Original Article

Rapid Purification of Drug Enantiomers using Supercritical Fluid Chromatographic Method: Ibuprofen as a Model Compound

Hwa Jong Lee[2], Jasper Gahm[2], Jong Sung Jin[3], Yun Gyong Ahn[1,*]

[1]Western Seoul Center, Korea Basic Science Institute, University-Industry Cooperation Building, 150 Bugahyeon-ro, Seodaemun-gu, Seoul, REPUBLIC OF KOREA.
[2]Verdant Technology, University-Industry Cooperation Building, 150 Bugahyeon-ro, Seodaemun-gu, Seoul, REPUBLIC OF KOREA.
[3]Busan Center, Korea Basic Science Institute, 30 Gwahaksandan 1-ro 60-gil, Gangseo-gu, Busan, REPUBLIC OF KOREA.

ABSTRACT

Background: The purification of drug enantiomers is an essential technique because pharmacological activity differs depending on individual enantiomers. Nowadays, supercritical fluid technology is utilized for various purposes in the pharmaceutical field. **Methodology:** In this study, an efficient and streamlined method development strategy for finding an effective analytical method in supercritical fluid chromatography (SFC) is presented in detail for scaling up to preparative scale and achieving enantiomerically pure product, using ibuprofen as a model compound. **Results:** Through the optimized preparative method presented, the individual (R) enantiomer of the commercial racemate of ibuprofen can be obtained with a recovery yield of 80.0% and an enantiomeric excess of 95.1 and the individual (S) enantiomer can be obtained with a recovery yield of 77.6% with an enantiomeric excess of 99.3, respectively. **Conclusion:** The use of analytical and preparative SFC systems has advantages over the conventional chromatography systems in terms of separation time, reduced solvent consumption and high productivity for ibuprofen's enantiomeric purification.

Key words: Ibuprofen, Analytical supercritical fluid chromatography (Analytic-SFC), Preparative supercritical fluid chromatography (Prep-SFC), Drug, Enantiomer, Purification.

INTRODUCTION

There has been a dramatic increase in interest in chiral drugs which do not indicate whether they are racemic, single enantiomeric, or a mixture of diastereoisomers. Chiral drugs were mostly presented as racemates, a mixture of equal parts left-handed and right-handed enantiomers with the same molecular formula and structure.[1] The pharmaceutical activities of the enantiomers in the human body are often dissimilar and sometimes reversed because of their optical property differences.[2] Chloroquine and hydroxychloroquine which are mentioned most recently as potential cures for corona 19, have been reported to be toxic in the state of S(+) enantiomer in mammals.[3] Thalidomide, a typical example of nervine medicine, also exists in a racemic mixture of (R)- and (S)-enantiomers. Though the (R)-enantiomer is responsible for its intended sedative effects, the (S)-enantiomer is, unfortunately, teratogenic and was directly responsible for the tragic births of thousands of severely disfigured babies in the 1960s.[4,5] The racemic drug benaxoprofen, though a highly effective anti-inflammatory medicine, is no longer sold on the market because the active (S)-enantiomer accumulates in the body to a dangerous degree, causing severe kidney and liver impairment to elderly patients.[6] Furthermore, the (R)-enantiomer directly contributes to the (S)-enantiomer accumulation by inhibiting specific metabolic pathways.[7,8] As a result, the levels of the (S)-enantiomer almost doubles in some patients, resulting in an overdose.[9]

Submission Date: 28-08-2020;
Revision Date: 13-10-2020;
Accepted Date: 22-01-2021

DOI: 10.5530/ijper.55.2.101

Correspondence:
Dr. Yun Gyong Ahn
Western Seoul Center, Korea Basic Science Institute, University-industry cooperation building, 150 Bugahyeon-ro, Seodaemun-gu, Seoul-03759, REPUBLIC OF KOREA.
Phone no: +82 2 6908 6232
Email id: ygahn@kbsi.re.kr

www.ijper.org

In the case of ibuprofen, it is one of the most commonly sought-after over-the-counter medications for patients experiencing anything from toothaches, headaches and minor injuries to back pain, arthritis and menstrual cramps.[10] It is sold under many brand names and even more as generics, but most notably, it has been sold as a racemic mixture of its (R) and (S) enantiomers. To provide an enantiomerically pure ibuprofen medication to maximize benefit and minimize risk to the patient, preparative purification methods are required.

