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SUSTAINABLE APPROACHES IN PHARMACEUTICAL DISCOVERY AND DEVELOPMENT OF SULFA DRUGS

A recommendation of Green Chromatography

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ABSTRACT

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As the environmental awareness is rising, the need for sustainable development emerges. This has given birth to Green Chemistry concept. Within this context, researchers are seeking for innovative approaches to reduce the negative impacts caused by hazardous chemicals on the environment. Being one of the industries that utilize and generate a vast amount of toxic organic substances, pharmaceuticals requires more attention into minimizing its environmental effects associated with the production and consumption of medicines. One of the most widely used drugs discussed in this paper is sulfonamides, also known as sulfa drugs. This class of drugs possesses a variety of biological activities ranging from antibiotics, anti-inflammatories to diuretics, hypoglycemics, carbon anhydrase inhibitors, and protease inhibitors. This is why sulfonamides are involved in many therapeutic medications, thus the environmental concerns relating to the preparation of this drug class needs to be considered. In fact, the production of sulfonamides exploits numerous toxic reagents, time, and energy, coupled with a remarkable generation of organic waste.

The discovery and development phases are considered as the most important process in the production of drugs. In this literature review thesis, green chromatography was suggested as a good technique to reduce the environmental problems associating with the analyses during pharmaceutical R&D phase yet ensuring the high-quality requirements of medicinal products. Gas chromatography with the use of hydrogen as a carrier gas in mobile phase was considered as the greenest technique in chromatographic analysis. Liquid chromatography is less green than gas chromatography, however, its versatility offers various approaches toward green chemistry goals. For example, choosing continuous operating instead of conventional batch mode can considerably reduce the solvent and time consumption. In other approaches, toxic organic solvent is replaced by green solvents such as supercritical carbon dioxide or superheated water.

The studied applications of green chromatographic techniques in this thesis involve, but are not limited to, the effective detection and separation of sulfonamides. Further development of these techniques into preparative scale for routine analysis of sulfa drugs is still required.

Key words
Green chemistry, Green chromatography, Sulfonamide

CONCEPT DEFINITIONS

List of abbreviations

AIDS	Acquired immunodeficiency syndrome
ASE	Accelerated solvent extraction
CA	Carbonic anhydrase
CCC	Counter current chromatography
CNS	Central nervous system
DBU	Diazabicycloundecene
DCM	Dichloromethane
DNA	Deoxyribonucleic acid
EF	Enhanced fluid
GC	Gas chromatography
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
IL	Ionic liquid
LC	Liquid chromatography
m-CPBA	Meta-Chloroperoxybenzoic acid
MLC	Micellar liquid chromatography
MPLC	Medium-performance liquid chromatography
MS	Mass spectroscopy
MSPD	Matrix solid phase dispersion
NLC	Nano liquid chromatography
NMP	N-Methyl pyrrolidone
NMR	Nuclear magnetic resonance
NP	Normal phase
PFP	Pentafluoro phenyl
RP	Reverse phase
SBSE	Stir bar sorptive extraction
SDS	Sodium dodecyl sulfate
SEC	Size exclusion chromatography
SF	Supercritical fluid

SFC	Supercritical fluid chromatography
SFE	Supercritical fluid extraction
SMB	Stimulated moving bed
SOSA	Selective optimization of side activities
SPE	Solid phase extraction
SPME	Solid phase microextraction
SSR	Steady state recycling
SW	Superheated water
SWC	Superheated water chromatography
TCT	2,4,6-trichloro-1,3,5-triazine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UHPLC	Ultra-high-performance liquid chromatography
UV	Ultraviolet

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1 INTRODUCTION

Sulfonamide is a term referring to a class of synthetic organic compounds with a sulfonyl functional group bonded to an amine functional group in their chemical structure. They are also well known by the name “sulfa drugs”. These compounds have played a significant role in pharmaceutical industry since the discovery of Prontosil’s antimicrobial effect in early 1900s. Prontosil is a red azo dye containing sulfonamide structure. Later on, it was found that a metabolite of prontosil formed in the intestine, sulfanilamide (para-aminobenzene sulfonamide), is the proper antibacterial agent. This biologically active substance is the first of its kind to be synthesized and commercialized as a medication against a wide range of infections. (Mok 2008; Patrick 2013.). The medical success of sulfanilamide had drawn the attention of researchers around the world to study and develop various bioactive sulfonamide derivatives. As a result, the sulfa drugs family has been extended to a total of over twenty thousand compounds with different types of pharmacological properties beside antibacterial effect. (Kołaczek et al. 2014.). To date, recent studies have reported various bioactivities of sulfonamide derivatives such as diuretic, hypoglycemic, anti-inflammatory, antifungal, anti-hypertensive, anti-tumor, antidepressant, antiviral, carbonic anhydrase (CA) inhibitory, and protease inhibitory abilities (Ashfaq et al. 2013; Kołaczek et al. 2014; Apaydın & Török, 2019).

Currently, sulfonamides are involved in numerous common medications as therapeutic agents. Although they were found nearly a century ago, their development in term of quantity, quality, capability, and productivity seems certain to prolong owing to the increasing number of studies on the synthesis of new and old sulfonamide derivatives. Unfortunately, the sustainable and environmental concernment in their production has not been thoroughly considered. The synthesis of these derivatives of sulfonamide generally involves multiple reactions in conjunction with toxic organic solvents and/or activating agents like thionyl chloride which influences human health and endangers the environment. Moreover, the excessive highly sensitive substrates as well as undesirable by-products, intermediates, and catalysts from multi-step syntheses might result in some toxicity and difficulty in the isolation of the targeted product. (Eid et al. 2018.). In addition, conventional commonly used analytical techniques involved in the R&D process require massive consumption of organic solvent. Those factors above have contributed to a great amount of hazardous waste produced annually. (Miller et al. 2019.). To overcome this problem, researchers have brought forward an idea of green chemistry in which chemicals and chemical processes are designed to minimize the use and generation of hazardous substances (Lu 2012.).

Chromatography is often the most precise analytical methods to meet the strict requirements in the pharmaceutical research. Indeed, chromatography is widely used in the separation of bioactive compounds such as therapeutic agents in medicines resulting from its high selectivity and purification efficiency. Analytical chromatography focuses on solving and identifying the components of a mixture. (El-Shaheny et al. 2019.). Typically, chromatography separates component into fairly pure fractions by means of selective continuous adsorption and desorption in the mass transfer zone at different rates. A regular chromatographic instrument requires a sorbent stationary phase packed in a column and a mobile phase carrying solute through the column. The carrier fluid in mobile phase can be a liquid or a gas (Henley, Seader & Roper, 2011).

As a matter of fact, the inert gas carriers involved in chromatography are often non-renewable (e.g. Helium) (Płotka et al. 2013). Also, most of the commonly used liquid carriers are hazardous organic solvents such as acetonitrile, methanol, dimethyl sulfoxide, dichloromethane (Dembek & Bocian, 1982). Therefore, the term of green chromatography was born to overcome these drawbacks. Green chromatography is one of the most favorable approaches to reach the goals of green chemistry by reducing or replacing the use of organic solvents and lessening the production of organic waste during either analytical or preparative separation processes. In addition, chromatographic technique is able to be greener at various stages, from sample collection and preparation to separation and final determination. The usable methods to make chromatographic separations greener vary based on the type of chromatography. (Płotka et al. 2013.). There has been a number of researches on the applicability of green chromatography on chemical analysis and determination in pharmaceutics. (Alkio 2008; El-Shaheny et al. 2019).

Having conducted literature study on various noteworthy scientific publications regarding to sulfonamides and green chromatographic technique, an idea of applying green chromatography to identify therapeutic sulfonamides for drugs discovery is proposed and presented in this paper. The review also makes use of published achievements in the determination of some sulfonamides using different green chromatographic methods as a firm basis for the proposal. At the end of the paper, a personal evaluation on the effects of this idea to a sustainable development of chemical industry in the present and future will be drawn.

2 SULFONAMIDE DERIVATIVES

Over decades of systematic development, the presence of sulfonamides is commonly found in many popular medicine's ingredients, owing to their vast valuable biological activities in term of medical treatments. Regardless of their powerful functions, the misuse of sulfonamides has contributed to the exponential growth of antibiotic-resistant bacteria. This promising chemical class also possesses a number of negative influences on human health and other living creatures at some levels. In the end of this chapter, a sufficiently comprehensive view of sulfonamide derivatives is provided.

2.1 History of discovery

The history of sulfonamide is determined in 1935 when Gerhard Domagk published his findings about the antibacterial activity of Prontosil. Prontosil is a red azo dye with sulfonamide functional group in its chemical structure. Prontosil Red then became the first drug to be found effective against general bacterial infections. This finding brought Domagk the Nobel Prize in Medicine in 1939. (Sneader 2001.). By discovering that Prontosil could only be effective in living bodies but could not kill bacteria raised in test tubes, researchers found that Prontosil was metabolized by intestinal bacteria to form a colorless compound named Sulfanilamide (see FIGURE 1). This compound is the true antibacterial agent which was then employed as a base to develop a wide variety of antibacterial sulfonamides.

