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THE TRIMETHOPRIM STUDY: MECHANISM, PHARMACOLOGY, TOLERANCE AND DETERMINATION USING SPECIFIC SPECTROSCOPIC STRATEGIES

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ABSTRACT
Trimethoprim is an aminopyrimidine antibiotic whose structure consists of pyrimidine 2,4-diamine and 1,2,3-trimethoxybenzene moieties linked by a methylene bridge. Primarily it is used to treat urinary tract infection. Trimethoprim found with a combination of sulfamethoxazole has a synergistic effect due to the inhibitor effect during the mandatory sequence of enzymatic reactions in the bacteria occurring in more than one step. It is used individually in the treatment of respiratory tract infections, urinary tract infections, intestinal infections, and other diseases. In this review article, the mechanism, pharmacology, detection methods, of Trimethoprim in both pure and bulk dosage form has been discussed. Moreover, the marketed preparations and patents on trimethoprim are listed and some of the micro and nanoparticles of trimethoprim is mentioned in this review article.

KEYWORDS: Trimethoprim, Urinary tract infection, Patent, Nanoparticles, Pharmacology.

INTRODUCTION
Trimethoprim [2, 4-diamino-5-(3', 4', 5'-trimethoxybenzyl) pyrimidine] is a synthetic chemotherapeutic compound. It is a 2,4-diaminopyrimidine and inhibits the enzyme dihydrofolate reductase, resulting in interference in folic acid and subsequent pyrimidine synthesis in the bacterial cell.[1-3] Trimethoprim was first used in the year 1962.[4] According to World Health Organization, it is one of the recommended medicines, which is effective and safe medicine for use in healthcare system. Trimethoprim (TMP) is generic term which is available with the brand name as Proloprim, Monotrim, Triprim. Trimethoprim should not be use if patient is suffered from Anaemia caused by folate (Folic acid) deficiency.[5-6] Trimethoprim is combined with Sulfamethoxazole (SMX) to overcome a variety of bacterial infections. This combination contains 1:5 ratio of Trimethoprim and Sulfamethoxazole. It is used for infections of urinary tract methicillin resistant Staphylococcus aureus (MRSA) skin infections, diarrhoea of passengers, infections of the respiratory tract. It can be given orally, as a tablet or suspension or through intravenous route. TMP/SMX was first sold in the year 1974.[7-9] Another formula incorporates isoniazid, pyridoxine, sulfamethoxazole and trimethoprim. It is primarily used for the prevention of tuberculosis, toxoplasmosis, pneumonia, malaria and isosporiasis.[10-11] The chemical structure of trimethoprim is shown in figure 1.

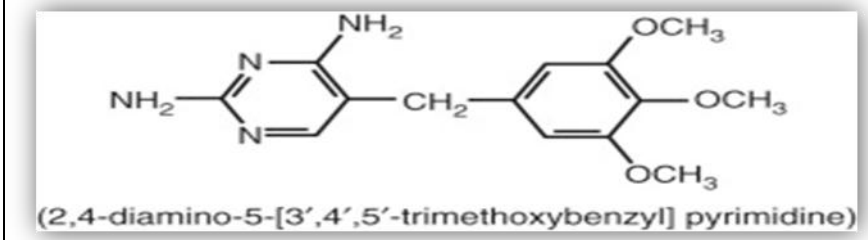

Figure 1: Structure of Trimethoprim.

Mechanism of action -Trimethoprim attaches to dihydrofolate reductase and reduxctase and interrupts the transformation of dihydrofolic acid (DHF) to tetrahydrofolicacid (THF). Tetrahydrofolate is an

important primer in the synthesis pathway and interfering with this pathway inhibits the synthesis of bacterial DNA. The affinity of Trimethoprim for reductase of bacterial dihydrofolate is several thousand times greater than its affinity for reductase of human dihydrofolate. Sulfamethoxazole inhibits the synthase of dihydropteroate, an enzyme that starts on the same pathway upstream. Due to possible synergistic effects and reduced resistance development, trimethoprim and sulfamethoxazole are commonly used in combination.[12-14] Figure 2 represent the flow diagram explaining the mechanistic role of trimethoprim.

