International Journal of Management, IT & Engineering
Vol. 12 Issue 12, December 2022,
ISSN: 2249-0558 Impact Factor: 7.119
Journal Homepage: http://www.ijmra.us, Email: editorijmie@gmail.com
Double-Blind Peer Reviewed Refereed Open Access International Journal - Included in the International Serial Directories Indexed & Listed at: Ulrich's Periodicals Directory ©, U.S.A., Open J-Gate as well as in Cabell's Directories of Publishing Opportunities, U.S.A

EFFECTIVENESS AND METABOLITES OF SULFONAMIDE AND THEIR USES IN MEDICINE

SHYAMASRI MAITY (M.Sc),
Ph D Scholar, Deptt. Of Chemistry,
CMJ University, Jorabat, Meghalaya,

Dr Harsh Sharma (M.Sc, Ph D),
Supervisor
CMJ University, Jorabat, Meghalaya.

ABSTRACT

Environmental water samples have been shown to contain sulfonamide residues in a wide variety of forms. Very few papers, however, have examined these compounds' metabolic byproducts or breakdown products as part of their analysis. This article's primary purpose is to examine research articles in which both parent medicines and their respective metabolites have been considered jointly. These antibiotics are examined in terms of analytical methods and biotic and abiotic degradation pathways, and their potential toxicity in the environment is briefly evaluated. All rights reserved 2008 Elsevier Ltd. As an antibacterial agent, sulfonamide benefits both humans and animals suffering from infections. It's a lifesaver in the agriculture sector. It's being used more and more for the improvement or benefit of society as time goes on. In addition, the products' toxicity and the possibility of retransformation back into the parent medication must be considered. Despite the presence of high levels of microbial activity, sulfonamides are resistant to destruction in wastewater treatment procedures. Sulfonamides have been explored in this paper, as well as their usefulness and structure.

Keywords: Sulfonamide, Metabolites, Human, Animal, Photocatalytic

1. INTRODUCTION

In aquaculture, animal husbandry, and human medicine, sulfonamides are synthetic antibacterial drugs, derivatives of sulfanilamide, that are used to treat a wide range of infections caused by bacteria and other microbes. P-aminobenzoic acid is inhibited in its conversion by these drugs, which prevents bacteria from using it to synthesise folic acid, purine, and DNA. When it came to treating human infections, sulfonamides were the first antibacterial medicines to see widespread use. For example, they can be used to treat urinary tract infections (UTIs) and ear infections (EIs), as well as bacterial meningitis (BMI), certain eye infections (EIs), and Pneumocystis carinii pneumonia (PCP). Veterinarians are using more suitable volumes to treat cattle herds and, at

subtherapeutic doses of growth boosters and to increase feed efficiency. Sulfonamides are the second most often prescribed veterinary antibiotic in the European Union. In the UK, they accounted for approximately 21% of sales in 2000, while in various other European nations, they accounted for between 11% and 23% of sales. Sulfonamides make up 2.3 percent of all antibiotics prescribed in the United States (mainly sulfamethoxypyridazine, sulfachloropyridazine, sulfamethazine and sulfathiazole). Sulfonamides represent for 22% of the 14,600 kg of active antimicrobials used in the manufacturing of animal feeds in Kenya, where data is scarce.

2. Metabolites ofSulfonamides

Sulfonamide metabolism is species specific. Other tissues, such as the pancreas and the intestines, also break down these substances. Phase I oxidation and phase II acetylation dominate biotransformation, resulting in the N1 and N4 compounds illustrated in Fig. 1, although no microorganisms are involved in the process. Conjugation of glutaraldehyde with the parent compound's hydroxyl radicals and aromatic hydroxylation are other processes that occur.

2.1. From Humans

There aren't many studies on the distribution and destiny of pharmacological metabolites. In order to produce N4 -acetylsulfadiazine and N4-hydroxysulfadiazine, it is well-known that the N4 -nitrogen atom is involved in sulfadiazine metabolism. It is also possible to conjugate hydroxyl metabolites with glucuronic acid and sulfurate [4,5]. This product is removed in urine together with the remaining parent chemicals and should be cleared from the body faster than the parent medication (5-methylhydroxysulfamethoxazole, N4 -acetyl-5- methylhydroxysulfamethoxazole, and sulfamethoxazoleN1 -glucuronide were identified from human urine.). Photodegradation of both parent and metabolites can occur after they are discharged into the environment, therefore it's important to keep this in mind. This means that sulfonamides and their metabolites released into the environment by sulfonamides used in hospitals or prescribed by doctors are the primary sources of sulfonamides and their metabolites in the environment. Recent years have seen an increasing number of investigations on the prevalence and distribution of sulfonamides in WWTP sewage. However, only a few of these studies included metabolites in their list of target chemicals; however, they frequently reported wastewater treatment elimination rates that may be interpreted as both full sulfonamide breakdown and transformation into other intermediate products.