There are several methods to produce enantiomerically pure compounds including preparative high-performance liquid chromatography (HPLC),[11-13] supercritical fluid chromatography (SFC),[14-16] and diastereomeric crystallization.[17,18] Diastereomeric crystallization is a commonly applied technique, but it is often confined to a particular case, requiring reagents that are only effective for a particular system.[19] Consequently, HPLC and SFC have been standard first alternative purification methods to crystallization. However, compared to HPLC, SFC provides a unique selectivity and is an environmentally friendly technology, where the carbon dioxide mobile phase is non-toxic, non-flammable and recyclable and replaces hexane or heptane as a solvent.[20-24] Over the past two decades, supercritical fluid technology has greatly grown in importance in many fields, such as the food, cosmetic and pharmaceutical industries.[25]

This study aims to establish a suggested approach for enantiomeric purification in SFC by streamlining the analytical method development optimization process and preparative method development scale-up process for large scale production of single enantiomers. A fast and effective SFC method was developed using ibuprofen as a model compound. Additionally, (R) form of ibuprofen was obtained in such high purity that it could be considered to be of standard, which is not currently commercially available.

MATERIALS AND METHODS

Chemicals and Reagents

Carbon dioxide (99.9% purity) was obtained from Samjung Industries Co. (Gyeongsangbuk-do, Korea). All solvents (methanol, ethanol and isopropanol) were of high purity HPLC grade purchased from J.T. Baker (Philipsburg, NJ, USA). Ammonia solution, 2.0 M in methanol was obtained from Alfa Aesar Inc. (Ward Hill, USA). A 20mM ammonia solution was prepared from dilution of a stock solution of 2.0 M ammonia in methanol. The racemate standard of ibuprofen [(±)-2-(4-isobutylphenyl) propanoic acid] and (S) form of ibuprofen [(S)-(+)-2-(4-Isobutylephenyl) propionic acid] were purchased from Sigma-Aldrich (St. Louis, USA). All of the samples were dissolved in methanol. The sample concentrations were 1 mg/mL and 25 mg/mL in the analytical and preparative conditions, respectively.

Instrumentation

For the rapid screening of multiple columns with different solvent conditions, a Nexera UC Analytical SFC System (Shimadzu Corporation, Kyoto, Japan); equipped with dual head solvent pumps for carbon dioxide (CO_2) and co-solvents, a column oven, a back pressure regulator (BPR) and a diode-array detector; was used for SFC analysis. The chiral columns used were Chiralpak® AD- H, AS-H, IC, AZ-H, Chiralcel® OD-H, OJ-H and OX-H (all with the following dimensions: 4.6 mm x 150 mm, 5 μm) (Chiral Technologies, Inc. West Chester, PA). The flow rate of the mobile phase was set at 3.0 mL/min. The injection volume was 3 μL. The back pressure regulator (BPR) was maintained at 10 MPa. For the purification of ibuprofen's enantiomers, an SFC-PICLAB PREP100 (PIC Solution Inc., CA, USA); equipped with dual head solvent pumps for CO_2 and co-solvent, a column oven, a BPR and UV Detector; was used for SFC preparative purification. Additionally, its fraction collection system consists of one waste and four collection fractions. Fractions were collected based on time and UV threshold with slope. The UV detection wavelength was set at 220 nm for preparative SFC.

RESULTS AND DISCUSSION

Analytical SFC

The analytical method development was approached with a column-focused strategy to develop an optimized separation method for racemic ibuprofen efficiently. Of the many factors contributing to a successful chiral separation; such as column, mobile phase, temperature and pressure; column choice is generally the most important factor.[26,27] However, many factors remain to be tested; such as modifier choice, isocratic modifier concentration and modifier additive choice. Testing these all individually in isocratic methods with every column would take a prolonged time. The approach taken in this study was to combine all modifier choices into one "cocktail" modifier and use it in a gradient method to screen the potential columns. If a chromatogram showed even just a partial separation, it could be deduced that at least one of the solvents in the cocktail is effectively contributing to the separation and would be a good choice for further method optimization. In this study, seven chiral stationary phases (CSPs) were

tested: Chiralpak AD-H®, Chiralpak AS-H®, Chiralpak IC®, Chialpak AZ-H®, Chiralcel OD-H®, Chiralcel OJ-H® and Chiralcel OX-H®. These CSPs were tested with a gradient method using a mobile phase consisting of a mixture of commonly used SFC modifiers: an equal volume mixture of methanol, ethanol and isopropanol with 20mM ammonia. The gradient method was used at this point as it is commonly initially used to see the full profile of a sample; isocratic methods were optimized afterward for the prep SFC. Ammonia was added because basic additives are commonly used to improve peak shape and efficiency in SFC chiral separations.[28,29] The modifier gradient conditions were 7% (at t=0), 7-55% (from t=1 to t=8) and 7% (at t=8.01). As shown in Figure 1, Chiralcel OX-H® demonstrated the best separation among the seven CSPs.