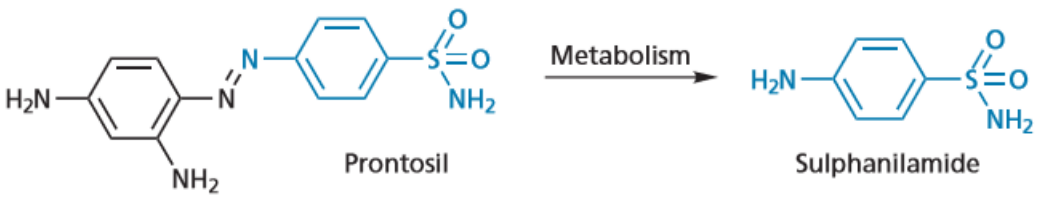


FIGURE 1. The metabolism of Prontosil. (Adapted from Patrick 2013).

The invention of sulfa drugs was a real breakthrough, as they were the first and only effective antibiotics before the introduction of penicillin in the early 1940s (Aronson 2016). Even after the predominant use of penicillin and other early antibiotics, sulfonamide derivatives remained favorable owing to their low cost and oral usability. However, the increase of bacterial resistance to some sulfonamides has reduced

their use in modern antibiotic treatments. Although sulfonamides were primarily developed as antibacterial drugs, their use has recently been extended to target more complicated diseases than bacterial infections by the selective optimization of side activities (SOSA) approach. This approach aims to enhance the desired side effect and eliminate the original bioactivity. In fact, while studying some antibacterial sulfonamides, researchers have found several “undesirable” side effects which can be optimized to become distinct therapeutic agents. (Patrick 2013.). Consequently, sulfa drugs remain an important class in pharmaceutical industry as well as a promising topic for researchers.

2.2 Characterizations of Sulfonamides

The general structure of sulfonamide derivatives is constituted of a sulfonyl functional group attached to an amine functional group at sulfur atom (see FIGURE 2). By altering R^1, R^2, R^3 substituents in sulfonamide structure, thousands of derivatives with various biological activities can be obtained. They can be categorized in different ways based on their chemical structure or medical properties. In regard to their structures, sulfonamides can be classified into primary, secondary, and tertiary according to the number of hydrogen atoms bonded to nitrogen in the sulfonamide group. Indeed, when the amine group of a sulfonamide consists of two hydrogen atoms, the sulfonamide is recognized as primary (e.g. sulfanilamide). If one of the substituents in the amine group is an organic radical and the other one is a hydrogen atom, the sulfonamide is secondary (e.g. sulfathiazole). If both N-substituents in sulfonamide structure are organic radicals, the sulfonamide is tertiary (e.g. amprenavir). (Apaydin & Török 2019.).

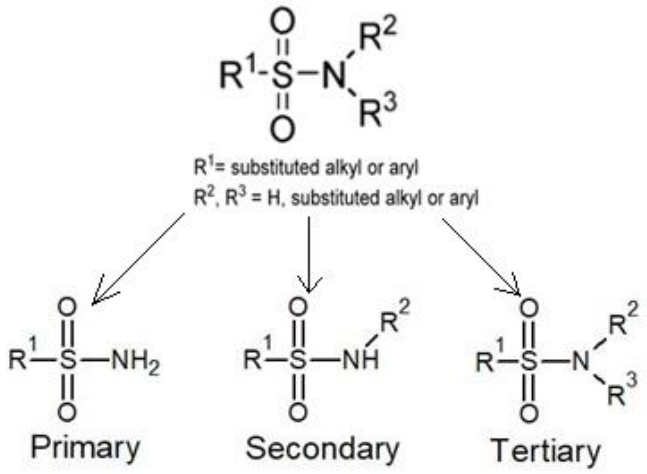
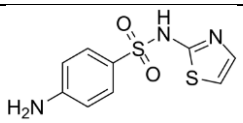
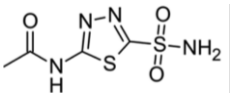
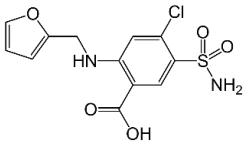
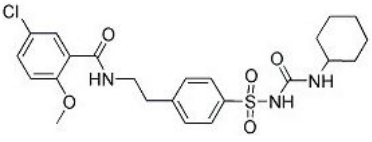
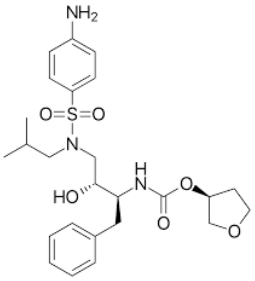
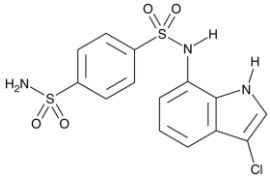


FIGURE 2. General structure and classification of sulfonamides . (Adapted from Carta, Scozzafava & Supuran 2012).

Based on their medical functions, the classification varies from their clinical use in veterinary and human medicines to their therapeutic activities. In veterinary medicine, sulfonamides are characterized into standard use, highly soluble, poorly soluble, potentiated, and topical use. In human medicine, they are grouped as short, medium, and long acting. According to the differences in metabolism and excretion mechanism, the categorization in veterinary medicine is invalid for human medicine and vice versa. (Tolika et la. 2010.). Concerning pharmacological agents, the main classes of therapeutic sulfonamides currently in use are antibacterial, CA inhibitors, diuretics, hypoglycemic agents, anti-HIV agents, and anti-cancer. The representatives of each class are introduced in Table 1 along with their structures. (Supuran et al. 2004.).

TABLE 1. Main therapeutic classes of sulfonamides and their representatives. (Adapted from Supuran et al. 2004).

Therapeutic class	**Representatives**	**Chemical Structures**
Antibacterial	Sulfathiazole	
CA inhibitor	Acetazolamide	
Diuretics	Furosemide	
Hypoglycemics	Glibenclamide	
Anti-HIV	Amprenavir	
Anti-cancer	Indisulam	

The physical appearance of sulfonamide derivatives is usually white or slight yellow, odorless powder, and some of them taste bitter. Generally, they are weak acidic molecules, thus they are fairly polarized. The presence of basic aromatic amino group combined with the acidic amide group containing a labile hydrogen atom makes some of them have amphoteric properties. Their solubility in acids and alkalis differ according to their acidic and amphoteric characteristics. Most of sulfonamides are poorly and sometimes not soluble in water, but small molecular sulfonamides (molar mass 177-300 g/mol) are found to be water soluble. (Baran et al. 2011; Dmitrienko et al. 2014.). They are not easily adsorbed by activated carbon but slightly absorbed by soil. Sulfonamides are classified by Koschorreck, Lehmann, and Naulin as photo- and thermally stable substances at half-life degradation (DT_{50} > 1 year) (Koschorreck et al. 2005). Baran and co-workers also reviewed that sulfonamides are easily hydrolyzed by alkalis as well as reacted with phenols, amines, and hydroxyl radicals (Baran et al. 2011).

2.3 Bioactivities and applications of sulfonamides in pharmaceutics

The first-found and most well-known property of sulfonamides is antimicrobial. The mechanism of this property is by means of preventing the metabolism in bacterial cells. Sulfonamides inhibits dihydropteroate synthetase enzyme from synthesizing tetrahydrofolate which is an enzyme cofactor required for the synthesis of pyrimidine nucleic acid bases, therefore Deoxyribonucleic acid cannot be formed. This antimetabolism results in the disruption of Deoxyribonucleic acid replication and transcription in the cells, thus bacterial cells cannot grow and divide. Sulfonamides do not actively kill bacteria but they stop the growth of bacteria so that the immune system of the body can easily fight against them. Those antibacterial drugs which inhibit bacterial cells growth are classified as bacteriostatic. (Patrick 2013.). Nowadays, common sulfonamide antibiotics still in circulation are sulfathiazole, sulfaquinozaline, silver sulfadiazine (commercialized as Silvadene), sulfasalazine (commercial named Azulfidine), and sulfamethoxazole (known as Gantanol on the medicinal market) (Fookes & Pharm, 2018). They are useful for various treatments of urinary tract, mucous membranes, and gastrointestinal tract infection as well as malaria and Crohn's disease (Mok 2008). They are also effective against fungi and protozoa (Tačić et al. 2017).

Sulfonamide derivatives are also found to be effective in CA inhibitory. CA is an enzyme responsible for the hydration of carbon dioxide and the dehydration of bicarbonate at conditional pH. CA regulates the transmission of carbon dioxide inside the body. It is also in charge of electrolytes emission in tissues

and organs, accompanied by homeostat maintenance. There are 14 different CA isozymes with distinctive cellular location and tissue distribution in the human body. In consequence of its versatile activities, CA has been the target for inhibitors in clinical therapy to cure numerous diseases. CA inhibitory Sulfa drugs have been in use for over 50 years to reduce blood pressure in the treatment of heart failure, glaucoma, and epilepsy. Besides acetazolamide, mathazolamide, ethoxzolamide, dichlorophenamide, dorzolamide, and brinzolamide are CA inhibitory sulfonamides currently used in clinics. (Mok 2008; Carta et al. 2012.).

As CA is involved in the formation of bicarbonate which is an essential step of key metabolic pathways in gluconeogenesis, lipogenesis, ureagenesis, as well as the biosynthesis of amino acids and pyrimidines, sulfonamide hypoglycemic, diuretic, anticancer, antiviral, and protease inhibitor. were developed accordingly. Tolbutamide, glibenclamide are currently served as anti-diabetic agents in clinic owing to their glucose lowering effect. (Abbink et al. 2002; Loubatières-Mariani 2007.). The discovery of an increase in urine volume and pH when taking CA inhibitory sulfa drugs has led to the foundation of the diuretic class. Furosemide, torsemide, indapamide, chlorthalidone, and thiazides are among the most popular derivatives used in diuretic treatments. (Supuran 2008.). Another well-known clinical sulfa drug developed from CA inhibitor drugs by SOSA approach is Sildenafil (Viagra), an anti-impotence drug originally created as a vasodilator to treat angina and hypertension (Patrick 2013). By the inhibition of a selective CA isozyme, the formation of solid tumors in certain organs can be prevented. Several researches have been conducted on sulfonamides as a chemotherapy of cancer. Amongst all the studied derivatives, indisulam has shown the most promising anti-tumor activity in human lung and colon carcinomas. It is currently in phase II of clinical trials to be approved as an anticancer drug. (Ozawa et al. 2001.).

