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Review Article

NOVEL DELIVERY APPROACHES OF CO-TRIMOXAZOLE FOR RECREATING ITS POTENTIAL USE-A REVIEW

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ABSTRACT

Co-trimoxazole appropriates to category of broad-spectrum antimicrobial. They are active upon administration *in vitro* against an extensive collection of microorganisms. Their application in medical field has roughly spanned over decade now. There are numerous approaches that were progressed for improving their effectiveness towards their antimicrobial potency. However, routine use of this could accelerate the chance of bacterial resistance, and portrait it ineffective when required to treat infection. Consequently, newer investigations are necessary to keep the drug effective by minimise the development of resistance and maximise its safe use. Safe use is meant by safe delivery of drug in low dose, low frequency at the targeted molecule by effective ways. This can be achieved by using nanocarrier systems as they possess smart characteristics of effective drug delivery. These nanocarrier systems are including nanoparticle, liposomes, nanogels etc. Present review article deals with the historical perspectives with regards to co-trimoxazole, their mechanism of act/resistance and spectrum of activity in first section. In second portion different novel carriers, importance and application of nanogels, rational for co-trimoxazole nanogels are discussed. In conclusion, different literatures have proved the efficacy of nanogels in delivery of antimicrobial drug similar to co-trimoxazole. In the present time very less data is available for delivery of this drug with novel carriers. Therefore, this review aims to encourage researchers for creating some new findings in this perspective.

Keywords: Co-trimoxazole, Nanocarriers, Antimicrobials, Antibiotics and Drug resistance

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INTRODUCTION

Phenomenon pertaining to multidrug-resistant (MDR) is presenting an intensifying tendency and signifies key challenge for a system of health care [1]. The situation is particularly more drastic for "ESKAPE" pathogens containing *Enterococcus* spp., *Klebsiella* spp., *Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter baumannii* and *Enterobacter* spp. A few of these pathogens like *Acinetobacter. baumannii,* already become pan-resistant [2]. Co-trimoxazole (CTX) is a combination of sulpahamethoxazole and trimethoprim (SMX/TMP) in the proportion of 5:1. The combination is having potential synergistic effect. Both the drugs have equal $t_{1/2}$ of approximately 10 h, making them suitable for this combination. They block the sequential obligate enzymatic reaction in bacteria. Sulfamethoxazole is a close congener of sulfisoxazole. The same combination is also popularly known as Bactrim, Septran and proven as clinically successful antimicrobials. It is originated as the agent of first choice only in *Pneumocystis carinii* infections; however, it is essential in several infectious diseases like UTI, throat, ear infections, enteric fever and acute exacerbations of chronic bronchitis [3].

CTX is primarily available in tablet (TMP 80/160 mg and SMX 400 mg) and suspension (TMP 40 mg/5 ml and SMX 200 mg/5 ml) form. However, for treatment in advance cases parenteral preparations like injection concentrate for IV infusion (TMP 16 mg/ml and SMX 80 mg/ml) is also available. Fig. 1 depicts its different functional attributes.

From the historical perspective, CTX belongs to the family of the renowned sulphur family of sulphanilamides, which are derivatives sulphanilamide, which is chemically known as para-amino benzene sulfonamide. Major groups of sulfonamides are relatively water insoluble, but their sodium, potassium salts is water-soluble. The antibacterial action of these compounds is inherited due to sulfanilamide structure itself, which portrays the sulphur linked directly to the benzene ring having a substitution in the amide NH_2 group [4].

Sulfonamides competitively block bacterial enzyme dihydropteroate synthase, responsible for the conversion of para-aminobenzoic acid into folic acid. TMP shows a synergistic action with all sulfonamides by selectively blocking bacterial dihydrofolate reductase. This enzyme is responsible for reducing dihydrofolate to tetrahydrofolate. The potential combination of these two drugs for the broad-spectrum action is 20:1 of SMX and TMP. Generally, all the sulfonamides get well absorbed when administered orally with peak plasma levels around 2–6 h. They have good volume of distribution (50–80%). They easily reach the cerebrospinal fluid [5, 6)].