To determine the optimal mobile phase conditions, each constituent of the "cocktail" mobile phase was tested with the Chiralcel OX-H® column. Methanol, ethanol and isopropanol, each with 20mM ammonia, were used in a 10% modifier isocratic condition, as shown in Figure 2. As there was no significant difference in separation and elution time between the modifiers, methanol with 20mM ammonia was chosen for further investigation because it is the easiest to evaporate among the three solvents and is the most inexpensive, both of which are important considerations in the preparative purification stage.

With the Chiralcel OX-H® column and methanol chosen as the modifier, modifier additives were further investigated. Diethylamine (DEA) and monoisopropylamine (MIPA), each at a 0.2% concentration in methanol, were used in a 10% isocratic condition as shown in Figure 3.

As the MIPA additive displayed the best baseline separation, MIPA was chosen as the additive in methanol. As a result, the final optimized analytical method used the Chiralcel OX-H® column in a 10% isocratic method using methanol with 0.2% MIPA as the modifier as shown in Table 1.

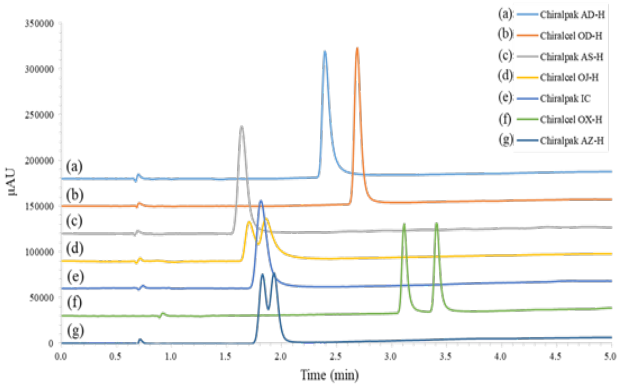


Figure 1: Chromatograms of ibuprofen enantiomers on different CSP columns by analytical SFC.

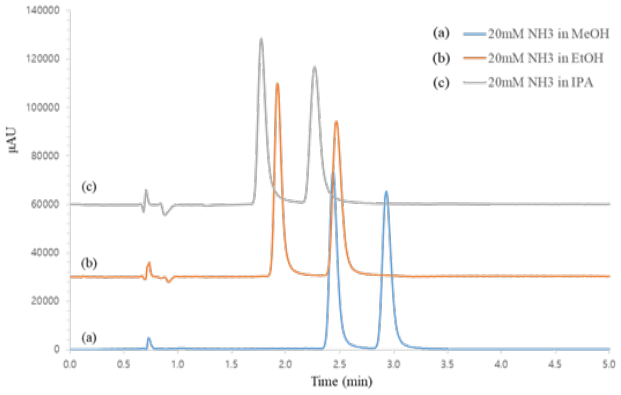


Figure 2: Chromatograms of ibuprofen enantiomers on Chiralcel OX-H® column using three different co-solvents.

Preparative SFC

With the optimized analytical SFC method obtained above, preparative purification scale-up of the ibuprofen enantiomers was attempted. Unfortunately, these conditions did not scale-up perfectly and baseline separation was not achieved as in the analytical scale (Figure 4a). As a result, several variables, such as injection volume, co-solvent percentage and flow rate, were explored. Adequate preparative scale separation was achieved with a 7% isocratic method of methanol with 0.2% MIPA at 60mL/min with 0.1 mL injections

Table 1: Optimized separation method of analytical and preparative scale for ibuprofen enantiomers.