The protease inhibitory activity of Sulfonamides has been investigated, targeting cystein and HIV protease. Cystein protease constitutes a ubiqitory group of enzymes responsible for cell turnover and apoptosis. They are also involved in cellular inflammatory regulation and intracellular proteolysis. Novel studies have pointed out the potential of sulfonamide cysteine protease inhibitors in the treatment of Alzheimer's and other central nervous system (CNS) disorders, alongside osteoporosis, and arthritis. (Scozzafava et al. 2013.). The inhibition of HIV protease is able to stop the growth of viral particles, thus hindering the infectious process. Amprenavir and tipranavir are among the clinically approved drugs against HIV-AIDS (Supuran et al. 2004).

2.4 Considerable drawbacks of sulfa drugs

It is fair to say that Sulfa drugs have become the victim of their own success. As one of the oldest antibiotics accompanied by their versatile pharmacological abilities and low cost, sulfonamides have been utilized not only in medical but also in agricultural industry. Farmers use sulfonamide antibiotics in animal husbandry to protect them against bacterial diseases as well as in cultivation to prevent fungi and wild grasses. It is estimated that over 20,000 tons of antibacterial sulfonamides are produced every year (Baran et al. 2011). They can enter the soil and water from food chains that involve human and animal waste. A considerable portion of them is discharged to the environment through wastewater from pharmaceutical as well as agricultural industry. Additionally, sulfonamides are recognized as poor or non-biodegradable substances (Koschorreck et al. 2005). The trace of sulfonamides in the environment possess high risks to the ecology and human health.

The most significant risk is the exponential generation of antibiotic resistant bacteria, which has become a major global problem. The increasing number of sulfonamide antibiotic resistant strains of various bacterial species has led to treatment failures and caused difficulties in medical therapy, especially for older people, children, and patients with weak immunity. The drug resistant ability of bacteria is stimulated when bacteria are rapidly exposed to sub-lethal dose of antibiotics. Bacteria can acquire this ability from mutation, inheritance, or genetic material transfer. Another risk of sulfonamide residue in the environment is the decline of some microorganisms in the soil and the waste water treatment process due to the highly inhibitory activity of sulfonamides (Msagati & Nindi, 2004). According to Baran et al., low concentrations of sulfonamides may dramatically affect the growth of some plants (Baran et al. 2011).

Besides valuable therapeutic effects, sulfonamide derivatives also have some adverse effects which can be toxic at high concentrations. Poorly and insoluble sulfonamides might result in crystallization in kidney tubules. Overdose of sulfa drugs can cause hypersensitivity reactions, gastrointestinal symptoms, headache, and drowsiness. Hepatotoxicity and carcinogenicity were recorded with the use of some sulfonamides. Other important adverse effects associated with sulfa drugs involve anaphylactic shock, systemic vasculitis, suppression of enzyme activity, severe skin reactions, pneumonitis, hepatitis, and pancytopenia. (Aronson 2016.).

3 COMMON METHODS TO SYNTHESIZE SULFONAMIDE DERIVATIVES

This chapter provides a brief review on a number of main synthetic protocols of sulfonamide derivatives. One of the most traditional methods is coupling sulfonyl chloride with an amine. Another less conventional method is using transition metals as catalyst for the C-N bond formation to add aryl substituent to the nitrogen atom in the initial primary or secondary sulfonamide. This reaction is called N-arylation. Some innovative synthetic pathway of sulfonamides from sulfenamides and sulfonate esters was studied and developed. The chapter also studies novel approaches that concern the sustainability factor.

3.1 Sulfonamide synthesis from sulfonyl chloride

The combination of a sulfonyl chloride and a primary or secondary amino compound in the presence of a base or catalyst (see FIGURE 3) is the oldest method to form a sulfonamide. The earliest example of sulfonamide formation through this synthetic route took place in 1903. This reaction often results in high efficiency and can tolerate a broad range of substrates containing various functional groups such as hydrocarbon, halogen, carbonyl, alcohol, ether, and heterocycle. (Mok 2008.).

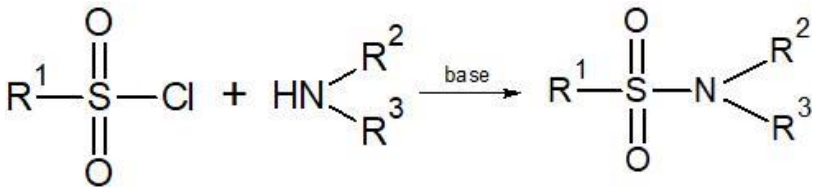


FIGURE 3. General sulfonamide synthesis from sulfonyl chloride and amine. (Adapted from Mok 2008).

Conventionally, sulfonyl chlorides can be prepared by the oxidation of thiols or chlorination of sulfonic acid/sulfonate salts. The oxidant commonly used to convert thiols into sulfonyl chloride are chlorine gas (Cl_2), sodium hypochlorite (NaOCl) or the combination of hydrogen peroxide (H_2O_2) and thionyl chloride ($SOCl_2$). The chlorination of thiol carried out by bubbling Cl_2 gas takes place in an aqueous acid or a biphasic mixture containing thiol. This method was first employed with a heteroaryl thiol in the presence of hydrochloric acid in 1942 (Caldwell & Kornfeld, 1942). Unfortunately, it requires an excessive oxidant and aqueous acid which is unfavorable in the case of sensitive substrates, coupled with the hazards associated with chlorine gas (Ashfaq et al. 2013; Kołaczek et al. 2014). In 2006, Wright and his coworkers introduced the use of NaOCl to form a sulfonamide from a thiol via an in-situ sulfonyl chloride

as illustrated in Figure 4. The readily available and safe reagents accompanied by high yields and a controllable oxidant amount are the advantage of this approach. Moreover, by trapping the generated sulfonyl chloride with an amine, the decomposition of sulfonyl chloride can be avoided, thus ensuring a complete conversion. (Wright et al. 2006.).

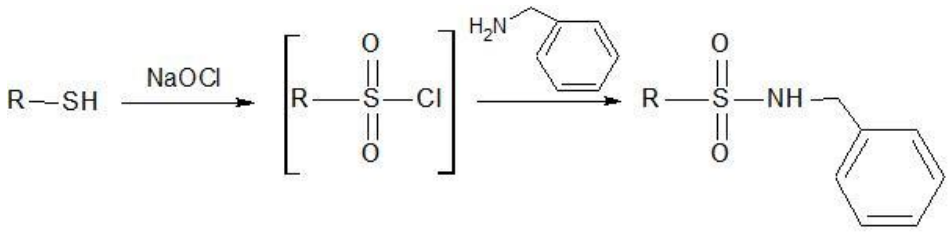


FIGURE 4. Sulfonamide synthesis using sodium hypochlorite. (Adapted from Wright et al. 2006).

Direct oxidative conversion of thiols using highly reactive reagents like H_2O_2 and $SOCl_2$ was another noteworthy approach to collect sulfonyl chlorides. The sulfonamides resulted from the aminolysis of the corresponding sulfonyl chlorides reached excellent yields within couple minutes at room temperature. In additions, the reagents involved are cheap and widely available. By applying this protocol (see Figure 5), a broad range of thiols and amines was able to be converted into sulfonamides. (Bahrami et al. 2010.).

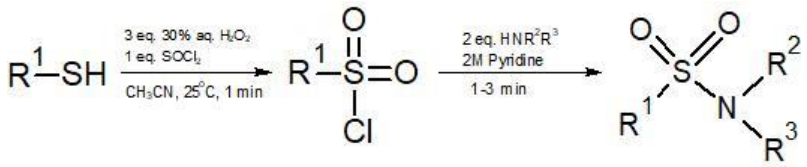


FIGURE 5. Sulfonamide synthesis using hydrogen peroxide and thionyl chloride. (Adapted from Bahrami et al. 2010).

Apart from thiol, sulfonic acids and their salts are also good starting materials for the preparation of sulfonyl chlorides. The oldest and most common way is coupling sulfonic acids/sulfonates with either thionyl chloride, phosphorus pentachloride (PCl_5) or phosphoryl chloride ($POCl_3$), which was reported in the late 1900s (Barco et al. 1974; Fujita 1982; Cremlyn & Cremlyn 1996). It can be seen that these chlorinating reagents are harsh in addition to the toxic and corrosive by-products they generate. Therefore, some other alternative reagents were proposed such as triphenylphosphine dichloride (PPh_3Cl_2), 2,4,6-trichloro-1,3,5-triazine (TCT), or a complex of trichloro acetonitrile and triphenylphosphine (Cl_3CCN/PPh_3) (Kataoka et al. 1998; De Luca & Giacomelli, 2008; Kijrungphaiboon et al. 2012). All of these reagents were reported to provide high efficiencies on a wide range of alkyl and aryl substituents. The synthetic pathways of sulfonyl chloride from sulfonic acid is summarized in Figure 6.

