A Review on Nanoparticles of Co-Trimoxazole

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Abstract

With the growth in antimicrobial resistance by infectious microbes poses a severe concern for human health worldwide. There is an exponential trend in the overall incidence of such antibiotic resistant bacteria were observed in the past several decades. Researchers were continuously taking efforts on developing approaches over employing the pursuit of an effective antimicrobial agents emphasising on molecules which could be approved clinically and can be applied for latter stages of development for treating against such antimicrobial resistant species. Cotrimoxazole is one such wonder drug which belongs to the category of broad spectrum antimicrobial. They are effective when administered in vitro against a wide array of microorganisms. Their application in medical field has roughly spanned over a decade now. Still there are numerous approaches that were developed for improving their effectiveness towards their antimicrobial activity. The hybridized NGs antimicrobial properties based on NG kind & microbial conditions. Hybrid nanogels has elevated the need of lowermost inhibition concentration (MIC). The therapeutic drug were inserted constitute DDS, cross-linked networks of amphiphilic polymers with composed NGs, as displayed unique properties are biodegradability and biocompatibility, as well as confer improved stability of drug and reduced drug-mediated cytotoxicity. However, maximum within 1 hour killing bacterial efficiency, if bacteria are exposed to hybridized NGs along with minor Ag NPs whereas agitating the medium. These outcomes recommend that NG properties along with antibacterial activity may be modified through changing content of lysozyme. In this review article, a detailed. In this review article, the Historical perspectives with regards to Co-trimaxazole, Their mechanism of action and resistance, spectrum of activity, and preeminent members of each class are discussed and most importantly on the preparation of nanogels for Co-trimaxazole.

Introduction

Multidrug-resistant anomaly is displaying an escalating tendency and represents key threat to the health care system (Levy and Marshall, 2004). The situation is particularly more drastic for "ESKAPE" pathogens containing Enterococcus spp., Klebsiella spp., Staphylococcus aureus, P. aeruginosa, A. baumanniiand Enterobacter spp. A few of these pathogens like A. baumannii, already become pan-resistant (Tacconelli et al., 2018). Accurate data on MDR prevalence is not available from many countries, particularly from Nano-antimicrobials: A Viable Approach to tackle for the developing countries. Nonetheless, few studies have reported more than 80% occurrence of ESBL positive E. coli (Nahid 2013; Shakya, 2017), whereas 32.5% occurrence of bla NDM-1 was observed in K. pneumoniae by Dadashi et al. (2017).

Experience in clinical with using Co-trimaxazole agent now spans a decade or more in several countries. Whether it is founded as the agent of first choice only in Pneumocystis carinii infections, it is essential in several infectious diseases (Goldberg and Bishari, 2012). Therefore it revealed to be effective in acute and persistent or recurrent UTI nose, throat, and ear infections, enteric fever and acute exacerbations of chronic bronchitis. Gonorrhoea, prophylaxis in neutropenic patients and in several other less well-known areas of possible usefulness (Sujatha&Nawani, 2014). With their parenteral preparation had greatly expanded potential clinical application of the drug (Wormser, et al., 1982). The major contribution for treating diseases is Co-trimoxazole and that continuous for more time is yet to come.

It was given for treatment, and the patient improved after treatment. For the treatment of numerous infections the newer antibiotics have swapped Sulfonamides, still great value and the agents choice in several infections. Sulphonamides are widespread antimicrobial activity in contradiction of both bacteria of Gram-positive & negative, then their effectiveness has weakened with the emergence of resistant strains (Rasi and Khatami, 2006).