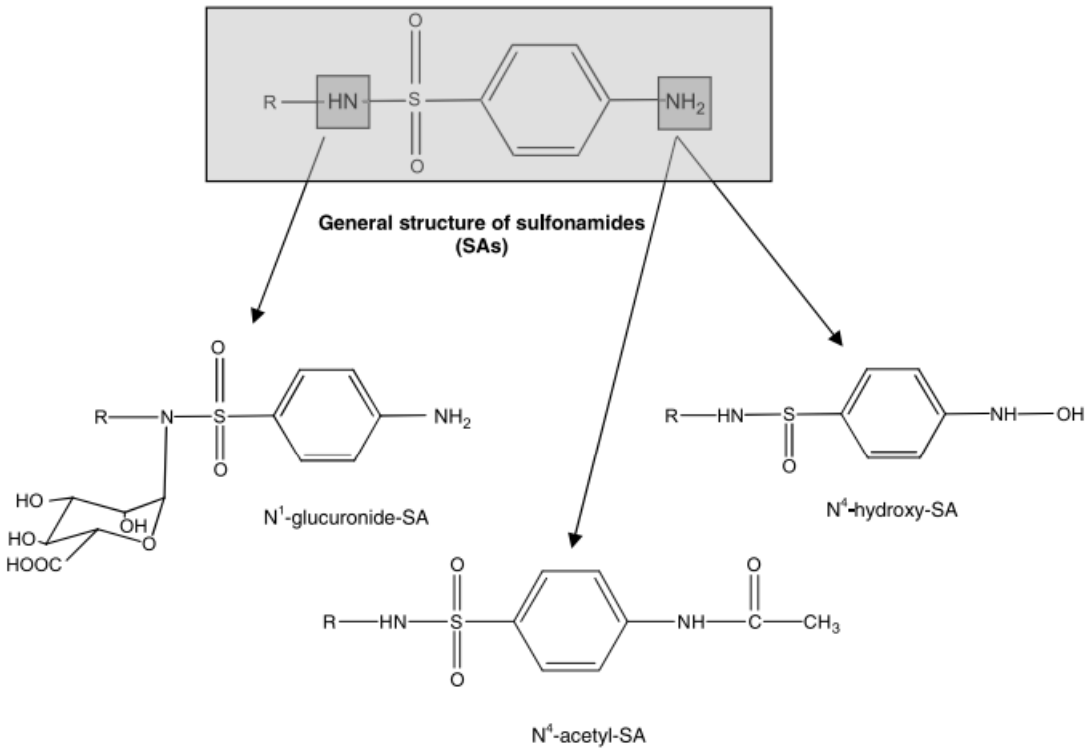

Figure 1. Major metabolites of sulfonamide antibiotics.

2.2. From animals

Veterinary antibiotics can infiltrate the environment in a variety of ways, the most common of which is through the excretion and urine of treated animals and the subsequent fertilisation of agricultural land with the contaminated manure. Within a few days of therapy, cattle will typically excrete 50–90% of the supplied dosage, with the parent medication accounting for 9–30%. Aceticacid conjugates account for 5–60% of the excreted dosage, however the acetyl moiety can be broken by bacteria during storage, causing the molecule to return to its parent chemical. Unused sulfonamides are excreted in varying amounts, depending on the kind of sulfonamide is used and the age and species of animal. As in humans, the major sulfonamide metabolism pathway in animals is N4 -acetylation, and these metabolites usually have weak, reduced activity against bacteria; for example, sulfamethazine is known to metabolise into N4 -acetylsulfamethazine, desaminosulfamethazine, and N4 -glucose conjugate in pigs.).

