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# Sulfacetamide: An ophthalmic Anti-infective Agent

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**ABSTRACT**

**Sulfacetamide is an anti-infective and bacteriostatic agent that belongs to the class of sulfonamides. It is extensively used as an anti-infective agent for ophthalmic disorders in a concentration of 5–30%. It inhibits the bacterial enzyme dihydropteroate synthase. It is active against susceptible strains of the eye pathogens such as** *Escherichia coli* **and** *Staphylococcus aureus***. Major therapeutic indications include acute conjunctivitis, minute abrasions of cornea and conjunctiva, and prophylaxis of ocular infections after injuries or burns. Side effects of sulfacetamide drops are edema of the eyelid, tearing, stinging, burning, local irritation, reactive hyperemia, blurred vision, and brow ache. Sulfacetamide interacts with porfimer and increases photosensitivity reactions leading to severe tissue damage. Sulfacetamide alone or in combination are available in various compositions.**

**Keywords:** Sulfacetamide, Anti-infective Agent, Ophthalmic Preparations, Bacteriostatic.

## INTRODUCTION

Sulfacetamide is chemically N-[(4-aminophenyl) sulfonyl] acetamide and is also known as Acetosulfamine, N-Acetylsulfanilamide, Sulfanilacetamide, N-Sulfanilylacetamide and N-Sulfanilylacetamide. It belongs to the family of sulfonamides and is used mainly as an anti-infective and bacteriostatic agent [1–3]. It appears as a white or yellowish-white, crystalline powder freely soluble in water but slightly soluble in anhydrous ethanol. It is commonly used in its salt form by the name of sulfacetamide sodium in order to achieve better solubility and hence stability in pharmaceutical dosage forms. It is considered as the most popular and potential drug for delivery in ophthalmology and is one of the widely prescribed sulfonamide in the form of eye-drops and ointments for treating ophthalmic infections. Its use has been associated with a variety of therapeutic indications such as urinary tract infections [4], acute conjunctivitis, minute abrasions of cornea and conjunctiva, in the prophylaxis of ocular infections after injuries or burns, treatment of acne and seborrhetic dermatitis [5], endogenous endophthalmitis [6], curvularia keratomycosis [7], nocardia keratitis [8], chronic blepharitis [9], pityriasis versicolor [10], etc. Sometimes, a burning or itching effect may be encountered in the case of local application to the

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eyes but it is rarely severe enough to cause discontinuation of the treatment.

With the rapid development of widespread resistance against sulfonamides, soon after their introduction, and the increase in use of other broader-spectrum antimicrobials such as penicillins, cephalosporins, etc. for the treatment of infectious diseases, the usefulness of sulfonamides was greatly diminished. However, in the mid-1970s, the development of a combination of trimethoprim and sulfamethoxazole demonstrated its usefulness in the treatment and prophylaxis of certain opportunistic microbial infections that lead to resurgence in the use of some sulfonamides [11,12].

## PHYSICOCHEMICAL PROPERTIES OF SULFACETAMIDE SODIUM

Some of the basic physicochemical properties of sulfacetamide sodium [1,2,13,14] are as follows:
**Chemical name:** N-[(4-aminophenyl) sulfonyl] acetamide.

*Molecular formula:* C8H9N2NaO3S.H2O.
Percent composition: C 40.68%, H 3.84%, N 11.86%, Na 9.73%, O 20.32%, S 13.57%.

*Molecular mass:* 254.2.

*Chemical structure:*

**State / form:** White or yellowish-white, crystalline powder.

*Description:* Odorless powder with bitter taste.
**Solubility:** It is freely soluble in water (1.5 g/ml), sparingly soluble in (96%) ethanol, while practically insoluble in benzene, chloroform and in ether.
**Melting point:** 181–185 °C.

**pKa:** 1.8 (–NH2) and 5.4 (–SO2NH2).
**pH:** 8.0–9.5 (5% aqueous solution).
**UV maxima:** 230–350 nm (pH 7.0).
255 nm (A1%, 1 cm = 660–720) (Aqueous).
271 nm (A1%, 1 cm = 260) (Aqueous acid).
256 nm (A1%, 1 cm = 750) (Aqueous alkali).

**IR spectrum:** 1145, 1264, 1552, 1090, 825, 1600 $cm^{-1}$ (principal peaks).

*Partition coefficient:* Log P (octanol/H2O) –1.0.