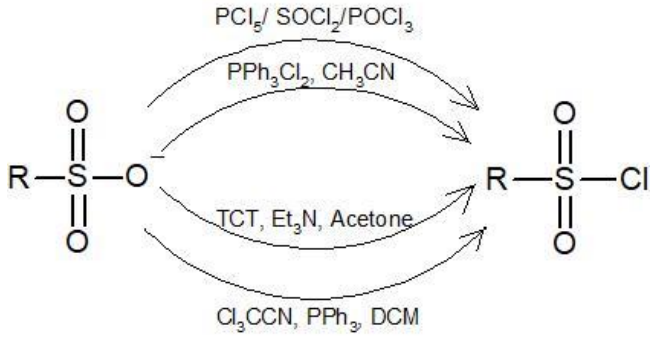


FIGURE 6. Sulfonyl chloride synthesis from sulfonic acid. (Adapted from Barco et al. 1974; Fujita 1982; Cremlyn & Cremlyn 1996; Kataoka et al. 1998; De Luca & Giacomelli 2008; Kijrungphaiboon et al. 2012).

3.2 Sulfonamide synthesis using transition metal catalyst

Even though the use of sulfonyl chlorides to produce sulfonamides has been the most conventional method so far, it is not enough for a high demand of diverse sulfonamides in medicinal industry since it possesses a severe limitation in the storage and accessibility of sulfonyl chlorides. Therefore, the need of alternative methodologies arises. One of them is the catalytic formation of higher N-substituted state sulfonamides (secondary and tertiary sulfonamides) with the help of transition metals (FIGURE 7). Some transition metals such as Copper (Cu) and Palladium (Pd) are able to catalyze the synthesis of a tertiary or secondary aryl sulfonamide from a secondary or primary sulfonamide, respectively. This method utilizes a wide range of aryl derivatives, for example, aryl halides, aryl nonaflates, and aryl boronic acid. (Lam et al. 2001; Deng et al. 2005; Shekhar et al. 2011; Rosen et al. 2011.). Moreover, some transition metals such as Ruthenium (Ru) and Rhodium (Rh) are also effective with aromatic as well as aliphatic aldehydes, amines, and alcohols (Chan, Baucom & Murry 2007; Watson, Maxwell & Williams, 2011). This pathway allows the synthesis of various complex sulfonamide therapeutic agents from available source of sulfonamides.

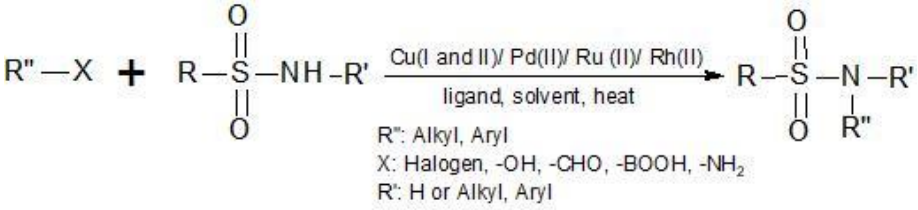


FIGURE 7. Transition metal catalytic synthesis of Sulfonamide. (Adapted from Lam et al. 2001; Deng et al. 2005; Shekhar et al. 2011; Rosen et al. 2011; Chan et al. 2007; Watson et al. 2011).

3.3 Sulfonamide synthesis from sulfenamide and sulfonate ester

The mechanism of organic synthesis is so complicated that, in some cases, the sulfonyl chloride synthetic methods might fail to produce the desired sulfa drug or provide insufficient yield. Hence, alternative approaches from different intermediates towards sulfonamides synthesis are always in search. Sulfenamide, a reduced form of sulfonamide, is a high potential starting material to furnish sulfonamide by oxidation. Common oxidant reagents used in this conversion are Potassium permanganate ($KMnO_4$) and meta-Chloroperoxybenzoic acid (m-CPBA) in which m-CPBA is more preferable owing to its enhanced yields over $KMnO_4$ (Glass & RJ 1977). This methodology (see Figure 8) has been applied in the synthesis of potential antifungal (Triazole sulfonamide) and anticancer (Pyrimidine-4-sulfonamide) agents (Revankar et al. 1990; Tasaka et al. 1994).

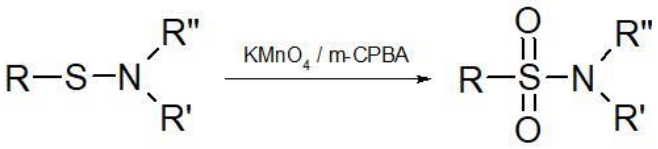


FIGURE 8. Oxidation of Sulfenamide to form Sulfonamide. (Adapted from Glass & RJ 1977).

Beside sulfenamide, pentafluorophenyl (PFP) sulfonate esters were found to be shelf stable alternative to sulfonyl chloride. This substance possesses a range of advantages over sulfonyl chloride, including high stability under a variety of conditions, easy removability, and ready employability under aqueous conditions. Caddick and his coworkers revealed that this synthetic protocol provided a good tolerance upon various functional group with excellent yields as well. Although PFP sulfonate esters are not as reactive as sulfonyl chlorides, it was reported that their reactivity can be enhanced by microwave heating under refluxing condition. The aminolysis mechanism of PFP sulfonate ester is similar to that of sulfonyl chloride (FIGURE 9). It also requires the presence of a base (e.g. Triethylamine (Et_3N), Diazabicycloundecene (DBU)) in addition to a solvent (e.g. Tetrahydrofuran (THF), Toluene, N-methyl pyrrolidone (NMP)). Like sulfonyl chloride, PFP sulfonate ester can be synthesized from sulfonic acid salt. (Caddick et al. 2004.).

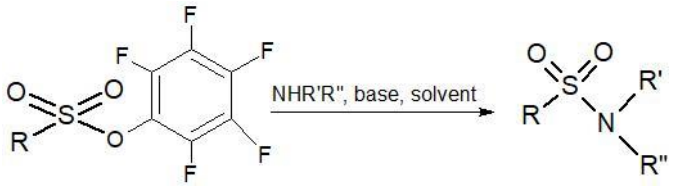


FIGURE 9. Sulfonamide synthesis from PFP sulfonate ester. (Adapted from Caddick et al. 2004).

3.4 Sustainable synthetic route toward sulfonamides production

An ideal sustainable chemical synthesis demands non-toxic solvents and reactants usage, easy separation and purification by energy efficient processes. However, all the methods described above require various organic solvents and toxic activating reagents, in combination with multi-step syntheses, which are the major challenges in purification process afterwards. Indeed, some amines were reported to have negative impacts on human health (Greim et al. 1998; Skipper et al. 2010). Additionally, metallic residues from the catalytic process are not suitable for therapeutic agents like sulfa drugs (Committee for Medicinal Products for Human Use 2008). Therefore, in 2018, Eid and co-workers proposed an innovative one-step strategy to synthesize sulfonamides using Nitroarenes as amide sources, Sodium sulfinates as sulfonyl sources, and water as the only solvent (FIGURE 10). The products were collected by simple filtration without using any organic solvent, providing a high mass efficiency. This method has fulfilled the sustainable concerns of green chemistry, which the conventional methods could not succeed. Moreover, the authors confirmed that a high chemoselectivity and yield over a wide range of sulfonamide derivatives were obtained by their strategy. However, there has not been any reported work on the application of this approach using Nitroalkanes to produce alkyl N-substituted sulfonamides. Further research on the applicability of this sustainable strategy is expected. (Eid et al. 2018.).

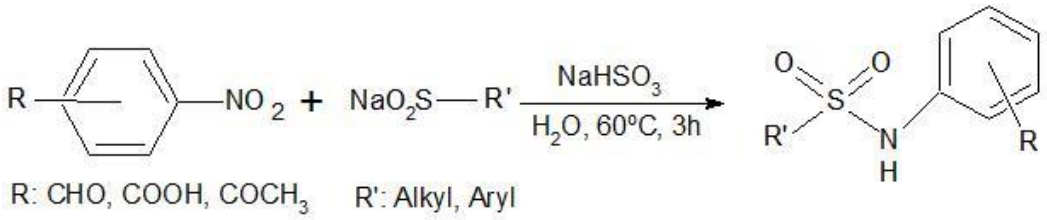


FIGURE 10. Sustainable approach to synthesis Sulfonamide. (Adapted from Eid et al. 2018).

4 GREEN CHROMATOGRAPHIC TECHNIQUES

One of the most crucial stage in the production of pharmaceutical products is the drugs discovery and development. In fact, this is a complicated process which takes approximately 10 years and costs billions of US dollars to successfully develop an approved drug. For decades, chromatographic analysis has been an essential instrument in every research and development of medicines. Traditionally, this process takes a considerable amount of time, energy, money, as well as toxic organic solvents. As environmental and sustainable concerns are gaining more and more attention globally, greener purification techniques are necessary for pharmaceutical industry. (Miller et al. 2019, 267.). This chapter highlights the green chromatography concept, accompanied by the parameters and approaches toward reaching it.

4.1 Concept of green chromatography

Green chromatography is recognized as a branch emerged from green chemistry context. Having been first introduced by Anastas since 1991, Green chemistry concept continues to be developed by Badami, Nameroff, and Kletz (Korany et al. 2017). To date, the concept of Green chemistry constitutes a set of principals designed to limit the use and generation of hazardous substances in chemical processes. It is an innovative modern solution that takes all life cycles of chemical processes into consideration. The application of Green chemistry benefits not only the environment but also the industry since it reduces the environmental compliance costs as well as energy spending. Therefore, pharmaceutical companies should implement green chemistry in their manufacturing processes to reduce the toxic waste produced. (Peterson et al. 2014.).