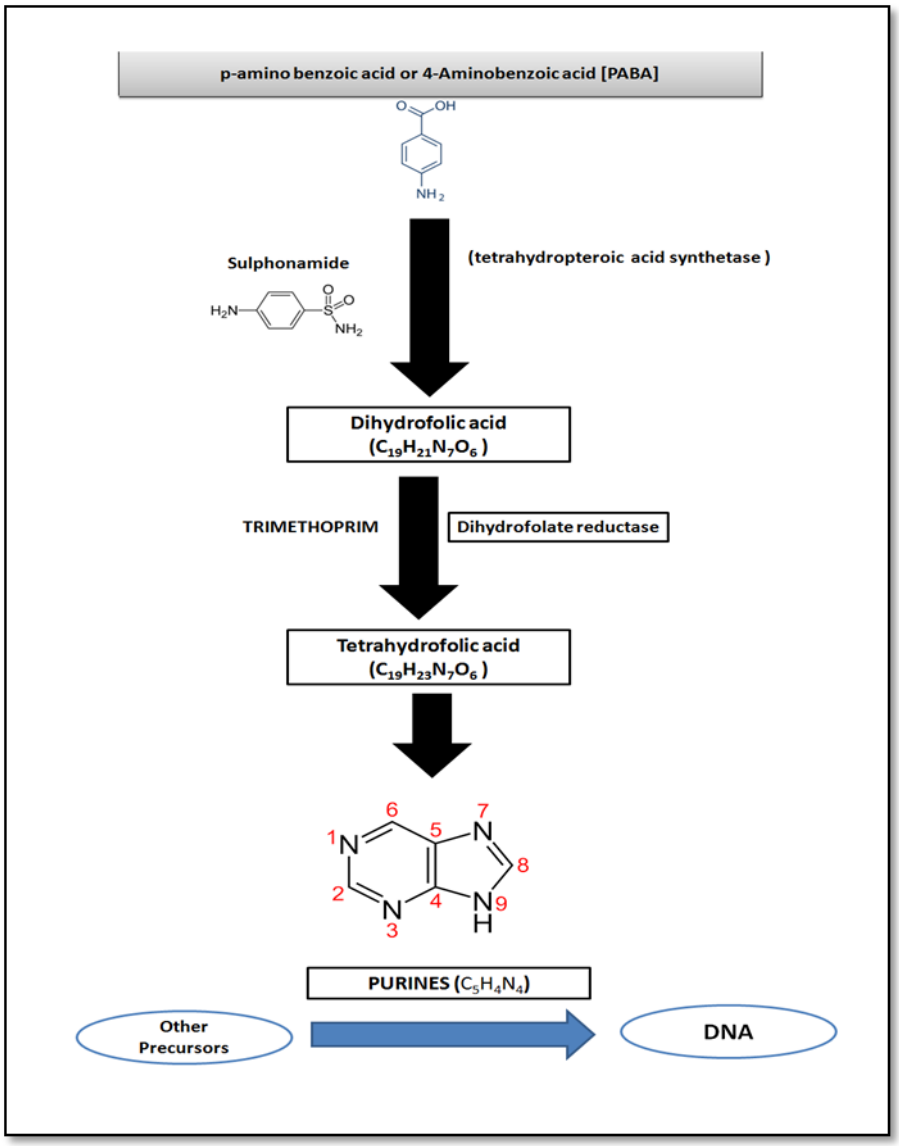

Figure 2 - Mechanism of action of trimethoprim.

Pharmacokinetics - This drug is structurally similar to folic acid. It is a weak base and is trapped in acidic environments, reaching high concentrations in prostatic and vaginal fluids. A large percentage of trimethoprim is excreted unchanged in the urine. The half-life of this drug is similar to that of sulfamethoxazole (10–12 hrs). From the studies the following data has been reported listed in table 1.

Table no. 1 Pharmacokinetic parameter.