Condition	Analytical SFC	Preparative SFC
Column	Chiralcel OX-H	Chiralcel OX-H
Column Dimension	5µm 4.6x150mm	5µm 21x150mm
Mobile Phase	0.2% Monoisopropylamine in methanol	0.2% Monoisopropylamine in methanol
Isocratic Method	Organic 10%, CO_2 90%	Organic 7%, CO_2 93%
Flow Rate (mL/ Min)	3	60
Injection Volume (µL)	3	100
Sample Concentration (mg/mL)	1	25
Back Pressure Regulator (MPa)	10	10
UV detection	222	220

of a 25mg/mL sample of racemic ibuprofen (Figure 4b) (Table 1).

With this preparative method, ten injections were stacked and the (R)- and (S)-form enantiomers were purified and collected within 50 min as shown in Figure 5. The peaks of (S)-ibuprofen enantiomer at the retention times from 3.5 to 3.8 and from 4.0 to 4.4 for (R)-ibuprofen enantiomer were collected. The retention times for ten runs were measured and the relative standard deviations (RSDs) were calculated to ensure the accurate collection of fractions. The percentage RSD values of around 0.31% were acceptable for the preparative separations. This demonstrates the reproducibility of the mobile phase composition and also that of the sample injection system.

Table 2 showed the collection parameters for the purification of ibuprofen enantiomers. The cycle time (5 min) was the time between the elution of the front of the first peak and the tail of the final peak and the separation time (6 min) was the time elapsed between the injection and the elution of the tail of the final peak. The real amount of two enantiomers recovered by preparative SFC system was calculated in percentage (%) according to equation 1.

$$(\%)R = \frac{m_{measur}}{m_{theo}} \times 100$$

Wherein, $(\%)R$ is the recovery of each enantiomer; m_{theo} is the theoretical weight; and $m_{measur.}$ is the measured weight after purification in respective load injected.[30] Products were recovered at 80.0% yield for (R)-enantiomer and 77.6% yield for (S)-enantiomer as shown in Table 3.

Contrary to the previous reports,[30,31] whose results took more than ten minutes to separate ibuprofen enantiomers, the method presented in this study reduced the separation time to be within five minutes. Gowramma *et al.* (2011) reported that the retention times were 6.3 and 10.4 min for (R) and (S) ibuprofen respectively on Lux 5µ cellulose column in a mobile phase of mixture of perchloric acid (pH 2) and acetonitrile with their optimized HPLC procedure. Another result (Reshetova, *et al.* 2012) showed that although it may depend on parameters such as temperature, sample volume, mobile-phase composition, on the chiral stationary phase (S,S)-Whelk-O1 in a prep-LC system, separation time of (R) and (S) ibuprofen took more than 15 min. Furthermore, the concentration and injection volume of the sample was minimized to complete separation. Prep-SFC is more efficient than prep-LC under this condition since Prep-SFC relative to prep-LC offers increased flow rates.[32,33] In addition, after separation, CO_2 can be passively removed through a gas-liquid separator in

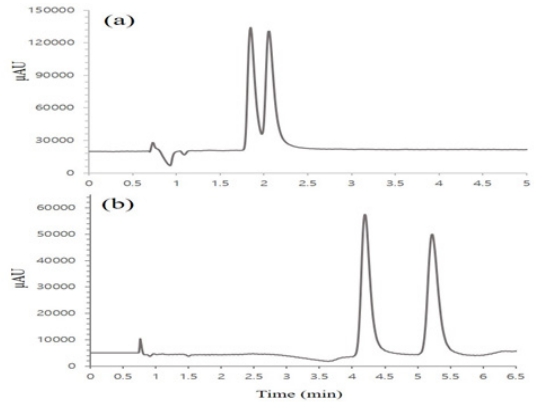


Figure 3: Chromatograms of ibuprofen enantiomers on Chiralcel OX-H® column depending on the two types of modifier additives. (a) 0.2% DEA in methanol (b) 0.2% MIPA in methanol.

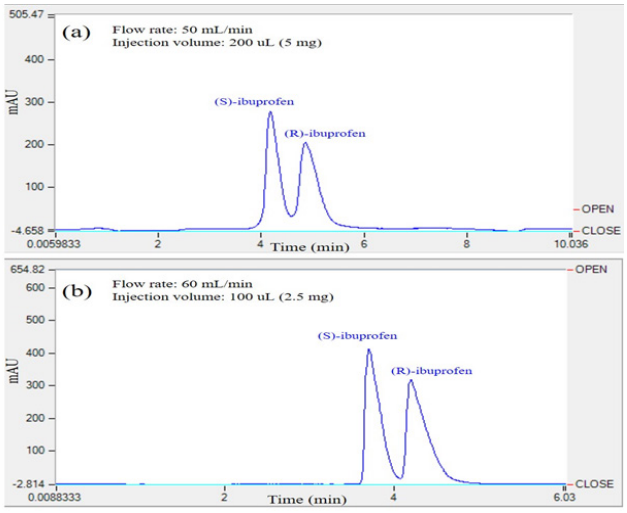


Figure 4: Preparative scale separation of ibuprofen enantiomers (a) before and (b) after optimization.