From the historical perspective, before the advent of ART scale-up, cotrimoxazole prophylaxis lesser morbidity & mortality in pediatric & geriatric with HIV by avoiding bacterial infections, malaria, diarrhoea, and Pneumocystis in spite of high levels of microbial resistance (Walker et al ., 2010). Co-trimoxazole prophylaxis decreases initial mortality in adults by 58% begins ART. Co-trimoxazole delivers an ongoing protection against both non-malaria infections malaria afterwards the immune reconstitution by individuals of sub-Saharan Africa are ART-treated, heading to alteration in guidelines of WHO, which is recommend as long-term CTP in adults and children under the circumstances, wherein high prevalence of malaria severe bacterial infections (Maimberg et al., 2013). Prophylaxis of Co-trimoxazoleis suggested for HIV infants since age 4–6 weeks; therefore, the challenges of co-trimoxazole at the time of infancy are indistinct (Church et al., 2015). CTP reduces anaemia and increases children growth along with HIV, probably by decreasing inflammation, moreover direct immunomodulatory activity and over special effects on the microbiota foremost to reduced microbial translocation.

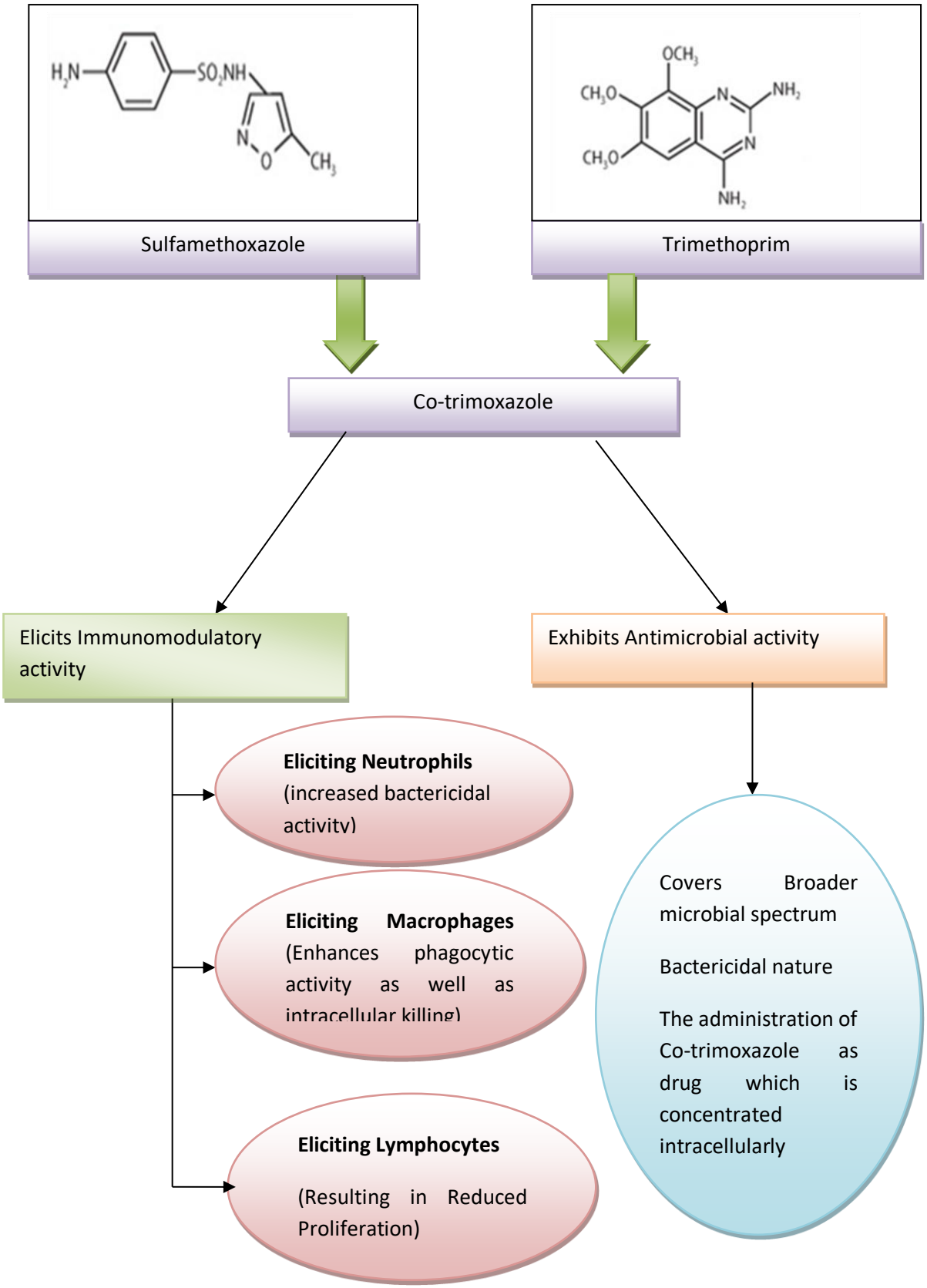

Figure 1: Functional attributes of Co-trimoxazole (Church et al., 2015)

The finest dosage regimen for cotrimoxazole in the life threatening infections treatment for susceptible organisms that encountered in seriously ill patients is unclear despite spans of usage of drug (Brown, 2014). For the explanation of therapeutic drug monitoring the suitable dosing for the effective infection annihilation is not extensively available. The clinician must use of published pharmacodynamics, pharmacokinetic and to regulate potential dosing regimens for the patients once treatment of particular pathogens. By using lesser