Sr. No	Parameters	Data	Reference
1.	Bioavailability	90–100%	[15]
2.	Protein binding	44%	[15]
3.	Metabolism	hepatic	[16]
4.	Elimination half-life	8-12 hours	[15]
5.	Excretion	Urine (50–60%), faeces (4%)	[16]

Pharmacology

1. **Routes of administration**

Trimethoprim is available for oral use as a 100mg tablet. Trimethoprim is absorbed from the intestinal tract quickly and almost completely. After 100 mg intake, peak levels appear 1 to 4 hours and reach 1 µg / mL.[16]

2. **Distribution** - Trimethoprim is distributed widely in tissues and may appear in kidney, lung, and sputum in higher concentrations than in plasma and in bile, saliva, human breast milk, and seminal fluid. Trimethoprim is usually present two to three times the serum concentration in prostatic fluid, although lower levels can occur in patients with chronic prostatitis. Concentrations of cerebrospinal fluid are about 40% of the serum levels.[17,18,19]

3. **Metabolism and excretion** - Trimethoprim excretion is mainly by glomerular filtration and tubular secretion by the kidneys. Trimethoprim urine concentrations are significantly higher than those in the blood. After a single oral dose of 100 mg, the urine concentrations of Trimethoprim ranged from 30 to 160 mcg / mL during the period of 0 to 4 hours and declined to around 18 to 91 mcg / mL during the period of 8 to 24 hour period. A single oral dose of 200 mg would result in urine levels of Trimethoprim being approximately twice as high. After oral administration, 50% to 60% Trimethoprim is excreted in the urine within 24 hours, of which about 80% Trimethoprim is not metabolized.[20-21]

Resistance- Bacteria may become resistant to trimethoprim by the following:[22]

1. Reduced bacterial uptake.
2. Alterations or mutations in dihydrofolate reductase.
3. Overproduction of dihydrofolate reductase.

Marketed preparations of trimethoprim

Table no. 2: Marketed preparation of Trimethoprim.[23]

Sr. No	Name of drug	Dosage form	Dose(mg)	Brand name
1.	Trimethoprim	Tablet	70	Trimethoprim I.P
2.	Trimethoprim	Tablet	200	Trimethoprim I.P

Table no. 3: Marketed preparations of trimethoprim in combination form.[24,25]

Sr. No	Name of drug	Dosage form	Dose(mg)	Brand name
1	Trimethoprim – sulphamethoxazole	Oral suspension	Trimethoprim(40mg) sulphamethoxazole(200mg)	Antrima
2	Sulphadiazine + trimethoprim	Tablet	410 + 90	Aubril
3	Sulphamethoxazole + trimethoprim	Tablet	100 + 20	Bactrim
4	Sulphamethoxazole + Trimethoprim	Film coated tablet	800 +160	Supristol-DS
5	Sulphamethoxazole + Trimethoprim	Film coated tablet	800 +160	Bactrim -DS

Spectroscopic method for determination of Trimethoprim

Extensive literature report the estimation of Trimethoprim through spectroscopic and chromatographic techniques. Some of them are listed in table No. 4

Table no. 4: Spectroscopic methods for determination of Trimethoprim.

S. No	Name of the method	Outcome	References
1	Extractive spectrophotometric	Sample : trimethoprim λ max = 422,418 nm Concentration Range= 4.0-24 and 5.0-25, µg/ml R2=0.9969,0.9973 %Re=99.95,99.93 Slope=0.000391,0.000572 %RSD=1.600,0.8593	[23]
2	UV-VIS Spectrophotometric-Colorimetric	Sample : trimethoprim Concentration Range= 1–35,20–90µg/ml r2= 0.9976, 0.9981 LOD= 2.72 4.90 µg/ml %Average recovery= 99.07±1.46, 99.86±2.35	[24]
3	Derivative Spectrophotometry	Sample : trimethoprim–sulphamethoxazole λ max =257.8,251.5 nm R=0.9992,0.9995	[25]

		Concentration Range=2.00 to 25.00 mg/ml LOD=0.36,0.382 mg/ml %Re= 97.23, 102.13	
4	First-order derivative spectrophotometric	Sample : trimethoprim–sulphamethoxazole λ max = 247.8, 257.9 nm %RSD= 2.08,1.79 R=0.998	[26]
5	Spectrofluorometry	Sample : trimethoprim–sulphamethoxazole λ max =295, 330 nm Concentration Range= 0.5 to 40,1 -400 µg/ml R=>0.99	[27]

HPLC for determination of Trimethoprim-

Table no. 5 HPLC for determination of Trimethoprim.