Table 2: Preparative purification system's collection parameters.

Line	Time (min)	Fraction	Threshold	Slope	- (sec)	+ (sec)
1	3.5	1	100	Positive	60	60
2	3.8	Waste	50	Negative	60	60
3	4.0	2	100	Positive	60	60
4	4.4	Waste	50	Negative	60	60

Table 3: Recovery yields of each enantiomer from isolation process by prep SFC.

Enantiomer	Theoretical weight (mg)	Measured weight after purification (mg)	Recovery (%)
(R)-form	12.5	10	80.0
(S)-form	12.5	9.7	77.6
Total Sample	25	19.7	-

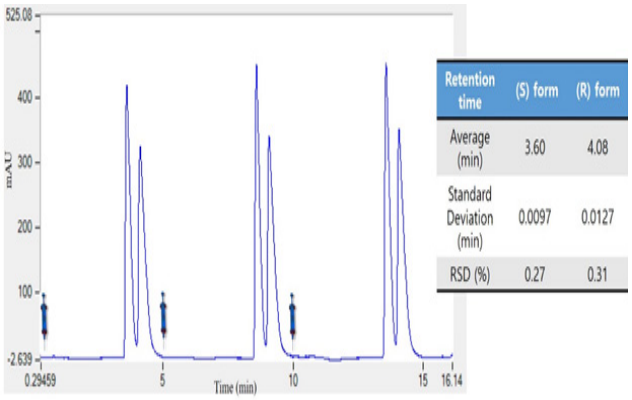


Figure 5: Enantiomer separation and purification of ibuprofen with stacked injections and collections by prep SFC (three of ten total injections are shown).

Prep-SFC, whereas prep-LC systems require a greater amount of the solvent to be evaporated.[34,35] Although these LC studies did not disclose the enantiomeric excess of the separated (R)- and (S)-ibuprofen enantiomers, this study discloses below the process of determining the enantiomeric excess of the collected enantiomers after preparative purification.

Determination of (R)- and (S)-ibuprofen enantiomeric excess after purification

The optical purity (expressed as a percentage) is a comparison of the optical rotation of a pure sample of unknown stereochemistry versus the optical rotation of a sample that is neither optically pure, nor a racemic mixture.[36] In the majority of cases, enantiomeric excess (ee) is a measurement of purity used for chiral substances and was equated with optical purity.[37,38] It reflects the degree to which a sample contains one enantiomer in greater amounts than the other,[39] and is more commonly expressed as a percent enantiomeric excess, as detailed in the following equation 2.

$$\%\ Enantiomeric\ excess = \frac{excess\ of\ one\ enantiomer\ over\ other}{entire\ mixture} \times 100$$

$$= \frac{|(S)\ form\text{-}(R)form|}{(S)\ form + (R)\ form} \times 100$$

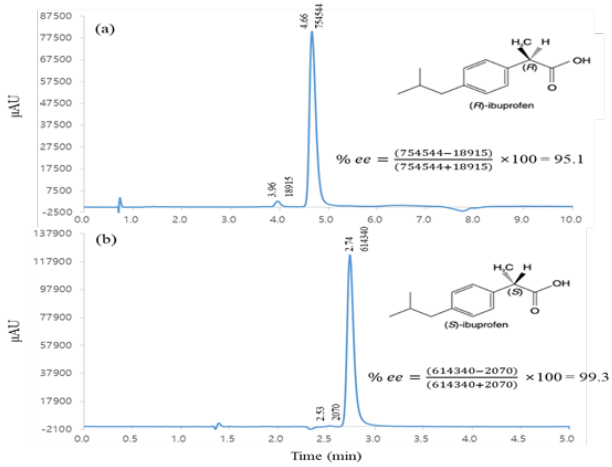


Figure 6: Chromatograms of the enantiomeric excess of (a) (R)-ibuprofen and (b) (S)-ibuprofen after preparative SFC purification.