amount of inhibitory concentrations that already identified to effectively block development for target pathogens, the pharmacokinetics of utilizing in combinations of sulfamethoxazole and trimethoprim in order to create empiric dosing regimens for patients in critical situations though considering organ of clearance impairment.

Nano-Antimicrobials: Next course of action against pathogenic microbes

For the Escalating resistance to mostly each and every class of antibiotics is decreasing the utilities of presently available antimicrobial drugs (Laxminarayan et al., 2013). A portion of this menace is recognized to poor pharmacokinetics and pharmacodynamics drug. Development in DD is likely maximum exciting task that come across by pharmaceutical industries, though nanotechnology that can take along a revolution in design and DD. Nano-antimicrobials, they have activity of individual intrinsic antimicrobial or augment complete efficiency of antibiotics enclosed, thus the contribution in mitigation or retrieving the resistance phenomenon (Jamil and Syed, 2017).

Individual intrinsic antimicrobial activity having by NP, that destroys the microbes by imitating killing course by phagocytic cells, by creating large quantity of reactive species of oxygen and reactive nitrogen species (Beyth et al., 2015). NPs are killing microbes by concurrently substitute on numerous vital life procedures or metabolic routes of microbes. That as various genetic mutations to improve resistance alongside them that look like to be impossible (Jamil et al., 2017). Nano-carriers increase the pharmacokinetics of drug are enclosed. Likewise, the key methods by which NAMs can overcome resistance is DD target to disease (Park, 2013). The following illustration detail about the method of action of NAMs is presented in context to multidrug-resistance phenomenon.