## MECHANISM OF ACTION

Sulfacetamide is a bacteriostatic agent and its spectrum of activity is almost similar to that of the other sulfonamides. They competitively inhibit dihydropteroate synthase, the bacterial enzyme responsible for the incorporation of para-aminobenzoic acid (PABA) into dihydropteroic acid, the immediate precursor of folic acid (Fig. 1). The sulfonamide sensitive microorganisms must synthesize their own folic acid, while bacteria that can use preformed folate are not affected. Mammalian cells require preformed folic acid and, therefore, are not usually affected adversely by sulfonamides [12]. The bacterial resistance against sulfonamides may originate by random mutation and selection or by plasmid transfer of resistance which usually does not confer cross-resistance to other classes of

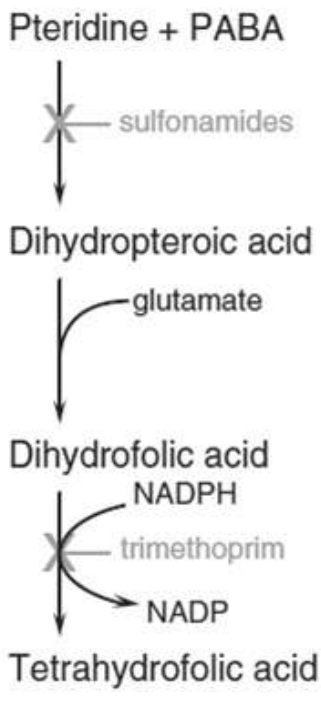


**Figure1.** Steps of folate metabolism blocked by sulfonamide and trimethoprim.

antibiotics. Resistance to sulfonamides results from altered constitution of the bacterial cell that may cause a lower affinity for sulfonamides by dihydropteroate synthase, decreased bacterial permeability or active efflux of the drug, an alternative metabolic pathway for synthesis of an essential metabolite, or an increased production of an essential metabolite or drug antagonist. Plasmid mediated resistance is due to plasmid-encoded, drug-resistant dihydropteroate synthetase [11,12].

*PHARMACOKINETICS*

The systemic absorption of sulfacetamide in the GI tract may occur rapidly after its application and reaches to the peak plasma level in 2–6 hours depending upon the drug [12]. Sulfacetamide sodium in the form of solution and ointment can easily pass through the lacrimal drainage system into the nose and throat when placed into the eyes. However, the contact time of ointment is much higher but the absorption is quiet slow as compared to the solution and suspension forms [1,15]. In the presence of conjunctival inflammation and acute bacterial conjunctivitis, sulfacetamide sodium is absorbed into the blood by the penetration into the ocular tissues and fluids but it is usually preferred to be used topically in the treatment of eye infections [1]. It is also absorbed after intravaginal or oral administration and is rapidly excreted in the urine, as unchanged form, after absorption [3,16–19]. The plasma half-life of sulfacetamide sodium is 7–14 hours with the protein binding of 15–18% [1,3]. In an attempt to study the time and concentration of the drug after topical application in the form of drops and ointment to the conjunctiva of the eye, the concentration of sulfacetamide sodium in tears has decreased to a value of 50 µg/mL in 30 min, 2 hours, and 5 and a half hours after the single application of 10 µL of 15% and 30% drops and 25 µL of the three ointments, respectively. Since the composition of the three ointments differed greatly, yet the ocular contact time has been found similar as it has been reported to increase by increasing the concentration of the drug [20].

*THERAPEUTIC USES*

Sulfonamides inhibit a variety of Gram-positive and Gram-negative bacteria, Nocardia, Chlamydia trachomatis, and some protozoa [11]. Sulfacetamide, particularly when applied in the form of drops and ointment to the conjunctiva of the eye, has been found active against susceptible strains of the eye pathogens such as *Escherichia coli* and *Staphylococcus aureus* with the minimal inhibitory concentrations (MICs) of 20 and 50 µg/mL, respectively [20]. Other susceptible strains include *Streptococcus pneumonia, Streptococcus viridians group, Haemophilus influenza, Klebsiella* and *Enterobacter species*. However, it does not provide adequate coverage against various *Neisseria species*, *Serratia marcescens* and *Pseudomonas aeruginosa* and a significant percentage of staphylococcal isolates are also completely resistant to sulfa drugs [11,20]. Topical betamethasone-sulfacetamide sodium therapy in patients with meibomian gland dysfunction (MGD) appears as the most effective one among the others [21]. Trimethoprim selectively inhibits microbial dihydrofolate reductase, the enzyme that reduces dihydrofolate to tetrahydrofolate which is the form required for one-carbon transfer reactions. The co-administration of a sulfonamide and trimethoprim thus introduces sequential blocks in the biosynthetic pathway for tetrahydrofolate (Fig. 1) [11,12]. The other therapeutic indications include urinary tract infections [4], acute conjunctivitis, minute abrasions of cornea and conjunctiva, in the prophylaxis of ocular infections after injuries or burns, treatment of acne vulgaris, seborrhetic dermatitis, secondary bacterial skin infection [3,5,16–19] endogenous endophthalmitis [6], curvularia keratomycosis [7], nocardia keratitis [8] chronic blepharitis [9,18] and pityriasis versicolor, etc. [10].