In this study, enantiomeric excess (e.e.) of ibuprofen enantiomer was measured after purification according to equation 2. When analyzed with the Chiralcel OX-H® column, the (S)-form ibuprofen enantiomer was shown to elute before the (R)-form ibuprofen enantiomer. Analyzing the (R)-form fraction obtained by prep SFC purification, the fraction was shown to have an enantiomeric excess (e.e.) of 95.1, as shown in Figure 6 (a). Unfortunately, the e.e. of the (S)-form fraction obtained by prep SFC purification was difficult to accurately determine because the impurity peak had co-eluted with the tail of the major peak. Thus, other columns were investigated to determine if the elution order of the enantiomers would be reversed. The Chiralpak AZ-H® column showed a reversed elution order of the (R) and (S)-form enantiomers of ibuprofen and was used to determine the e.e. of the (S)-form fraction. As a result, the (S)-form fraction obtained by prep SFC purification was shown to have an e.e. of 99.3 on the Chiralpak AZ-H® column as shown in Figure 6 (b).

CONCLUSION

An SFC method for the separation of ibuprofen enantiomers was developed at an analytical scale on a Chiralcel OX-H® column with a mobile phase of CO_2 and 0.2% MIPA in methanol. The analytical method was scaled up to a preparative SFC method to fractionate (R)- and (S)-enantiomers of a racemic ibuprofen sample. Each enantiomer was purified with high enantiomeric excess (95.1 and 99.3 e.e. respectively). Supercritical Fluid Chromatography is particularly attractive as it makes it drastically easier to achieve enantiomerically pure product in a shorter time compared to the

conventional HPLC purification methods and could become an alternative method to separate chiral drug substances and intermediates.

ACKNOWLEDGEMENT

The authors acknowledge the Ministry of Science, ICT and Future Planning through the National Research Foundation Basic Science Research (Bio-Synergy Research Project: NRF-2017M3A9C4065961) and the Korea Basic Science Institute (Grant number: C030370) for providing financial supports.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

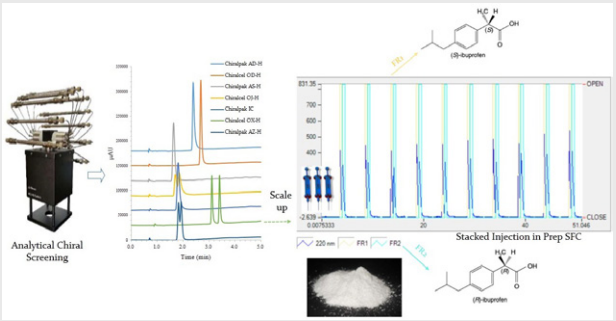
SFC: Supercritical fluid chromatography; **Analytic-SFC:** Analytical supercritical fluid chromatograph; **Prep-SFC:** Preparative supercritical fluid chromatography; **BPR:** Back pressure regulator; **CSPs:** Chiral stationary phases; **DEA:** Diethylamine, **MIPA:** Monoisopropylamine; **HPLC:** High-performance liquid chromatography.