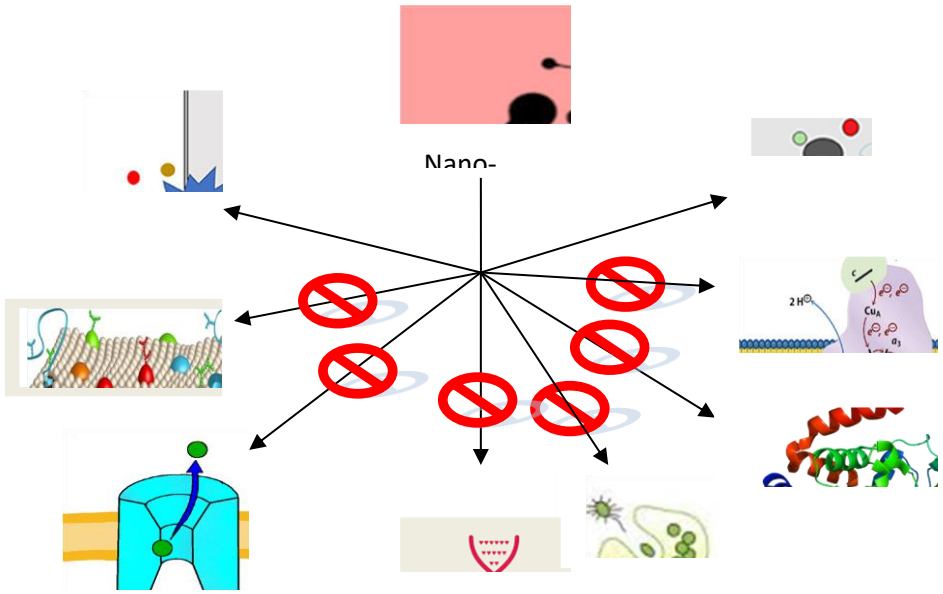

Figure 2: Nano microbials and their mode of action (1*- Generation of ROS; 2*- Disruption of microbial cell membrane; 3*- Damage/ disruption of proton pumps; 4*- DNA damage; 5*- Prevention of Biofilm formation; 6*- Protein damage; 7*- Disruption of electron transport chain; 8*- Attachment to 30s ribosomes subunits)Nanogels (NGs)

Hydrogels usually having the capability to swell in the water, retentive a major fraction of water in their structure deprived of dissolving (Ahmed, 2015). It has been studied for number of applications in various fields: pharmacy, medicine, controlled drug release and biotechnology. New technique of medicine regenerated, drug delivery and tissue engineering highlight the necessity for new biomaterials which are processable biodegradable and biocompatible (Boisseau, P., &Loubaton, 2011).

Thus, the growth of biomaterials using natural polymers is an important and promising channel of research. Chitosan is low cost and renewable material with more number of applications in biotechnology, pharmaceuticals, food science and cosmetics.

The Size of NG lies between 20-200 nm and they could effectively escape the renal clearance and expresses a extended serum half-life period as a result of their size (Li et al., 2015). They form a three dimensional hydrophilic networks which expresses the tendency for imbibing water/ physiological fluid in large amounts, without changing in the internal network structure (Peppas et al., 2000). The chemical modifications aids in incorporating plenty of ligands that can serve as targeted DD, stimulus reactive drug release/ preparation for composite materials (Emerich and Thanos, 2017). Nanogelsexhibit great qualities, thereby contributing to the drive towards their delivery system. These include stability in thermodynamic, capacity elevated over its solublilization, and expresses a relatively low viscosity, and their capability over undergoing vigorous sterilization techniques (Ryu et al., 2015).

Nanogels tend to entrap the drugs as well as biological molecules. Thus it is vastly employed for delivery of targeted protein and gene of interest (Kateb et al., 2011). Certain nanogels also possess, Nanogels provide new means for DD of drugs with poor solubility that doesn't improve the stability and but increases the opportunity of their cellular uptake than the free drug (Bhatia, 2016). As it reflects relatively high affinity over the aqueous solutions, with its outstanding stability, inertness of systemic circulation and internal fluids, and their appropriateness over incorporation of molecules for the bulk, are considered as essential and promising carriers in its delivery and cellular uptake of the underlying peptides, proteins, as well as other biological compounds of interest (Gu et al., 2013).

The structure of a hydrogel could be developed through introduction of physical/chemical crosslinks between the synthetic or using hydrophilic natural polymers (Gupta ., 2002). Such crosslinks poses to be crucial for the stability of hydrogel structure as it prevents from the dissolution of the polymer chains when introduced in aqueous environment. In case of chemical crosslinks developed via forming a covalent bonds that leads to insoluble polymeric network (Qiu et al., 2001).

By applying emulsion/ precipitation polymerisation facilitates in obtaining nanogels, rather than microgels as they are more likely to be developed while chemical crosslinking. In case of noting physical interaction in the form of weak Van der Waals forces, hydrogen bonding, electrostatic interaction etc., that interacts between the polymeric chains could aid in development of a stable form of hydrogel (Hamidi et al., 2008).

Physical self-assembly aided for controlled development or formation of the nano-aggregates in function of polymeric concentration or through environmental factors specifically temperature and pH. In order to develop an appropriate selection as well as designing of Nano carriers remain crucial for accomplishing preferred pharmacological impacts. Based on the cross-linking type, polymer used for formulation and the responsive behaviour of external stimuli were represented in the following figure.