Within the economical and sustainable framework of green chemistry, the concept of green chromatography focuses on a number of crucial objectives as following. Firstly, direct chromatographic methods are encouraged so as to avoid sample pretreatment and restrict the use of solvent. Secondly, the separation time and energy consumption are preferred to be shortened. In addition, the use of organic and toxic or unrenewable reagents during chromatographic process should be avoided or replaced. Last but not least, the integration of multistep procedure into a single step procedure should be promoted, yet the quality of purified products must be ensured. (Lu 2012; Płotka et al. 2013; El-Shaheny et al. 2019).

4.2 Parameters and approaches to make chromatography greener

Chromatography is capable of being greener at every operation step. By modifying the parameters involved in chromatography like preparation technique, type of chromatographic method, mobile phase, stationary phase, size of column, and temperature; the goal of green chromatography can be achieved. (Płotka et al. 2013.). Recent studies on possible and effective approaches towards greener chromatography are summarized as below.

4.2.1 Green sample preparation

Sample separation is a crucial part of chromatographic separation in which the impurities unable to elute from the column are removed. However, it is often the most polluting stage in the whole chromatographic procedure as it involves the use of toxic chemicals, thus its presence or absence is considered as an important factor of green chromatography. Direct chromatographic methodologies without sample preparation are highly recommended from a green perspective. The application of direct chromatographic methodologies fulfills the objectives of green chemistry in resources saving of time and materials. However, these methodologies are limited to relatively clean matrices so as to avoid the deterioration of columns due to the deposition of the retained components. Gas chromatographic methods are more readily adaptable than liquid chromatographic ones when it comes to the elimination of the sample preparation step. (Płotka et al. 2013; Mohammad & Inamuddin 2014.).

Although the absence of sample preparation would be an ideal approach, it is not always feasible. Miniaturization, integration, and simplification have become crucial concepts that effectively contribute to overcome some drawbacks of conventional sample preparation methods. Those concepts can be approached by the reduction, replacement, or elimination of organic solvent along with the performance enhancement. Many techniques for the fast, effective, and reproducible extraction and concentration of target products have been developed or improved to reduce or substitute the organic solvents extracted from non-renewable resources like oil. Such techniques include Accelerated Solvent Extraction (ASE), Supercritical Fluid Extraction (SFE), membrane extraction, ultrasonic extraction, and microwave extraction. (Mohammad & Inamuddin 2014.).

ASE has been known as a good green sample preparation technology for its advantages in short extraction time and low solvent consumption. ASE is performed at high pressures (10–15 MPa) and high temperatures (50–200 °C) so as to maximize the extraction efficiency by increasing the solubility and mass transfer of the analytes. Unlike ASE, the other green extraction techniques are able to operate at room temperature, allowing thermolabile compounds to be extracted. Apart from ASE, SFE employs a supercritical fluid (SF) where the physical state of a substance has intermediate physicochemical properties between liquid and gas above the critical conditions. The extraction efficiency in SFE is mainly affected by the choice of fluid, pressure, temperature, matrix-refined filling materials, and co-solvents. The most widely used fluid in SFE is supercritical CO_2 and superheated water (SW). Recently, membrane extraction has gained attention as a green alternative for analyte isolation and pre-concentration owing to its selective barrier between donors and acceptors phases. In 2012, a membrane extraction protocol in combination with liquid chromatography-mass spectrometry to determine 18 pesticides in red wine was developed and validated by Moeder and co-workers. (Mohammad & Inamuddin 2014.).

Besides the solvent-less techniques mentioned above, solvent-free sample preparation has gained much attention lately. The complete elimination of solvent involvement in sample preparation can be carried out by selective extraction of impurities or products from liquid or gaseous matrices via a sorbent phase. Solid Phase Extraction (SPE), Matrix Solid-Phase Dispersion (MSPD), Solid Phase Microextraction (SPME) and Stir Bar Sorptive Extraction (SBSE) are typical solvent-free sample preparation techniques. These techniques generally involve the adsorption of a target compound on a solid phase or solid support and the recovery of the compound by either thermal desorption or elution with a liquid or fluid. (Płotka et al. 2013; Mohammad & Inamuddin 2014.).

4.2.2 Green gas chromatography

Gas chromatography (GC) is a favorable technique to separate and analyze semi-volatile as well as volatile substances. GC separates a mixture based on the partition equilibrium of a component between a stationary liquid phase and a mobile gaseous phase. High process performance, strong separation power of complex mixtures, good precision and accuracy, coupled with simple operation as well as low cost and long instrument life are the key advantages associated with this technique. Furthermore, the principles of green chemistry are possible to implement in GC through several adaptations. In 2002, Wardencki and Namieśik presented a series of approaches towards green GC, which is summarized as the

reduction of energy consumption, chromatographic run time, matrix interferences, solvent usage, and wastes generation (Wardencki & Namieśik 2002).

As mentioned above, GC is likely to be proceeded directly without preparation as well as with green preparation techniques. Besides green preparation, the choice of column and carrier gas may also be considered to make GC greener. Columns in GC are designed in two ways: packed and capillary. Packed columns are generally a glass or stainless-steel coil either filled with a stationary phase, or a stationary-coated inert packing. GC employing packed columns is well-known for its large sample loading and preferred in separating non-polar samples. In green packed column GC, the solvent and run time can be cut down by using a shorter column packed with smaller particles, since column efficiency per unit length increases with decreasing particle size. Meanwhile, capillary columns are a thin fused-silica (purified silicate glass) capillary with stationary phase coated on the inner surface. These columns possess higher efficiency than packed ones and exhibit good separation against polar compounds. For capillary columns, green GC can be achieved by reducing column length and inner diameter, in combination with increasing inlet pressure and carrier gas velocity. (El-Shaheny et al. 2019.). With multi-capillary columns composed of a parallel arrangement of 900–2000 coated microcapillaries and 20–40 μm inner diameter, fast and effective separation of large sample volume is enabled (Mondello et al. 2004).

Selection of the carrier gas employs a significant impact on both column efficiency and separation speed. Typical carrier gases used as mobile phase in GC include helium, nitrogen, and hydrogen. The run time can be shortened at a specific temperature by boosting the velocity of carrier gas. In addition, gas viscosity tends to increase with temperature, which has a noticeable influence on GC performance. Among the three gasses, at any temperature, hydrogen has the lowest viscosity, thus producing higher speeds at a certain pressure drop. On the other hand, helium and nitrogen have similar viscosities and exhibit greater temperature dependence as compared to hydrogen. Moreover, helium is a non-renewable resource with environmental concerns in its production, and nitrogen is the least favorable choice as it possesses the most restricted operating range below the optimum linear velocity. Hydrogen, as an eco-friendly resource accompanied by a high optimum linear velocity that allows short operating time and energy saving, is the best choice of carrier gas for green gas chromatography. (Płotka et al. 2013; Mohammad & Inamuddin 2014.).

4.2.3 Green liquid chromatography

Liquid chromatography (LC) is considered “less green” than GC because its mobile phase can contribute to a large source of pollution; hence GC would be a better choice of chromatography whenever possible. However, LC offers many possibilities to be “greener” owing to their widely diverse operating styles. Most of the attempts are either the replacement of toxic organic solvents with greener ones or the reduction of solvent amount used and waste generated. (Lu 2012; Płotka et al. 2013.).

4.2.3.1 Solvent reduction approaches

Indeed, solvent consumption and waste generation can be reduced by several ways ranging from choice of column, stationary phase, and mobile phase to operation mode. One of the easiest ways is shortening the column length, consequently reducing the operation time and the solvent usage. The high-quality silica (small particle and/or spherical silica gel) packing as a stationary phase will also allow superior fast separation with minimum solvent amount needed. It is also recommended to use Thin Layer Chromatography (TLC) in the optimization of gradient or isocratic solvent mixture as the mobile phase for an effective low-wasted isolation of a desired compound. Once the efficient separation conditions for an analog in a series have been established, the method can be saved on the HPLC or Medium Pressure Liquid Chromatography (MPLC) machine for subsequent analog purification, because medicinal chemists often use a single reaction form to prepare a series of related analogues. (Peterson et al. 2014; Korany et al. 2017; Galyan & Reilly 2018.).

Miniature column dimension is also considered as an effective tactic to reduce the solvent consumption. In regard to this idea, the term of nano liquid chromatography (NLC) emerged as an environmentally friendly alternative to conventional separation methods. NLC makes use of 10–100 µm inner diameter columns for separations that operate at nanoliter flow rates. Advances in NLC provide a number of advantages over traditional HPLC such as: significant decrease in reagents consumption, high separation efficiency while remaining the retention behavior, easy coupling to mass spectroscopy (MS), low waste generation. However, its usage is limited by its high-cost instrumentation and specific technical knowledge it requires. NLC is mostly used as an analysis tool in pharmaceutical and biomedical research owing to its highly reliable and quickly achievable results. There has not been any publication reported about the preparative application of NLC because its nano scale and expensive cost makes NLC unpractical to scale up. (Gama et al. 2013; Asensio-Ramos et al. 2017.).