3. DEGRADATION

3.1. Biological

3.1.1. In WWTPs

Many investigations have shown that sulfonamide removal from sewage has been insufficient. For this reason, sulfamethoxazole is one of the most regularly prescribed sulfonamides and a compound that is examined in urban sewage treatment facilities on a regular basis. The amount of p-TSA in wastewater decreased significantly after treatment. Two of the WWTPs examined had o-TSA effluent concentrations higher than influent concentrations. This might be because of a site-specific wastewater treatment method that enhances o-TSA formation. BSA was identified at low quantities (0.05 lg/L) in the influent, while larger concentrations above 0.35 lg/L were found in the effluent. This is comparable to what happened with BSA. This transition may have been triggered by biodegradation. BSA may be a metabolite of high-molecular-weight sulfonamides, according to previous research (e.g., phenylsulfonamides).

3.1.2. In Surface Water

According to the high frequency of their discovery in streams and rivers, sulfonamides appear to be resistant to natural biodegradation. Sulfamethoxazole was found in rivers and streams at a rate of up to 27%, according to an analysis by the US Geological Service (USGS). As a result, they may travel over great distances in flowing water due to their low inclination to adhere to sediments. Sulfamethazine, sulfamethoxazole, and sulfathiazole degradability in surface-water samples was evaluated by Perez et al., as previously indicated. No surface-water microbes in the batch reactor destroyed these sulfonamides in over a month. We examined the acetyl-metabolites of five distinct sulfonamides, all of which were found to be abundant around Lake Greifensee in Switzerland's very productive grasslands. The results showed that no degradation products had been produced.

3.1.3. In Manure and Soils

Sulfonamide biodegradation kinetics in soil, manure, and soil treated with manure are mostly unknown. Concentrated animal feeding operations (CAFOs) are indirectly important contributors of antibiotic pollution in soils and groundwater because of the use of manure obtained from treated animals as fertiliser.

3.2. Photocatalytic

Sulfonamides can be eliminated by photocatalytic degradation, however little research has been done on the generation of photodegradation chemicals in the environment. According to Andreozzi et al, photocatalytic degradation of sulfonamides is similar to that of other organic molecules. Photodegradation half-life for Sulfamethoxazole was reported to be 2.4 days. The photodegradation process was sped up by the presence of NO3 in aqueous solutions. As a result, humic acids appeared to function as light-activators for it. In the photodegradation of sulfonamides, the

intermediate organic compounds include sulfanilamides, sulfanilic acids, anilines, hydroquinones, quinines, carboxylic acids, and dicarboxylic acids. Sulfonamidephotolysiscleavage sites and photodegradate structures are shown in Fig. 2.

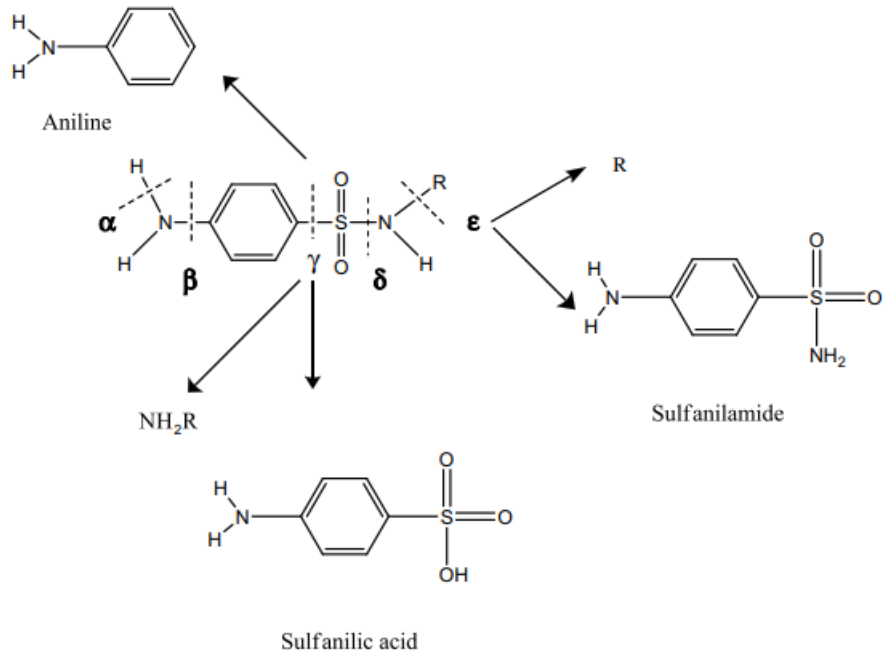

Figure 2. Potential photolysis-cleavage sites and derived products for sulfonamides