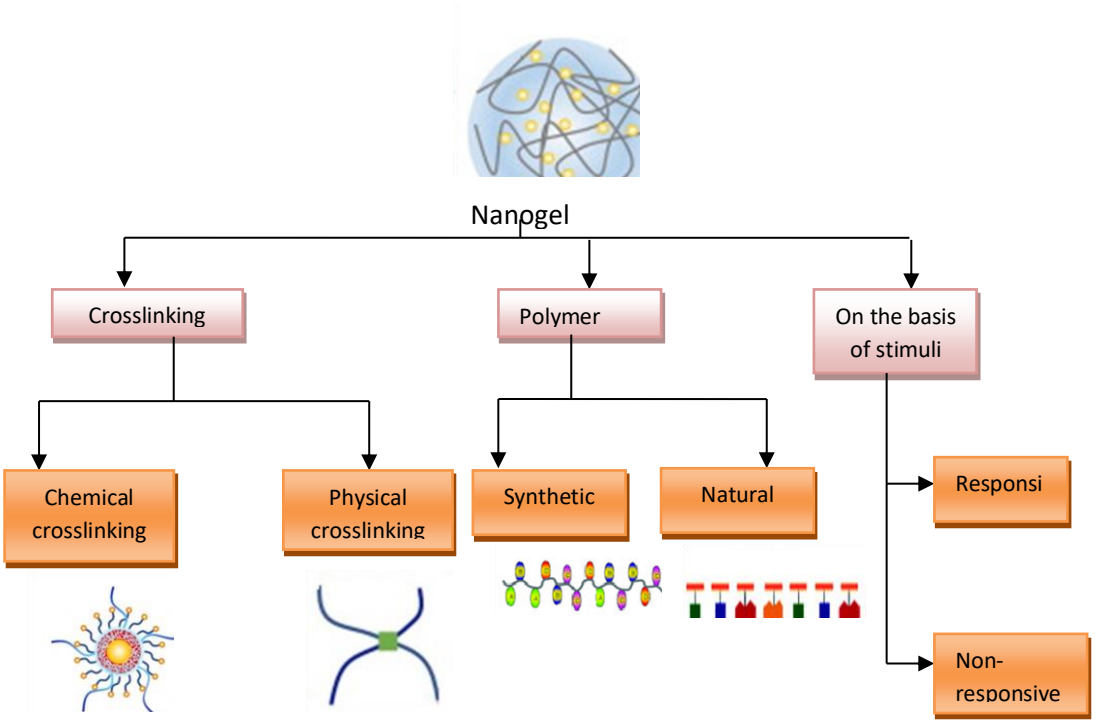

Figure 3: Nanogels classfification (Setia and Ahuja, 2018)

One alternative approach involves utilizing swollen hydrophilic polymer gels that are of nanoscale in size that are synthesized under the absence of drug and is further loaded with a drug, thereby resulting the collapsing of gel and finally the nanoparticles are formed. In actuality the mechanism involved in the drug loading usually achieved via self-assembly mechanisms that involves with a noncovalent interactions between polymer matrix with that of drugs through various physical cross-links (Jeong et al., 2006).

Also the molecules of drug could be put out of action with polymer gels through forming CCB with drug moiety to that of polymer matrix. The mechanism involved with using dispersed hydrogels appears quite simple and are relatively exhibit higher drug loading capacity and provide a stronger advantage under regulatory prospective since polymer gels being synthesised and evaluated under the absence of the drug (Kashyap et al., 2005). The following Table represents polymers that are used in NGs for DD.