Method	Column	Mobile Phase	Elution	Flow Rate	Results	Retention time	λ(nm)	Reference
Simultaneous HPLC	C18 column (5m, 150, 4.6 mm)	acetonitrile,0.5% triethylamine in 1% acetic acid, pH 3	(18:82, v/v)	1.5 ml/min	Conc. Range=35-101, 102-306 µg/ml, R= 0.9980, 0.9998 %Re= 99.7±0.92 %RSD=0.05-8.94	3.2,16 min	271	[28]
RP-LC	C18 (150 x 4.6 mm, 5 mm).	water, pH 3.5, and methanol	(60:40, v/v)	1.0 ml/ min	Conc. Range= 5 – 70, 1 -30 mg mL-1 µg/ml, R=≥ 0.99	-	213 and 230	[29]
RP-HPLC	C18 (250mm x 4.6 mm, 5 µm).	Triethylamine: Acetonitrile	(30:70)	1.0 ml/ min	Re=100.23,99.30 %RSD=0.6,0.4	2.688,4.388	260	[30]
High Performance Liquid Chromatography	C18 analytical column (stainless steel, 25 cm, 4.6 mm)	0.025 M sodium phosphate as aqueous phase, acetonitrile, 0.4% triethylamine as organic phase	(80/20)	1.2 ml/ min00	R= 0.986,0.949	-	260	[31]

Table 6: Patents available on Trimethoprim.

S.no.	Publication number	Priority date	Publication date	Assignee	Title	Reference
1	US2909522A	21-021957	20/10/1959	Burroughs welcome co	Trialkoxybenzylpyrimidines and method	[32]
2	US3985876A	05/01/1973	12/10/1976	Burroughs welcome co	Cgemotherapeutics solutions containing a sulphur and a salt of 2,4-diamino-5-benzylpyrimidine	[33]
3	US34198429A	25/06/1976	15/04/1980	Hoechst Aktiengesellschaft	Esters of 5-methyl-10,11-dihydroprostaglandin-A-1	[34]
4	US4645662A	26/7/1984	24/02/1987	Lion Corporation	Oral composition	[35]
5	US4935225A	11/09/1987	19/06/1990	Curtis John P	Appetite suppressant dentifrice	[36]

Table 7: Non - Patent citations on Trimethoprim.

S.no	Author	Title	Year & page no.	Reference
1.	Rajkumar et al.	Trimethoprim in Paediatric urinary tract infection child Nephrol	1988-1989, 77-81	[37]
2	Flory at el	Analytical Proficles of drug subsatnaces	1978, 445-475	[38]

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Nano or micro particles of Trimethoprim

Based on research, very rare information about micro and nano-sized particles of trimethoprim is available; some are discussed below -

1. The strong attachment of trimethoprim drug to bacterial enzyme Escherichia coli dihydrofolate reductase enables Trimethoprim-decorated iron oxide nanomaterials attach to bacterial enzyme Escherichia coli dihydrofolate reductase with a strong potential and specificity that enables the focal adhesion of the mammalian cells needed to adhere to the surface to be magnetically modulated. Besides being the primary indicator of selectively binding nanosubstances to bacterial enzyme Escherichia coli dihydrofolate reductase, the biocompatibility of the Trimethoprim-iron oxide nanoparticles conjugate offers an efficient and versatile medium for analyzing cellular responses to express, mechanical protein disturbance by magnetism.[39]
2. Nanoparticles (Z-Avg of 200-400nm) was prepared using polymer (D,L-Lactic -co-glycolic acid for instillative therapy to treat reoccurrence infection and increasing resistances of urinary tract infection.[40]

CONCLUSION

In the present article Trimethoprim drug was studied for its pharmacokinetics, pharmacodynamics, metabolism, excretion, resistance. Theoretical study of some analytical methods used for examination is also listed in this article. Marketed dosage form of trimethoprim is single form and in combination form is enlisted with their strength and brand name. From the study some nano and microparticles formulation of trimethoprim is mentioned which were design for treatment of urinary tract infection and patent citation with non-citation is also reported from the literature survey. Thus, more work on nano- sized particles could be done in future to explore its pharmacological activity for enhanced therapeutic effect.

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Conflict of interest

The work is original and is not published anywhere else. The authors report no conflict of interest.

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