REFERENCES

1. Shimazawa R, Nagai N, Toyoshima S, Okuda H. Present State of New Chiral Drug Development and Review in Japan. Journal of Health Science. 2008;54(1):23-9.
2. Han SK, Jin Y, Row K. Correlation Equation for Retention Factor and Resolution of Ibuprofen in SFC. Bulletin of the Korean Chemical Society. 2004;25(12):1807-11.
3. Browning DJ. Pharmacology of chloroquine and hydroxychloroquine. Hydroxychloroquine and Chloroquine Retinopathy: Springer. 2014;35-63.
4. Kim JH, Scialli AR. Thalidomide: The tragedy of birth defects and the effective treatment of disease. Toxicological sciences: An official journal of the Society of Toxicology. 2011;122(1):1-6.
5. Vargesson N. Thalidomide-induced teratogenesis: History and mechanisms. Birth Defects Res C Embryo Today. 2015;105(2):140-56.
6. Marshall E. Guilty plea puts Oraflex case to rest. Science. 1985;229(4718):1071.
7. Tucker GT. Enantiomer-specific pharmacokinetics. Acta Pharmaceutica Nordica. 1990;2(3):193-6.
8. ElMouelhi M, Ruelius HW, Fenselau C, Dulik DM. Species-dependent enantioselective glucuronidation of three 2-arylpropionic acids: Naproxen, ibuprofen and benoxaprofen. Drug Metabolism and Disposition. 1987;15(6):767-72.
9. Srinivas NR, Barbhaiya RH, Midha KK. Enantiomeric drug development: Issues, considerations and regulatory requirements. Journal of Pharmaceutical Sciences. 2001;90(9):1205-15.
10. Han SK, Jin YZ, Row KH. Correlation equation for retention factor and resolution of ibuprofen in SFC. Bulletin of the Korean Chemical Society. 2004;25(12):1807-11.
11. Sousa ME, Tiritan ME, Belaz KRA, Pedro M, Nascimento MSJ, Cass QB, *et al.* Multimilligram enantioresolution of low-solubility xanthonolignoids on polysaccharide chiral stationary phases using a solid-phase injection system. Journal of Chromatography A. 2006;1120(1):75-81.
12. Eraga SO, Arhewoh MI, Chibuogwu RN, Iwuagwu MA. A comparative UV–HPLC analysis of ten brands of ibuprofen tablets. Asian Pacific Journal of Tropical Biomedicine. 2015;5(10):880-4.
13. Reshetova E, Gorbunov A, Asnin L. Preparative chromatographic separation of ibuprofen enantiomers on Whelk-O1 chiral stationary phase. Pharmaceutical Chemistry Journal. 2012;46(9):568-72.
14. Speybrouck D, Lipka E. Preparative supercritical fluid chromatography: A powerful tool for chiral separations. Journal of Chromatography A. 2016;1467:33-55.
15. Bajpai L, Naidu H, Asokan K, Shaik KM, Kaspady M, Arunachalam P, *et al.* Integrating a post-column makeup pump into preparative supercritical fluid chromatography systems to address stability and recovery issues during purifications. Journal of chromatography A. 2017;1511:101-6.
16. Zehani Y, Lemaire L, Millet R, Lipka E. Small scale separation of isoxazole structurally related analogues by chiral supercritical fluid chromatography. Journal of Chromatography A. 2017;1505:106-13.
17. Keene FR. Chirality in supramolecular assemblies: causes and consequences: John Wiley and Sons. 2016.
18. Kovalenko VN, Kozyrkov YY. A simple method for resolution of endo-/exo-monoesters of trans-norborn-5-ene-2,3-dicarboxylic acids into their enantiomers. Chirality. 2015;27(2):151-5.
19. Fernandes C, Tiritan ME, Pinto MM. Chiral separation in preparative scale: A brief overview of membranes as tools for enantiomeric separation. Symmetry. 2017;9(10):206.
20. Majors RE. Preparative chiral SFC as a green technology for rapid access to enantiopurity in pharmaceutical process research. Advanstar Communications 131 W FIRST ST, DULUTH, MN 55802 USA. 2005.
21. Welch C, Leonard W, DaSilva J, Biba M, Albaneze-Walker J, Henderson D, *et al.* Preparative chiral SFC as a green technology for rapid access to enantiopurity in pharmaceutical process research. ADVANSTAR COMMUNICATIONS 131 W FIRST ST, DULUTH, MN 55802 USA. 2005.
22. Miller L, Potter M. Preparative supercritical fluid chromatography (SFC) in drug discovery. American Pharmaceutical Review. 2008;11(4):112.
23. Taylor L. Past, current and future directions in: Supercritical fluid chromatography. LC-GC Eur. 2013;28-31.
24. Bennett R, Biba M, Liu J, Ahmad IAH, Hicks MB, Regalado EL. Enhanced fluidity liquid chromatography: A guide to scaling up from analytical to preparative separations. Journal of Chromatography A. 2019;1595:190-8.
25. Bin L, Janakiraman A, Syafiq F, Uddin ABM, Sarker MZ, Ming LC, *et al.* Supercritical Fluid Technology and its Pharmaceutical Applications: A Revisit with Two Decades of Progress. Indian Journal of Pharmaceutical Education. 2020;54:s1-3.
26. West C, Melin J, Ansouri H, Mengue MM. Unravelling the effects of mobile phase additives in supercritical fluid chromatography. Part I: Polarity and acidity of the mobile phase. Journal of Chromatography A. 2017;1492:136-43.
27. West C, Lesellier E. Effects of mobile phase composition on retention and selectivity in achiral supercritical fluid chromatography. Journal of Chromatography A. 2013;1302:152-62.
28. Ventura M, Murphy B, Goetzinger W. Ammonia as a preferred additive in chiral and achiral applications of supercritical fluid chromatography for small, drug-like molecules. Journal of Chromatography A. 2012;1220:147-55.
29. Silva CGAD, Collins CH. Super/subcritical fluid chromatography with packed columns: State of the art and applications. Química Nova. 2014;37(6):1047-57.
30. Filho F, Zocolo G, Canuto K, Junior I, Brito E. Productivity of a preparative high-performance liquid chromatography isolation of anacardic acids from cashew nut shell liquid. Separation Science Plus. 2019;2(6):192-9.
31. Gowramma B, Muralidharan S, Basvan B, Meyyanathan N, Elango K, Suresh B. Development and validation of direct chiral separation of ibuprofen enantiomers of sustained release dosage form. Journal of Pharmacy Research. 2011;4(6):1617-9.
32. Wilson WH. Direct enantiomeric resolution of ibuprofen and flurbiprofen by packed column SFC. Chirality. 1994;6(3):216-9.
33. Saito M. History of supercritical fluid chromatography: Instrumental development. Journal of Bioscience and Bioengineering. 2013;115(6):590-9.
34. Majewski W, Valery E, Ludemann-Hombourger O. Principle and Applications of Supercritical Fluid Chromatography. Journal of Liquid Chromatography and Related Technologies. 2005;28(7-8):1233-52.