Table 1: Polymers used in Nanogels for drug delivery (Source: Setia and Ahuja, 2018)

Polymer	**Application**
Lecithin	Liquid crystalline nanogels
Polyglycerol and PolyN- isopropylacrylamide	Semiinterpenetrating polymer network nanogels
Polyglycerol and Nisopropylacrylamide	Thermosensitivenanogel
PEGylated Poly ethyleneimine (PEG-gPEI)	Chemical crosslinking
Poly(ethylene glycol) modified hyaluronic acid (PEG-HA)	Ph-responsive nanogels
Polypropylene glycol	Temperature responsive nanogels
Poly-(N-vinyl Caprolactum)	Thermoresponsivenanogels
Polyglycerol (PG) and poly(glycidyl methyl ether-co-ethyl glycidyl ether) (p(GME-coEGE))	Thermoresponsive Nanogels (TNGS)

Poly-N-isopropylacrylamide dendritic polyglycero	Semiinterpenetrating polymer network nanogels
Poly(N-tertbutylacrylamide) (PNtBAm) grafted on methylcellulose (MC)	Self-assembled nanogels
Polyvinyl alcohol	pH-degradable nanogels
Dendritic polyglycerol cross-linked with various Polymers like— Poly(Nisopropylacrylamide) (pNIPAM), p(di(ethylene glycol) methyl ether methacrylate-co-oligoethylene glycol methacrylate) (DEGMA-coOEGMA475), and poly (glycidyl methyl etherco-ethyl glycidyl ether) (tPG)	Thermoresponsivenanogels
Poly(2-(dimethylamino) ethyl methacrylate) (PDMAEMA)	Multistimuli responsive nanogels (pH, temperature and UV lightsensitive)
Polyglycerol	Microrna functionalized nanogels
Poly(ethylene glycol) bis(3-aminopropyl) and branched polyethylenimine	Biohybridnanogels (Cellulase conjugated nanogels)
Oligoethyleneglycol (OEG) and pyridyldisulfide (PDS)	pH- and redoxresponsivenanogels
Gelatin	Stem cell membrane coated nanogels
Polyacrylic acid (PAA) grafted Dextran	Self-assembled redox sensitive biodegradable nanogels

Co-trimoxazole: Pharmacological characteristics and Mechanism of action

It is a combination of synergistic of two antimicrobial agents namely: sulfamethoxazole (SMX) and trimethoprim (TMP) (Hawser et al., 2006). The mechanism of action is its interference against synthesis of folic acid synthesis of bacterial species. Mechanism underlying co-trimoxazole tend to impact Bacteria which is able to take folic acid from infected host, thereby they are reliant on on its self-synthesis of folic acid (See Figure).

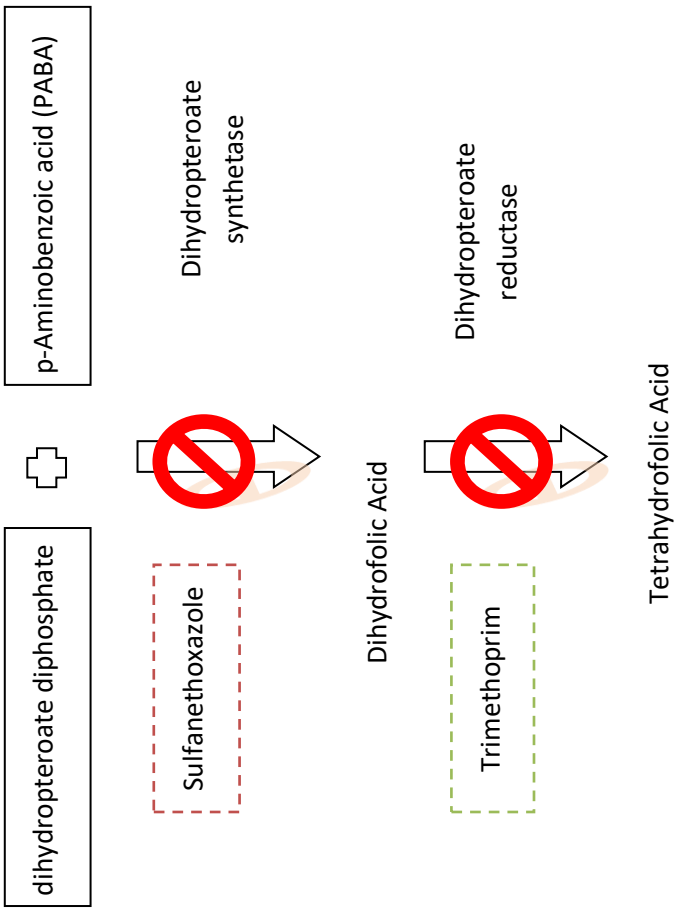

Figure 4: Mechanism of Co-trimoxazole (Pytliak et al., 2011)

