m/z* 167.99			√
Number of detected compounds				9

Abbreviations: BT, benzothiazole; CIC-MDI, ciclesonide metered-dose inhaler; IF, supplement of package inserts for Alvesco®; MBT 2-Mercaptobenzothiazole; N.D., not detected; qTOF-MS, quadrupole TOF-MS.
* This peak was tentatively identified. However, the separation from another peak was insufficient, respectively.

method can be applied not only to inhaled pharmaceutical products, but also to general pharmaceutical products.

CRediT authorship contribution statement

Seiji Tanaka: Investigation, Visualization, Writing - original draft, Writing - review & editing. **Nahoko Uchiyama:** Conceptualization, Supervision, Writing - review & editing. **Takahiro Goda:** Investigation, Visualization, Writing - review & editing. **Tetsuo Iida:** Investigation, Visualization, Writing - review & editing. **Shinnosuke Horie:** Methodology, Supervision, Writing - review & editing. **Sayaka Masada:** Investigation, Writing - original draft, Writing - review & editing. **Ryoko Arai:** Investigation, Writing - review & editing. **Eiichi Yamamoto:** Supervision, Writing - original draft, Writing - review & editing. **Takashi Hakamatsuka:** Supervision, Writing - review & editing. **Haruhiro Okuda:** Supervision, Writing - review & editing. **Yukihiro Goda:** Supervision, Writing - review & editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jpba.2021.114253.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Y. Liu, E.P. Romijn, G. Verniest, K. Laukens, T. De Vijlder, Mass spectrometry-based structure elucidation of small molecule impurities and degradation products in pharmaceutical development, Trends Analyt. Chem. 121 (2019), 115686.
[2] S. Görög, Critical review of reports on impurity and degradation product profiling in the last decade, Trends Analyt. Chem. 101 (2018) 2–16.
[3] L. Nováková, K. Plachká, Chapter 16 - Pharmaceutical applications, in: C.F. Poole (Ed.), Supercritical Fluid Chromatography, Elsevier, Amsterdam, 2017, pp. 461–494.
[4] A. Ríos, M. Zougagh, F. de Andrés, Bioanalytical applications using supercritical fluid techniques, Bioanalysis 2 (2010) 9–25.
[5] T. Uchikata, A. Matsubara, E. Fukusaki, T. Bamba, High-throughput phospholipid profiling system based on supercritical fluid extraction–supercritical fluid chromatography/mass spectrometry for dried plasma spot analysis, J. Chromatogr. A 1250 (2012) 69–75.
[6] J. Liu, F. Ji, F. Chen, W. Guo, M. Yang, S. Huang, F. Zhang, Y. Liu, Determination of garlic phenolic compounds using supercritical fluid extraction coupled to supercritical fluid chromatography/tandem mass spectrometry, J. Pharm. Biomed. Anal. 159 (2018) 513–523.
[7] C. Ichikawa, S. Horie, R. Kubota, SFE/SFC-MS, Jpn. J. Pestic. Sci. 41 (2016) 216–222.
[8] J.W. Lee, T. Yamamoto, T. Uchikata, A. Matsubara, E. Fukusaki, T. Bamba, Development of a polar lipid profiling method by supercritical fluid chromatography/mass spectrometry, J. Sep. Sci. 34 (2011) 3553–3560.
[9] A. Matsubara, T. Bamba, H. Ishida, E. Fukusaki, K. Hirata, Highly sensitive and accurate profiling of carotenoids by supercritical fluid chromatography coupled with mass spectrometry, J. Sep. Sci. 32 (2009) 1459–1464.
[10] H.S.H. Yip, M. Ashraf-Khorassani, L.T. Taylor, Feasibility of phospholipids separation by packed column SFC with mass spectrometric and light scattering detection, Chromatographia 65 (2007) 655–665.