Sulfadiazine's photodegradation products only showed inhibitory effects, while sulfacetamide, sulfathiazole, and sulfamethoxazolephotodegradation products showed both inhibitory and excitatory effects. Growth inhibition was less severe under UV irradiation, indicating that the intermediates were less hazardous than the parent chemicals. Intermediate products were also biodegradable, which provides a huge advantage over using photocatalytic processes for the mineralization of the intermediate products, which are substantially more expensive.

It was also shown that all sulfonamides were photodegradable under UV light when TiO2 was included in aqueous solution. Due to the high cost of this method, it should only be used to degrade compounds that are inherently resistant to biodegradation.

4. Analytical aspects

Many sulfonamides, it has been noted, go through a variety of transformations. Multi-residue approaches are consequently necessary for their examination since not only the parent compounds but also their TPs are of importance and relevance to the study. It might be difficult to identify and

quantify metabolites and other TPs due to their structural diversity and low quantities. The extraction and purification methods are not mentioned in this evaluation, which focuses on instruments. The relevant literature has in-depth explanations of each of these points.

Organic molecules in environmental matrices may be detected using MS, one of the most powerful methods. MS is often used in conjunction with liquid chromatography or gas chromatography in analytical procedures since multi-residue analysis necessitates the use of separation techniques first. Nonetheless, LC-MS has become the method of choice for the identification of pharmacological residues, particularly their metabolites or breakdown products, which are highly polar and water-soluble. In the field of metabolite identification and structural characterisation, LC-MS is frequently used because of its great sensitivity, selectivity and efficiency.

Single-quadrupole LC-MS is the traditional method of analysis. For example, Dodd et al. [57] found two primary chlorinated by-products of sulfamethoxazole, both having a m/z of 288, using LC-MS to obtain fragment spectra. As seen in Figure 3, their mass spectra are shown together with the corresponding structures. Co-fragmentation of matrix components other than those targeted can lead to inaccurate analysis when using this approach, albeit this is rare. tandem MS (MS/MS) approaches based on the fragmentation of the ionisation source's precursor ions are now chosen to overcome this limitation.