Another approach is to choose a Reverse Phase High-Pressure Liquid Chromatography (RP-HPLC) where aqueous mobile phase and non-polar stationary phase are used, leading to the decrease of organic solvent involvement. This technique allows a high rate of production and it is widely accepted in both analytical and preparative separations. Moreover, for highly polar compounds, RP-HPLC would generate less waste than normal phase chromatography (NP-HPLC). It should also be noted that columns in RP-HPLC are often reused for up to 1500 injections, which lessens column disposal waste. Typical mobile phase in RP is either an acidic eluent (MeCN-water or MetOH-water mixture) or a basic modifier (NH_4OH). However, for large scale purification, an RP-HPLC is not preferable due to the long time required to dry down the aqueous solvent, coupled with its associated high cost and energy. (Płotka et al. 2013; Peterson et al. 2014; Korany et al. 2017.).

Having been employed widely in the discovery and development of pharmaceuticals for decades, NP-HPLC remains to be the default technique in many organizations and industries for analysis and purifications. It can be conducted either in batch mode or continuous mode in which the second one is considered as “greener” choice. Though this technique exhibits significant disadvantages regarding solvent consumption and waste disposal, there have been many studies on its improvement. The two most outstanding continuous options are Steady State Recycling (SSR) and Simulated Moving Bed (SMB). SSR is performed with a single column where the unresolved fractions from the column outlet are recycle back to the inlet together with the fresh feed. (Ciurczak 2013; Galyan & Reilly, 2018.).

On the contrary, SMB (FIGURE 11) comprises a series of fixed bed columns in a looped, end-to-end configuration; in which not only the liquid phase is in motion but the solid phase also moves in countercurrent mode to the liquid by switching the inlet and outlet ports in the direction of the liquid flow. In other words, a typical SMB unit is divided into four zones with one or two columns per zone, and four distinctive streams (feed, eluent, raffinate, and extract). The separation takes place in zone 2 and zone 3, the feed is added in the connection between these two zones. The extract is collected before entering zone 2. The raffinate exits the unit after zone 3. Zone 1 and zone 4 are where the solid phase is regenerated by desorbing the more retained compound with the addition of eluent flow. The utilization of this technique results in solvent saving and productivity enhancement in purification. (Cano et al. 2005; Heinonen et al. 2019.).

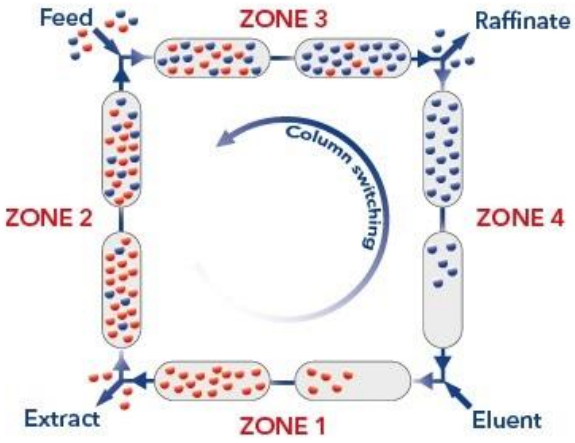


FIGURE 11. Simulated moving bed scheme. (Adapted from Azo Materials).

Another technique identified as green is counter current chromatography (CCC). CCC makes use of liquid partitioning between two immiscible liquid phases to separate pharmaceutical compounds in multiple tubes with minimal flow. At one end of the first tube, the sample is added, and the tubes are shaken. After a period at which solvents are completely separated, the selected phase (either top or bottom) is transferred to the next tube and the first tube is refreshed with fresh solvent (of the moved level). The device is shaken, and the process continues. Therefore, this technique provides a lower overall solvent consumption rate. It also presents a range of advantages over solid/liquid chromatography such as high loading allowance, easy scale-up potential, ability to conduct without preparation, and green solvent usability. Despite all the benefits CCC grants, it has not been widely adopted for routine analysis and purification. However, this technology has been recommended in many studies for further development and applications owing to its robustness. (Cue & Zhang 2009; Ciurczak 2013; Mohammad & Inamuddin 2014; Galyan & Reilly 2018.).

4.2.3.2 Solvent replacement approaches

To seek new and innovative ways of "greening" chromatographic processes, replacement of organic toxic solvents was found to be a high potential approach. Several guides on the selection of greener solvents used in organic chemistry have been published which can provide a helpful baseline for solvent choice in reactions and purifications. Dichloromethane (DCM), a common solvent in chromatography, is toxic to humans, poses environmental risks and is challenging to dispose. Some studies have suggested Ethanol and its mixture with Ethyl Acetate as green alternatives for chromatography solvent. The blend of EtOH – EtOAc can be used with both acidic and basic additives, which makes it superior to DCM. (Płotka et al. 2013; Peterson et al. 2014; Shen et al. 2015.).

Another option for this approach is ionic liquids (IL) which are salts in liquid state (either melted or vaporized without decomposing). ILs melt at or below 100°C. ILs have recently been used as additives in LC to improve peak shape by pairing ion mechanisms. Furthermore, they have been widely involved as stationary phase in GC, HPLC, and CCC. The key benefits of IL are negligible vapor pressure, thermal robustness, low waste generation, excellent solvents for organic, inorganic and polymeric materials, easy to buy, simple to prepare and non-flammable. In fact, with their low vapor pressures that keep the substance from releasing to the environment, ILs have become good green solvent candidates. Some examples of ionic liquids currently used in LC are: alkylimidazolium, dimethyldinonylammonium bromide, ethylcholine-bis-(trifluoromethanesulfone)-imidate, and N-alkyl-N-methylpyrrolidinium bromide. (Sun et al. 2010; Shen et al. 2015; Korany et al. 2017.).

SW has gained more attention lately as a high potential to replace organic solvent in RP-LC. SW chromatography (SWC) operates at 80 to 250°C, where the polarity of SW is lower enough to replace water–methanol and water–acetonitrile as eluents. However, the pressure in the column should be adjusted so that water remains in liquid state at such temperatures. Similar to usual water, deuterium oxide or heavy water is also able to be an alternative solvent in chromatography. SW offers a variety of advantages such as wide availability, renewable resource, non-flammability, and low cost. Nevertheless, there are some limitations like thermal stability and water solubility of the compound to be separated. Also, silica-based columns exhibit degradation at high temperature, thus the use of C_{18} columns is recommended when choosing SW. On the flip side, there are numerous benefits resulting from high-temperature chromatography, including the increase of speed and efficiency. Though SWC has not been accepted as a routine technique, further research into it is warranted. (Coym & Dorsey 2004; Shen et al. 2015; Korany et al. 2017.).

In recent times, SFs have been investigated by numerous industrial and academic R&D laboratories owing to their unique properties which make them outstanding candidates for green solvent. Supercritical point is defined as a state where the temperature and pressure of a substance exceed its liquid/vapor critical point. At this point, the phases of liquid and vapor merge, and their vaporization enthalpies become zero. Hence, SF presents liquid-like density and solvent power while remaining gas-like viscosity that facilitates good natural matrices penetration. As mentioned above, SF are able to be used as solvent in both extraction and chromatography. Supercritical fluid chromatography (SFC) resembles the properties of GC (fast separation) and HPLC (high loading capacity). (Berger et al. 2012; Lu 2012; Miller et al. 2019.).

The use of supercritical CO_2 as mobile phase in SFC is almost a solvent-free method except for the addition of methanol, ethanol, or isopropyl alcohol as modifiers. Though SFC is widely used in pharmaceutical research as an analytic instrument, it is not popular in large scale purification for manufacture processes. However, the increasing study on the combination of SFC and SMB has offered more opportunities for this alternative solvent in industrial separation and purification. (Alkio 2008; Peterson et al. 2014; El-Shaheny et al. 2019.). A comparison between HPLC batch mode with some noticeable green techniques used in pharmaceutical R&D like SSR, SMB, and SFC was reviewed by Galyan & Reilly 2018 and is presented below in Table 2. As can be seen from these data, SMB shows considerable green chromatography features with extremely high capacity yet ensuring a low solvent consumption. Besides the advantages it embraces, this technology is difficult to setup and handle, making it not suitable for small organizations.

TABLE 2. Comparison of some chromatographic techniques. (Adapted from Galyan & Reilly 2018).

	Solvent consumption	**Setup time**	**Expertise level requirement**	**Loading capacity**
Batch HPLC	High	Low	Low	mg-kg
SSR	Medium	Medium	Medium	mg-kg
SMB	Low	High	High	g-ton
SFC	Medium	Low	Low	mg-kg

Another comparison between SFC and batch HPLC methods conducted by the Courtesy of Water Corporation is highlighted in Table 3. The table exhibits remarkable green qualities of SFC over batch HPLC in terms of time and solvent expenditure as well as recovery percentage. Indeed, the solvent and operation time can be saved dramatically by replacing HPLC with SFC, even though they both share the same loading capacity as indicated in Table 2.

TABLE 3. Comparison between SFC and Batch HPLC. (Adapted from Courtesy of Waters Corporation).

	SFC	**Batch HPLC**
Separation time	3 hours	46 hours
Organic Solvent used	5 L Methanol	40 L Acetonitrile
Total workup time	1 hour	8 hours
Recovery	95%	80%

For separation of moderately polar to polar compounds in LC, enhanced fluidity (EF) liquid mixture can play the role of a green solvent. EF requires the use of liquified gases, such as CO_2 or CHF_3, in conjunction with polar liquids, such as alcohol, as the HPLC mobile phase. Such mixtures usually have high solvent strength, whereas their viscosities and diffusivities approach those of SF. EF enhances green chromatography not only as an eco-friendly reagent but also as a contribution to the fast and productive separation. Recently, EF has been applied in NP-, RP-HPLC, as well as Size Exclusion Chromatography (SEC). It was reported to be a better alternative than SF. (Sun & Olesik, 1999; Płotka et al. 2013; Korany et al. 2017.).