In past few years the uses of CTX accelerate the chance of bacterial resistance, and results in treatment failure. Therefore, there is a continuous demand of new therapeutic agents and delivery system which can keep the drug effective by minimise the development of resistance and maximise its safe use. Most of the research focussed on development of novel delivery system/nanocarrier like nanoparticle, liposomes, nanogels which possess smart characteristics of effective drug delivery. The present review highlights the importance and applications of nanogel and recent updates on the CTX loaded nanocarriers systems.

Authors conducted a systematic review of published literature to assess the current use and advancement of CTX and its nanocarrier system in the treatment of bacterial disease. In the present time very less data is available for the delivery of CTX with nanocarriers. Therefore, this review aims to encourage researchers for creating some new findings in this perspective.

A search of the computerized bibliographic database; PubMed, Google, Scopus and Google Scholar was performed. The keywords used in the search were co-trimoxazole, drug resistance, antimicrobials, nanocarriers and co-trimoxazole based nanocarriers. Original articles, review articles and expert's opinions published between 2009 to 2020 that investigated or discussed the nanocarrier system and novel delivery systems of CTX were used in this article.

Co-trimoxazole: pharmacological characteristics and mechanism of action

It is a combination of synergistic of 2 antimicrobial agents, namely: SMX and TMP. The mechanism of action is its interference against synthesis of folic acid synthesis of bacterial species. Mechanism underlying CTX tend to impact bacteria which are capable to take folic acid from infected hosts; thereby, they are dependent on its self-synthesis of folic acid (fig. 2).

Both TMP as well as the SMX exhibit better result upon combination compared to when they are administered separately since it inhibits successive steps that folate synthesis way. It is done by challenging with p-aminobenzoic acid (PABA) in the biosynthesis of dihydrofolate. TMP helps as a competitive inhibitor of dihydrofolate reductase [7-8].

Tetrahydrofolate is the synthesis of purines, which is vital, thymidine, and methionine, which are in necessity for DNA production and proteins through replication of bacteria. The consequence of both of these drugs is a stayed in bacteriostatic replication. If both are combined, SMX and TMP are bactericidal. Over enzymatic inhibition starves bacteria in 2 bases, which are (thymidine and uridine) as it is important for replication along with transcriptions of DNA. This particular mechanism of action resulted in their application mainly for treating urinary tract contaminations, prophylaxis and in treating *Pneumocystis jiroveci* pneumonia for human immune virus-contaminated patients [9-11]. Alsaad *et al.* observed the pharmacokinetic parameters for tuberculosis patients. Using CTX with regards to clearance, area under curve, the volume of delivery alongside with other indications also. From the analysis, it could be determined that it was safe and also well-tolerated; however, side effects pertaining to gastrointestinal were perceived [12].

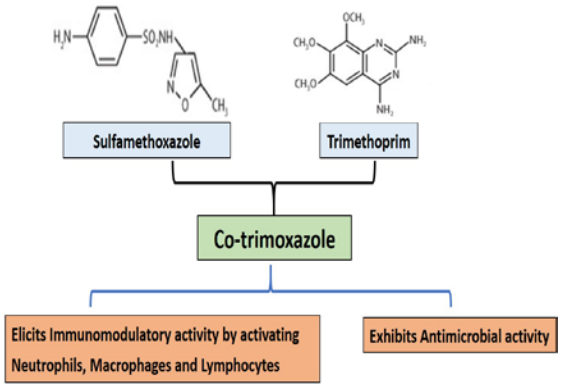

Fig. 1: Functional attributes of Co-trimoxazole [6]