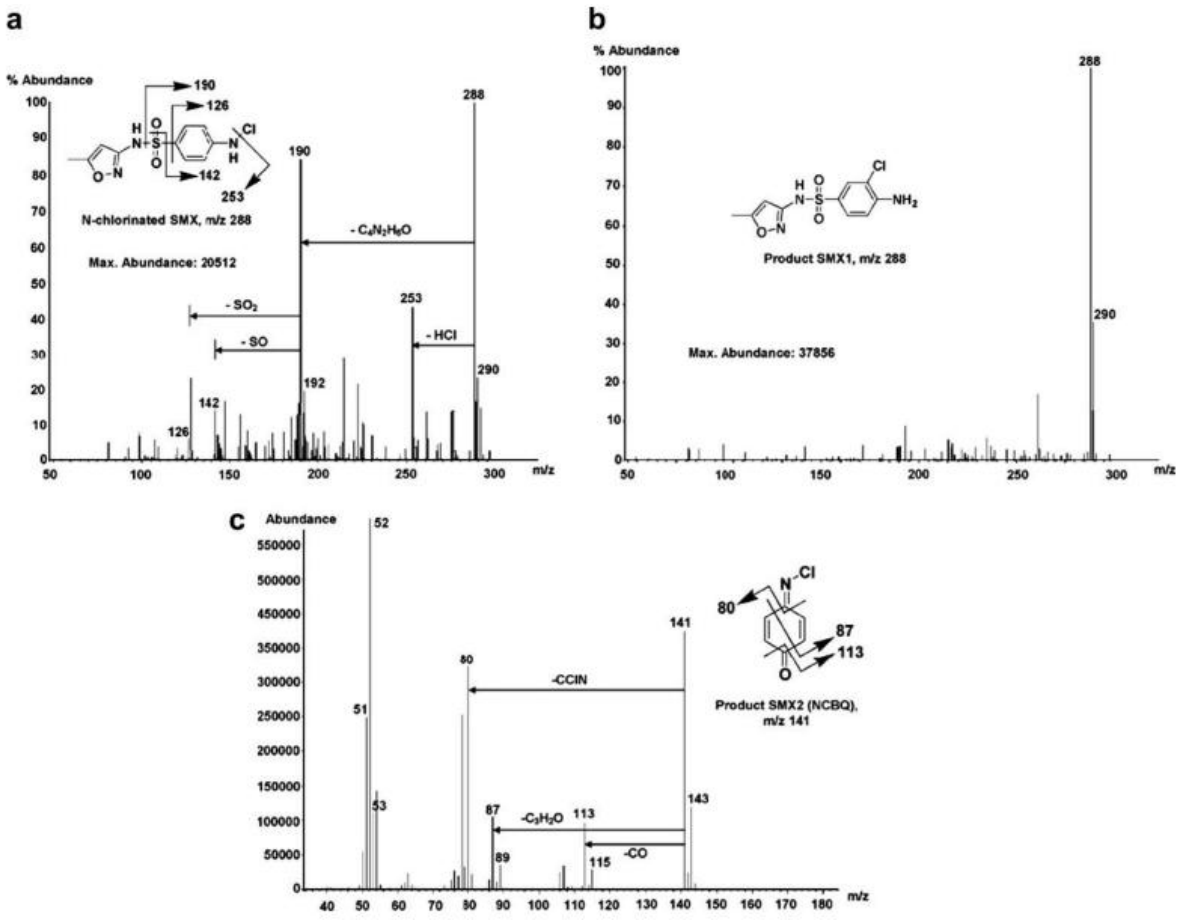

Figure 3. Mass spectra of the degradation products of sulfamethoxazole after chlorination with free available chlorine (FAC): a) N-chlorinated sulfamethoxazole; b) sulfamethoxazole-1; and, c) N-chloro-p-benzoquinoneimine (NCBQ). Spectra a) and b) were obtained by LC-(ESI+)-MS and spectrum c) was obtained by GC-MS.

The identification and quantification of metabolites and TPs are particularly well-suited to the capabilities of MS/MS. Sulfonamides and its TPs are typically detected using triple-quadrupole, ion traps (ITs), and quadrupole ITs. You don't need prior information of metabolite molecular weight to do precursor-ion and continuous neutral-loss scans, respectively. Precursor-ion scan can be used to find metabolites that are structurally linked to the parent substance since these molecules generally have a similar structural feature. The mass spectrometer may be programmed to look for these metabolites using a continuous neutral-loss scan if the drug and metabolites have one or more similar core structures.

It's also a good idea to use time-of-flight (TOF) equipment for structural elucidation of metabolic products and degradation products. Detection and identification of previously undiscovered compounds are made possible by this method. For example, Grant et al. [63] used a MALDI-TOF-MS apparatus to identify N4 -acetylsulfamethazine in ambient samples. The quadrupole time-of-

flight instrument (QqTOF), which has already been used to identify and quantify pesticides and their metabolites in food, may combine accurate mass measurement with very sensitive MS.

Higher sensitivity than triple-quadrupole instruments has led to a rise in the usage of ITs in recent years. Metabolites' structural investigation is made easier with the MSn -scan function (provide better sensitivity and allowing clarification of the fragmentation process, thereby significantly facilitating interpretation of spectra). It is possible to acquire the most structural information with the least number of analytical runs using built-in information-dependent acquisition (IDA) experiments [67]. Unknown chemicals can be identified using a QqTOF/QqIT equipment with MS3 capabilities, which is a potent combo.

5. CONCLUSIONS

The presence of sulfonamide metabolites, often at higher quantities than the parent medications, has been found almost everywhere sulfonamides have been found, despite the fact that very few research have been published to date on these metabolites and breakdown products. As parent products are still present but have been altered, excluding metabolites and degradation products from studies may lead to inaccurate assessments of the elimination rates. In addition, the products' toxicity and the possibility of retransformation back into the parent medication must be considered. Water treatment techniques and even medium with significant microbial activity cannot degrade sulfonamides (e.g., activated sludge). Sulfonamides' environmental destiny will be better understood if the patterns of concentration of parent chemicals, metabolites, and degradation products can be mapped out. Analytical approaches that can simultaneously identify parent substances, their metabolites, and their degradation products are desperately needed in this circumstance.

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