Micellar liquid (ML) is an alternative solvent which constitutes of amphiphilic micellar aggregates surrounded by water, or aqueous-organic solvent that contains surfactant monomers above its critical micellar concentration (CMC). Current environmental concerns also reveal ML chromatography (MLC) as an interesting "green" chemistry technique because its mobile phase contains more than 90 percent of water. Such mobile micellar phases are poor in toxicity and do not generate hazardous waste. The surfactant in MLC enhances numerous interactions among the eluted solutes, the stationary phase, the aqueous phase and micelles, which allows the analysis of various compounds with different polarities. The presence of a surfactant not only changes the interactions within the column, but also reduces the amount of organic solvent required in the mobile phase, which can be recovered due to low evaporation. Furthermore, this technique is found to be capable of direct inject without preparation, giving greater precision and lower cost to analytical procedures. (Rambla-Alegre 2012; García-Alvarez-Coque et al. 2015.).

5 CASE STUDIES

In the previous chapter, systematic approaches are described where regular chromatography methods are adjusted for green separation process. In order to emphasize their capability in the study of sulfonamide derivatives, published researches concerning the separation of some sulfonamides using green chromatography are reviewed for different case studies. Most of the known literatures have reported the results of analytical separation of sulfonamides, yet their preparative separation has been mentioned only with SFC techniques. Nevertheless, the successful analytical separation of sulfonamides by such methods support their potential application in preparative scale.

5.1 Case study 1: Micellar liquid chromatographic separation of sulfonamides

In 1995, Yang and Khaledi conducted a study about the retention behavior of twelve sulfonamide derivatives in MLC. These twelve sulfonamides were also isolated from physiological fluid samples obtained from human urine and cow milk using direct injection to study the suitability of MLC for direct on-column method. The micellar mobile phase involved was sodium dodecyl sulfate (SDS) which is a routinely used anionic surfactant in MLC. A hydrophilic endcapped C_{18} was selected as the stationary phase in this work. The twelve sulfonamides of interest were: sulfacetamide, sulfadiazine, sulfamerazine, sulfathiazole, sulfamethazine, sulfamethoxypyridazine, sulfachloropyridazine, sulfamonomethoxine, sulfabenzamide, sulfadimethoxine, sulfaquinoxaline, and sulfisomidine. The retention behavior and selectivity pattern of these sulfonamides in MLC was investigated by varying the concentration of surfactant and the volume fraction of an organic modifier. (Yang & Khaledi 1995.).

In the first part of the research, the twelve commercially obtained sulfonamides were diluted with the mobile phase which was prepared by dissolving SDS in distilled water followed by the addition of phosphate buffer as ionic strength adjustment and 1-propanol as organic modifier. The final solution after adding buffer and modifier contained 0.02 M phosphate and pH 3.0. The analytical process was maintained at 40°C in a water bath. After a series of experiments with different value of SDS concentration and 1-propanol volume fraction, the optimal condition for the separation of the interested sulfa drugs was found to be 0.070 M SDS and 6.0 %vol 1-propanol. The experiments also pointed out the good

separation of these 12 sulfonamides in 15 min under these conditions coupled with a high column efficiency of around 7000 plates/25 cm column. Because of the highly reproducible retention behavior in MLC separations, retention behavior of sulfonamides was repeatable with high precision. The authors also highlighted that the MLC separation can be influenced by modifying the stationary phase, ionic strength, pH, and temperature. (Yang & Khaledi 1995.).

In the second part of the research, the physiological fluid samples mentioned above were filtered and diluted with the mobile phase prior to on-column injection. Despite the presence of several unknown impurities, the twelve sulfonamides were successfully isolated without any interference. The good determination of these sulfonamides in these two physiological fluid samples has proved the high potential of MLC as a direct chromatographic method. (Yang & Khaledi 1995.). It can be draw from this case study that sulfonamides are able to withstand the conditions of this technique, giving evidence for the applicability of MLC in the green analysis of sulfa drugs. Further investigations on the development of preparative MCL and its scale-up ability are necessary in order to apply this technique to the routine R&D of pharmaceutical agents such as sulfonamides.

5.2 Case study 2: Nano liquid chromatographic separation of sulfonamides

D'Orazio, Rocchi & Fanali 2012 carried out a research on the determination of eighteen sulfonamides residue in food matrices using NLC methods by changing the stationary phases to investigate the column conditions for achieving the best result. The work also evaluated the effect of the other parameters such as: maximum injection volume, focusing solvent, and chromatographic conditions. A milk sample spiked with the same eighteen sulfonamides was analyzed using the conditions that was found earlier. The eighteen sulfonamides of interest were: sulfabenzamide, sulfachloropyridazine, sulfadiazine, sulfadimethoxine, sulfadoxin, sulfaguanidine, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethoxazole, sulfamonomethoxine, sulfanilamide, sulfapyridine, sulfaquinoxaline, sulfathiazole, sulfisomidine, and sulfisoxazole. The NLC separation was performed in a 100 µm inner diameter fused silica capillary column with a length of 25 cm. (D'Orazio, Rocchi & Fanali 2012.).

In the first task of the research, three columns packed with three stationary phases Phenyl, C_{18} porous silica and C_{18} non-porous core-shell were investigated. A binary mobile phase in gradient mode containing water and acetonitrile was employed so that the content of water was decreasing with an increasing amount of acetonitrile over the operation time. The separation was executed at ambient temperature. The

sample injection volume was in range of 200 – 1200 nL. The three columns took around 35 minutes to complete the separation, in which the best selectivity was observed in the two columns packed with C_{18} particles thanks to their effective resolution associated with the hydrophobic interaction with C_{18} chains. Moreover, it was found that C_{18} core-shell showed superior results to C_{18} porous silica and was selected for further experiments. The method sensitivity was examined by on-column focusing approach in which a high sample volume was injected while securing the column efficiency. Later on, it was found that 1000 nL was the maximum sample injection volume that provided high sensitivity with both UV and MS detectors. (D'Orazio, Rocchi & Fanali 2012.).

In the second task of the research, the optimized condition from the previous experiments was used to detect sulfonamide residue in food matrices. The food matrix of interest was commercially available pasteurized milk. The milk sample was submitted to a preparation process including acidic deproteinization and solid phase extraction prior to NLC analysis. Some parameters such as repeatability of retention time and peak areas, linear dynamic range, recovery, precision, limit of detection and quantitation of sulfonamides in NLC were studied utilizing the optimal conditions above. The authors concluded that the method they found was sensitive enough for the detection of residual sulfa drugs in the milk sample in accordance with EU regulations. (D'Orazio, Rocchi & Fanali 2012.). This case study successfully investigated the analytical aspect of a green chromatographic technique, including the separation and determination of some sulfonamides under NLC conditions. These results can be a guideline to apply analytical NLC in the discovery and development of new and old sulfa drugs in pharmaceutical industry.

5.3 Case study 3: Superheated water chromatographic separation of sulfonamides

Having emerged as a green substitution of organic solvent in RP-HPLC, SW has been investigated thoroughly in many scientific publications. Among the literature, there were two studies involving sulfonamides separation to examine different enhancements of SW in chromatography. The first research was carried out by Chienthavorn and Smith in 1999 concerning the potential of buffered SW as mobile phase for reverse phase chromatography. In their work, inorganic buffers were used to control the pH of SW eluent in chromatographic separation of sulfonamides. Their retention behaviors were also inspected over a range of pH and temperature. The studied sulfonamide derivatives were sulfanilic acid, sulfacetamide, sulfisomidine, sulfanilamide, sulfaguanidine, sulfathiazole, sulfapyridine, sulfamethazine, N^4-acetylsulfanilamide, and N^1, N^4- diacetylsulfanilamide. A set of phosphate salts were employed as the inorganic buffers. The separation of selected sulfonamides with unbuffered SW was reported to give

good peak shapes, yet their retention time and elution order differed over the repeated experiments. Therefore, the authors suggested the necessity of a buffered system. (Chienthavorn & Smith 1999.).

In their studied methodology, a gradient temperature profile was utilized to control the elution speed of the analytes. The column was placed in an oven with a temperature profile ranging from 70-190°C. A faster rate of temperature rise resulted in a shorter separation time. The sulfonamides were separated at pH 3, 7 and 11 phosphate buffers. The retention time and elution order of the ten sulfonamides of interest varied with different pH buffers due to the ionization of sulfonamides at high pH condition. The most reliable separation result was found to be at pH 3 where all the sulfonamides eluted in a single run with good separation and symmetrical peaks, accompanied by a consistent retention time. The effect of high temperature in SWC on the properties of sulfonamides was also examined. In this task, sulfanilamide, sulfacetamide, sulfathiazole, and sulfamethazine representing a range of pKa values were investigated. Their experimental pKa values measured in SWC were compared with the values obtained from literature, showing that the dissociation constants of the analytes in buffered SW slightly decreased when the temperature of SW increased above 100°C. (Chienthavorn & Smith 1999.).