Both Trimethoprim as well as sulfamethoxazole exhibit a greater effect upon combination compared when they are administered separately, since it inhibit successive steps that folate synthesis way. It is done by challenging with p-aminobenzoic acid (PABA) in the biosynthesis of dihydrofolate (Swarbrick et al., 2008).Trimethoprim serves as a competitive inhibitor of dihydrofolatereductase (DHFR), hence inhibiting the de novo synthesis of tetrahydrofolate, the biologically active form of folate (Bermingham& Derrick, 2002). Tetrahydrofolate is synthesis of purines which is crucial, thymidine, & methionine which are in the necessity for the DNA production & proteins during replication of bacteria (Rossi et al., 2011). The consequence of both of these drugs is a stayed in the bacteriostatic replication. If both are combined, SMX and TMP are bactericidal. Over enzymatic Inhibition starves bacteria in two bases which are (thymidine and uridine) as it is quint important for the replication along with transcription of DNA (Sharma et al., 2016).

This particular mechanism of action resulted in their application predominantly for treating urinary tract infections, prophylaxis and in treating Pneumocystis jiroveci pneumonia for HIV infected patients (Helweg-Larsen, et al., 1999). The pharmacokinetic parameters observed for TB patients by Alsaad et al., (2013) using Co-trimoxazole with regards to clearance, AUC, volume of distribution alongside with other indications as well. From the study it could be determined that it was safe and also well-tolerated, however side effects pertaining to gastrointestinal were observed.

Under the general note, Co-trimoxazole serves to be a safe medication and the drug is tolerated well. However certain possible side-effects that are witnessed with administration of the drugs such as: gastrointestinal intolerance, vomiting, nausea, diarrhoea and anorexia (Judd et al., 1995). Thus the Probable side effects are observed in blood such as hyperkalaemia, also with slight increase on serum creatinine levels observed and hypernatraemia. Such effects tend to occur predominantly among patients suffering

renal dysfunction. Also the Haematological abnormalities observed include leukopenia, thrombocytopenia, agranulocytosisand aplastic and haemolytic anaemia (Alsaad et al., 2014).

Researh investigations emphasising on the in-vitro activities of Co-trimoxazole pertaining to the antibacterial action were studied by researchers over the years. The following table depicts on various literature sources stressing on the In-vitro antibacterial activity of Co-trimoxazole.

Table 2: Literature sources on In-vitro antibacterial studies

In-vitro studies carried out by	Targeted bacterial species	Outcomes
Lewin et al., (1993)	Pseudomonas cepacia	The MICs in case ofceftazidime, meropenem, ciprofloxacin and PD compounds over 90% strains tested were lesser or equivalent to 4 micrograms/ml, whereas they were 32 micrograms/ml for chloramphenicol and **co-trimoxazole**
Betriu et al., (2001)	Stenotrophomonasmaltophilia	Isolates of the study showed that resistance towards co-trimoxazole has decreased
Hahn and Kirov (1980)	Klebsiellapneumoniae, Proteus vulgaris, Proteus mirabilis, and Streptococcus faecalis.	The study showed optimal antibacterial activities being achieved with a weight ratio benzylpyrimidine/sulfonamide of 1:1 or 1:5, respectively. In all instances, the combination trimethoprim/sulfamethoxazole proved to be of higher antibacterial in vitro activity than that of tetroxoprim/sulfadiazine.
Minkowski et al., (2001)	*Listeria monocytogenes*	At high concentrations of co-trimoxazole and TMP, lysis of cell matrix, membrane disruption, and fragmentation of bacteria
Forgacs et al., (2009)	*Mycobacterium tuberculosis*	43 out of 44 isolates of *M. tuberculosis* were sensitive to ≤1/19 µg/ml of TMP-SMX.