*ADVERSE EFFECTS*

A number of serious toxicities have been reported with the use of sulfonamides. Crystalluria may occur especially when the patient does not maintain normal fluid intake such as in case of acquired immune deficiency syndrome (AIDS) [11,12]. The sodium sulfacetamide products are meant to be applied for

skin and mucous membrane are known to be absorbed rapidly but some serious adverse effects may be expected such as mild peeling of the top layer of skin, rashes, irritation, redness, local swelling, pruritus, headache and scaling [11,12]. Some other side effects associated with the hypersensitivity of the sulfonamides like toxic epidermal necrolysis [22], erythema nodosum, erythema multiforme, Behçet's syndrome, Stevens-Johnson syndrome [23], exfoliative dermatitis, and photosensitivity [24] have also been reported. The administration of sulfonamides to newborn infants, especially if premature, may lead to the displacement of bilirubin from albumin, potentially causing kernicterus [11,12]. Some major side effects of sulfacetamide sodium may be encountered when used in ophthalmic drops and ointments, vaginal creams and topical preparations. Especially the ophthalmic preparations of sulfacetamide sodium may cause edema of the eyelid, tearing, stinging, burning, local irritation, reactive hyperemia, blurred vision, and brow ache [3,17]. Light and electron microscopic examination and X-ray energy dispersive analysis revealed a possible mechanism for the pathogenesis of a condition such as sulfur keratopathy with the use of topical sulfacetamide due to sulfur deposition in the cornea after retinal detachment surgery i.e. vitrectomy. No signs of anterior segment ischemia have been noted [25].

## INTERACTIONS

The interaction of drugs depends upon their chemical structure, amount and strength to be used [26]. Important drug interactions of the sulfonamides have been demonstrated with the oral anticoagulants, sulfonylureas (hypoglycemic agents) and phenytoin (hydantoin). In each case, sulfonamides can potentiate the effects of the other drug, either by inhibiting its metabolism or by displacing it from the albumin which may be controlled by the adjustment of the dosage [12]. Sodium sulfacetamide ophthalmic solutions (pH 8–9.5), transiently raise conjunctival fluid to greater than pH 7.4, and may cause precipitation of the pilocarpine while the administration of sulfacetamide as photosensitizing agent with porfimer increases photosensitivity reactions leading to severe tissue damage [16–19]. Silver preparations such as silver sulfadiazine, a skin product interact with sulfacetamide and also cause precipitation [11]. The risk of bone marrow suppression may also be increased when a sulfonamide is administered with methotrexate [27].

## CONTRAINDICATIONS

The sulfonamides are contraindicated in patients who respond to develop hypersensitivity to the drug. Sulfonamides should not be given to pregnant women near term because these drugs may cross the placenta and are secreted in milk [12]. If they are given near the end of pregnancy, significant blood levels of the drug may occur, causing jaundice or hemolytic anemia in the neonate. Additionally, the sulfonamides are not used for infections caused by group A beta-hemolytic streptococci because they have not shown to be effective in preventing the complications of rheumatic fever or renal disease such as glomerulonephritis [12,16–19].

## DOSAGE FORMS

Several dosage forms of sulfacetamide alone or in combination are available in various compositions for the treatment of different disease conditions such as:

- Eye drops (solution and suspension) 5, 10, 15, 20, 30%.
- Ointments 5, 10, 15%.
- Topical lotions 10%.

Different preparations containing 5–30% of sulfacetamide sodium are available under the proprietary names of Acetopt, Ak-Sulf, Albucid, Antebor, Beocid Puroptal, Bleph-10, Cetamide, Cetazin, Diosulf, Ocu-sul, Optamide, Optisol, Optosulfex, Prontamid, Sebizon, Sodium Sulamyd, Sulf-10, Sulfac, Sulfex Ultra, Vanocin, etc. [3].

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