In 2000, Smith and Chienthavorn collaborated with other researchers to conduct another study on SWC with heavy water to analyze a series of sulfonamides as model compounds. In this research, they separated a mixture of sulfacetamide, sulfadiazine, sulfamerazine, and sulfamethazine using buffered heavy water at pH 3 over a gradient temperature program from 160 to 200°C at a constant rate of 2°C per minute. The NMR and MS examination of the eluent showed good peaks shape. However, the spectra of sulfamerazine and sulfamethazine revealed an unexpected substitution of the protons on the pyridinium methyl groups by deuterium atoms. Afterwards, the authors discovered a selective deuterium exchange reaction took place during the elevated temperature conditions with the methyl groups on pyrimidine rings. It was believed that this discovery had provided a potential methodology to produce deuterium-labelled compounds. (Smith et al. 2000.). Overall, these two researches in this case study enable the confirmation of sulfonamide's stability under the temperature and pH conditions of this technique, suggesting the application of superheated water chromatography to be routinely used in the development of sulfa drugs.

5.4 Case study 4: Supercritical fluid chromatographic separation of sulfonamides

Among all the green approaches discussed previously, SFC is considered as the most favorable methodology in both analytical and preparative chemistry. This can be seen from a dominant number of published studies regarding the development of this technique. As a matter of fact, the topic of sulfonamide separation utilizing SFC method is not an exception. Dated back in 1986, in a research by Berry et al., the use of packed-column SFC using a moving-belt interface was recorded where a mixture of sulfonamide derivatives was chromatographed on a stationary silica layer (Berry et al. 1986). In 1991, Perkins et al. developed the same methodology with the same group of sulfa drugs on silica and amino-bonded stationary phases utilizing both moving-belt and modified thermos pray interfaces (Perkins et al. 1991). Based on the previous results from Berry and Perkins, Combs et al. continued the method development by employing a combination of silica-aminopropyl stationary phases, modifier gradient, and subtle temperature change, resulted in a good separation of eight sulfonamides in less than 20 minutes (Combs et al. 1997).

In 2008, the retention behavior of 32 sulfonamide derivatives in SFC was investigated by Cazenave-Gassiot et al. The authors employed a polycratic study of 32 sulfonamides using SFC with a 2-ethylpyridyl column and three different modifiers. Their work aimed to assess the relationship between the logarithm of retention factor and the proportion of modifier in the mobile phase, thus the retention behavior of the studied compounds can be predicted. This model was validated to allow the prediction of isocratic retention time. (Cazenave-Gassiot et al. 2008.). A more recent study in 2013 by Berger & Berger reported the utilization of Ultra-High-Performance Supercritical Fluid Chromatography (UHPSFC) in a fast separation of nine sulfonamides. These nine derivatives were described as difficult to isolate due to their similar structures. However, with the advance of extremely small particles packing in the UHPSFC stationary phase, such compounds were separated in less than 5 minutes. Their results exhibited a significant enhancement in complexity, resolution and speed compared with the previous studied SFC separations of sulfonamides, which used larger particles. (Berger & Berger 2013.).

As mentioned earlier, SFC possesses a high potential to be developed into preparative separation. Many papers have identified the benefits of using preparative SFC in the separation of fuels, crude oil, pharmaceuticals, and natural products in the last few years. Preparative SFC is faster than preparative HPLC and providing a wider application range than preparative GC. In 1997, a micro preparative scale separation and fractionation of three sulfonamides using commercially available SFC system was evaluated by Ashraf-Khorassani and co-workers. Their work investigated two instrumental setups (FIGURE 12) and

three collection protocols to optimize the effective model for each fraction. Both setups involved a feed pump and a modifier pump connected to an injection valve, a column which placed inside an oven, an UV detector, two back-pressure regulators, a T-valve where a rinse pump is equipped to wash the lines with methanol, and a fraction collector. The two setups differed in the position of the back-pressure regulators. In the first setup, two regulators were placed at two ends of the T-valve, whereas the second setup placed both of the regulators continuously after the T-valve. The results indicated that the second setup can minimize cross-contamination of the fractions, thus highly pure compounds can be obtained. The evaluation of the three collection protocols showed that good purities for the interested sulfonamides could be achieved by a constant 0.5-minute interval collection. (Ashraf-Khorassani et al. 1997.).

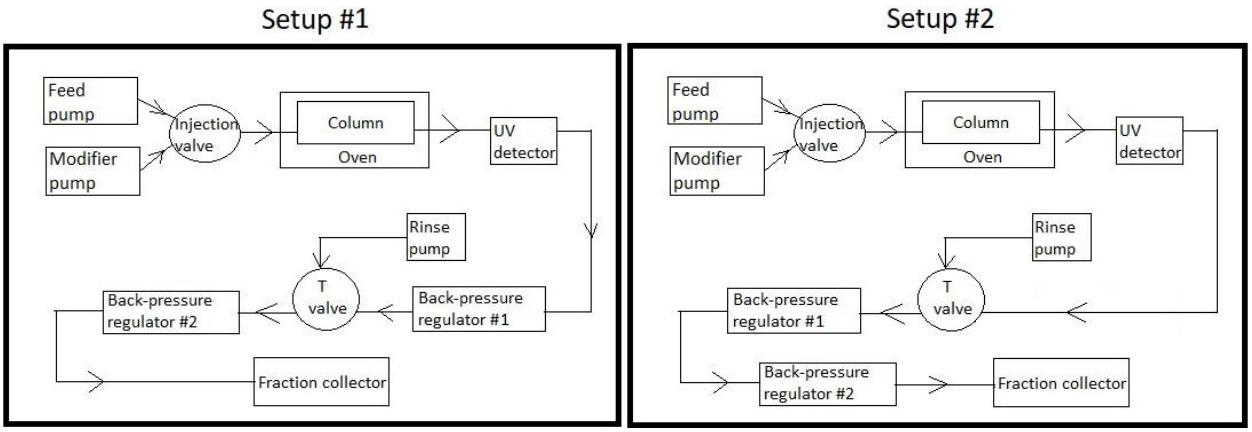


FIGURE 12. Preparative SFC setups. (Adapted from Ashraf-Khorassani et al. 1997).

Having rich references in sulfonamide analytical and preparative separation, supercritical fluid chromatography became the most potent methodology to be employed in the production of sulfa drugs. However, further development in this technique is required so as to meet the high demand of sulfa drugs in pharmaceutical industry.

6 CONCLUSION

The important contribution of sulfonamide derivatives in health science is undeniably assured to extend. With the increasing number of bioactivities and therapeutic effects discovered, sulfa drugs have always been one of the top candidates in the search of novel treatment for old and new diseases. The versatility of sulfonamide gave rise to an abundant appearance of its derivatives in a variety of medications. Countless literatures have been dedicated to this topic ever since its emergence as an antibiotic therapy. To date, the application of sulfonamides has been extended to diuretic, anti-diabetes, anti-tumor, anti-thyroid, anti-inflammatory, anti-hypertensive, antifungal, antidepressant, and antiviral therapies. Consequently, the global demand for this class of drug has been increasing dramatically, requiring a sustainable production pathway to overcome the drawbacks employed in the conventional methods.

As a matter of fact, the discovery and development of sulfonamide derivatives embraces a large consumption of hazardous reagents, time, and energy, as well as the considerable waste it generates. Numerous innovative approaches have been studied to reduce the environmental problems it poses, and at the same time improve the production yield. A noteworthy sulfonamide synthetic route using water as the only solvent has been examined lately. Though the literature limited the application of this methodology to aryl N-substitute sulfa drugs, it is expected to be a guideline for further study on green alternative synthesis of more compounds beyond the mentioned ones.

Within the framework of sustainable sulfonamides production, the effects of discovery and development phases on the environment should be taken into consideration. These phases are crucial parts where thousands of compounds are synthetized and analyzed. These stages are also known to be time and energy consuming, coupled with significant toxic organic solvent involvement. Chromatography, a reliable analytic technique preferred in pharmaceutical R&D, is not an exception of this drawback. However, chromatography possesses a wide range of approaches toward the goals of green chemistry. Gas chromatography is considered as a greener technique than liquid chromatography. With the employment of Hydrogen as the alternative carrier gas, chromatographic analysis can be performed in a short time with excellent results and low energy requirement.

Despite the extensive environmental risks LC causes due to its huge solvent consumption, a number of solutions to overcome this problem have arisen. Those attempts are designed to either reduce or replace the use of toxic solvents. By altering the column dimensions, packing particle size, and operating model, the decrease of solvent usage can be achieved. Besides, several potential candidates were found to substitute the toxic organic solvent in the mobile phase of LC. Among those, SW and SF are the most popular alternative green solvents that make use of completely inorganic substances. They have been widely employed in many analytical and preparative chromatography so far.

The application of green chromatography in the discovery and development of sulfonamides was investigated via reported studies on the chromatographic separation and identification of sulfonamides utilizing green approaches. Initially, those researches were dedicated to the determination of residual sulfonamides in the environment. However, the retention behaviors of many sulfonamides in the conditions of those green chromatographic techniques introduced their possibilities in the pharmaceutical R&D analyses of sulfa drugs. Among the four case studies discussed above, SFC exhibited the most promising potent to be employed in the purification of drugs manufacture. MLC, SWC, and NLC possessed remarkable advantages in separation efficiency and “green” characteristics yet requiring expensive costs and high expertise level to perform. These green techniques needed more investigation to improve their contribution in the discovery and development phases of sulfa drugs.

In conclusion, it is expected that this literature review provided a solid and comprehensive evaluation on the significant value of sulfonamide class and the need for an environmentally friendly method to produce them. The review also recommended the utilization of green chromatography in routine R&D process to reduce a number of negative impacts associated with organic solvent. Though there have not been many reports on the preparative application of this technique in sulfonamide separation, its future of further development shows highly promising opportunities as environmental concerns are rising. An idea of combining simulated moving bed setup using supercritical fluid solvent has been suggested, giving hopes for the efficient application of this methodology in industrial scale.

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