Formulation of nanogels for antibacterial drugs: An overview for development of hydrogels for Co-trimoxazole

Formulation of nanogels for antibacterial drugs: An overview for development of hydrogels for Co-trimoxazole

As many of the biologically active agents are basically characterized based on how relatively lower solubility ranges that acts as major hindrance for their pharmacological usage. However in certain conditions some compounds serves as ionogenic surfactants. These components facilitate in blocking ionomers complexes for delivering drugs in bodily system. By incorporating amphiphilic molecules such as Sodium oleate, retinoic acid and indomethacin could be ideal for hydrogel formulation since they amphilic in nature and also exhibit lower solubility with nanogels like PEO-cl-PEI (Li, Shuqiang et al., 2018).

For instance, formulation of hydrogels with that of synthetic antibacterial drugs/antibiotics, were predominantly observed. From the observed investigations from the literature sources emphasizing on

nitroimidazole based drugs, sulfanilamide groups, and other frequently used drugs, however the semisynthetically derived antibiotics and similarly the biological extracts appeared to be not included (Dax, 2012). Even though the chemical structures advanced synthetic drugs considerably tend to cause damages and risks to the tissues. Also it is trivial for a stable and efficient delivery system is quintessential.

For ornidazole delivery, the PAA and dextrin was utilized. The compound comprises Hydrogel containing nitroimidazole (An antibacterial drug used in digestive system). The drug exhibits inhibitory effect over anaerobic bacteria as well as with amoeba alongside with pH/ temperature release profiles (Ford et al., 2014). Also the hydrogel tend to have degradable nature as it exhibit null cytotoxic effect against mesenchymal stem cells when tested in human. Dextrin grafted with that of Hydrogels based poly (2-hydroxyethyl methacrylate) served to be excellent candidates for orally administration of delivery in colon (Das et al., 2013).

CS/gelatin/β-GP hydrogel composed of metronidazole tested in injectable form for treatment against periodontal infection. The tested drug was found to maintain metronidazole release in concentrations as the observed study showed effective against killing pathogenic bacteria like Clostridium sporogenes (Samanta et al., 2014).

Just put in the existence of CS, N′-methylene bis-acrylamide and the acrylic acid were cross linked by radical copolymerization to synthesize the CH. CHX is measured to be a auspicious antibacterial agent which holds a broad antibacterial spectrum containing G+ and G− bacteria (Lboutounne et al., 2002). CHX-contained poly (ethylene glycol)-block-poly(L-lactide) nanoparticles were loaded in hydroxyethyl cellulose hydrogel, allowing the hydrogel system to enhance its activity against Enterococcus faecalis for root canal system disinfection (Jones et al., 2008).

Besides the literature sources on formulation of Co-trimoxazole as hydrogel has been carried out only in minor cases. For instance Bodaghabadi et al., (2018) produced different concentrations of co-trimoxazole and rifampicin which were used for loading onto nanostructure of synthesized monomethoxy poly (ethylene glycol)-oleate. Studies showed co-trimoxazole efficiency didn't improve by stuffing onto nanoparticles, the co-trimoxazole ineffectiveness is expected not because of its insolubility or low penetration, & perhaps there are some other issues that persist to be make clear for the future investigations.

Conclusion

The review represents that currently numerous forms of hydrogel based compounds tailored for meeting up with various needs applications. The promising attributes for hydrogels primarily is as a result of its swelling under contact of aqueous environment. The review demonstrated literature pertaining to hydrogel classification on the basis of different bases, physic-chemical characteristics of products along with technical likelihood over utilization. Co-trimoxazole is one of the potent antibiotics with wide array of application for treatment against numerous bacterial species, for nearly two decades. However there still appears that there exists no proper investigation pertaining to nanogel loaded Co-trimoxazole or in combination. This review presents a better insights on numerous literatures that emphasised on hydrogel synthesis using pharmaceutically active agents and via studying its efficacy. It is quintessential to researchers in coming future towards synthesis of novel and efficacious co-trimoxazole loaded hydrogel.

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