35. Guiochon G, Tarafder A. Fundamental challenges and opportunities for preparative supercritical fluid chromatography. Journal of Chromatography A. 2011;1218(8):1037-114.
36. Mbah CJ. Determination of enantiomeric excess in pharmaceutical active agents: The role of high performance liquid chromatography. J Pharmacol Pharmaceut Pharmacovig. 2018;2(008).
37. Gawley RE. Do the terms "% ee" and "% de" make sense as expressions of stereoisomer composition or stereoselectivity?. J Org Chem. 2006;71(6):2411-6.
38. Kataoka M, Yamamoto K, Kawabata H, Wada M, Kita K, Yanase H, *et al.* Stereo selective reduction of ethyl 4-chloro-3-oxobutanoate by *Escherichia coli* transform ant cells expressing the aldehyde reductase and glucose dehydrogenase genes. Applied Microbiology and Biotechnology. 1999;51(4):486-90.
39. Barton B, Pohl P. A simple polarimetry technique for predicting the absolute configuration of the preferred enantiomer in chiral host-guest inclusion complexes. South African Journal of Chemistry. 2015;68:215-8.

PICTORIAL ABSTRACT



SUMMARY

In this present research project, a streamlined SFC method development strategy was utilized to purify preparative quantities of racemic ibuprofen into its respective (R) and (S)-form enantiomers. Analytical SFC method development was executed with rapid column screening techniques to find optimal column, modifier (co-solvent) and modifier additive conditions for preparative scale-up. Preparative SFC was executed with the conditions found in the analytical SFC method development phase and factors such as injection volume, mobile phase modifier percentage and total flow rate were optimized for the preparative scale. The streamlined method development strategy greatly reduced total solvent usage and total purification time, from the analytical method development stage to the preparative scale purification stage. The (R) and (S)-form ibuprofen enantiomers were successfully purified with 95.1 e.e. and 99.3 e.e., respectively.

About Authors

Lee Hwa Jong, M.S., Principal Scientist, SFE and SFC Researcher and Lab Manager at Verdant Technology in Seoul, Republic of Korea.

Gahm Jasper, B.S., President, Founder and President of Verdant Technology in Seoul, Republic of Korea.

Jin Jong Sung, Ph.D., Principal Research Scientist, Busan Center of Korea Basic Science Institute, Republic of Korea, Specialty in chiral resolutions using synthetic chiral columns for HPLC.

Ahn Yun Gyong, Ph.D., Principal Research Scientist, Western Seoul Center of Korea Basic Science Institute, Republic of Korea, Specialty in mass spectrometry-based analytical methods for the separation and quantification of pharmaceutical substances, and their QA/QC analysis for method validation.

Cite this article: Lee HJ, Gahm J, Jin JS, Ahn YG. Rapid Purification of Drug Enantiomers Using Supercritical Fluid Chromatographic Method: Ibuprofen as a Model Compound. Indian J of Pharmaceutical Education and Research. 2021;55(2):614-20.