[11] P. Prajapati, Y.K. Agrawal, SFC–MS/MS for identification and simultaneous estimation of the isoniazid and pyrazinamide in its dosage form, J. Supercrit. Fluids 95 (2014) 597–602.
[12] T.Sun J. Luo, Y. Xu, X. Sun, S. Yang, M. Yan, Ultra-high performance supercritical fluid chromatography method for separation and quantitation of saikosaponins in herbal medicine, J. Pharm. Biomed. Anal. 199 (2021), 114039.
[13] A.P. Wicker, D.D. Carlton Jr., K. Tanaka, M. Nishimura, V. Chen, T. Ogura, W. Hedgepeth, K.A. Schug, On-line supercritical fluid extraction—Supercritical fluid chromatography-mass spectrometry of polycyclic aromatic hydrocarbons in soil, J. Chromatogr. B 1086 (2018) 82–88.
[14] Shimadzu Corporation, Using the Nexera UC Online SFE-SFC-MS System to Analyze Residual Pesticides in Agricultural Products, 2015 https://www.shimadzu.com/an/sites/shimadzu.com.an/files/pim/pim_document_file/applications/application_note/11632/jpl215036.pdf/.
[15] Committee for Medicinal Products for Human Use, Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products, 2006 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-quality-inhalation-nasal-products_en.pdf/.
[16] Food and Drug Administration Center for Drug Evaluation and Research, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products-Quality Considerations, FDA Guidance Documents, 2018, Dock Number: FDA-2018-D–FDA-1098.
[17] The Japanese Association for Infectious Diseases and Fujita Health University Antiviral Observational Study Group, COVID-19 Ciclesonide Observational Study in Japan [Preliminary Report], 2020 https://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_ciclesonide_eng_1130.pdf.
[18] K. Iwabuchi, K. Yoshie, Y. Kurakami, K. Takahashi, Y. Kato, T. Morishima, Therapeutic potential of ciclesonide inahalation for COVID-19 pneumonia: report of three cases, J. Infect. Chemother. 26 (2020) 625–632.
[19] Y. Yamasaki, S. Ooka, T. Tsuchida, Y. Nakamura, Y. Hagiwara, Y. Naitou, Y. Ishibashi, H. Ikeda, T. Sakurada, H. Handa, H. Nishine, M. Takita, D. Morikawa, H. Yoshida, S. Fujii, K. Morisawa, H. Takemura, S. Fujitani, H. Kunishima, The peripheral lymphocyte count as a predictor of severe COVID-19 and the effect of treatment with ciclesonide, Virus Res. 290 (2020), 198089.
[20] Directorate for the Quality of Medicines of the Council of Europe, the European Pharmacopoeia, Ninth edition, 2016, pp. 2070–2071, Strasbourg, France.
[21] Teijin Pharma Ltd, Supplement of Package Inserts (Pharmaceutical Interview Form) of Alvesco®, 2012 https://medical.teijin-pharma.co.jp/iyaku/product/skhk4v0000000sow-att/skhk4v0000000sp7.pdf.
[22] D.M. Wong, R.L. Firor, Analysis of Extractable/Leachable Compounds from Generic Liquid Drug Formulations Using GC/MSD Systems, Application Note of Agilent Technologies, 2017 https://www.agilent.com/cs/library/applications/5991-5632EN.pdf.
[23] D.L. Norwood, D. Paskiet, M. Ruberto, T. Feinberg, A. Schroeder, G. Poochikian, Q. Wang, T.J. Deng, F. DeGrazio, M.K. Munos, L.M. Nagao, Best practices for extractables and leachables in orally inhaled and nasal drug products: an overview of the PQRI recommendations, Pharm. Res. 25 (2008) 727–739.
[24] ICH Expert Working Group, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, 2000 https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-7-good-manufacturing-practice-active-pharmaceutical-ingredients-step-5_en.pdf/.
[25] B.A. Olsen, A. Sreedhara, S.W. Baertschi, Impurity investigations by phases of drug and product development, Trends Analyt. Chem. 101 (2018) 17–23.