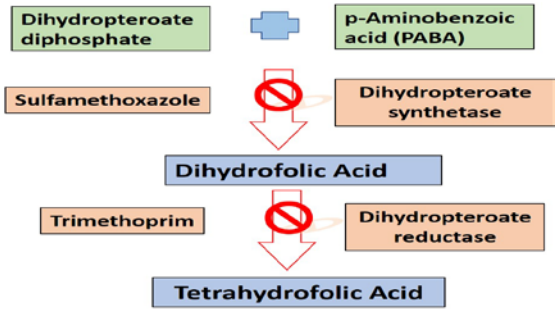

Fig. 2: Mechanism exhibited by Co-trimoxazole against microorganisms [6]

Under the general note, CTX serves to be a safe medication and the drug is tolerated well. However, certain possible side-effects that are witnessed with the administration of drugs such as: gastrointestinal intolerance, vomiting, nausea, diarrhoea and anorexia [13]. Thus, the probable side effects are observed in the blood, such as hypokalaemia, also with a small upsurge on serum creatinine levels observed and hypernatremia. Such effects tend to occur predominantly amongst patients suffering renal dysfunction. Also, the haematological abnormalities observed comprise leukopenia, thrombocytopenia, agranulocytosis and aplastic and haemolytic anaemia [14]. Research investigations emphasizing on the *in vitro* activities of CTX pertaining to the antibacterial action were studied by researchers for many years. The table 1 portrays on various literature sources, stressing on *in vitro* antibacterial activity of CTX.

Table 1: Literature sources on *in vitro* antibacterial studies

***In vitro* studies carried out by**	**Targeted bacterial species**	**Outcomes**
Lewin *et al.* [15]	*Pseudomonas cepacia*	The MICs in case of ceftazidime, meropenem, ciprofloxacin and PD over 90% tested strains were lesser or equivalent to 4 micrograms/ml, whereas they were 32 µg/ml in the case for chloramphenicol/co-trimoxazole.
Betriu *et al.* [16]	*Stenotrophomonas maltophilia*	Isolates of the study showed that resistance towards CTX has decreased
Hahn and Kirov [17]	*Klebsiella pneumoniae, Proteus mirabilis, Proteus vulgaris,* and *Streptococcus faecalis*.	It showed optimal antibacterial potency with a weight ratio ranging for benzyl pyrimidine/sulfonamide with equivalent 1:1 otherwise 1:5, respectively. Under all instances, combinatorial indications suggest trimethoprim/sulfamethoxazole as higher antibacterial from *in vitro* study than tetroxoprim/sulfadiazine.
Minkowski *et al.* [18]	*Listeria monocytogenes*	At maximal concentration ranges of co-trimoxazole/TMP exhibited matrix (cell lysis), disruption observed in membrane, and bacterial fragmentation
Forgacs *et al.* [19]	*Mycobacterium tuberculosis*	43 out of 44 isolates of *M. tuberculosis* were sensitive to ≤1/19 µg/ml of TMP-SMX.

Nano-antimicrobials: next course of action against pathogenic microbes

For the escalating resistance to mostly all classes of antibiotics is decreasing utilities of presently accessible antimicrobial drugs [20]. A portion of the threat is recognized to deprive pharmacokinetics and pharmacodynamics drug. Development of drug delivery is likely the maximum exciting task that comes across by pharmaceutical industries, though nanotechnology that can take along a rebellion in plan and drug delivery. Nano-antimicrobials, they consume action of separate intrinsic antimicrobial or augment complete efficiency of antibiotics surrounded, thus the contribution in mitigation or retrieving resistance phenomenon [21].

Individual intrinsic antimicrobial activity having by nanoparticle, that destroys the microbes by imitating killing course through phagocytic cells, by creating an enormous amount of responsive species of oxygen and responsive nitrogen species. Nanoparticles are killing microbes by concurrently substitute on numerous vital life procedures or metabolic ways of microbes [22]. Nano-carriers increase pharmacokinetics of drugs enclosed. Likewise, the crucial methods by which nanomaterials could overwhelm resistance is drug delivery target of disease. Nano anti-microbials exhibits various mechanisms (fig. 3) by which they combat the multidrug-resistance phenomenon [23].

The nanocarrier (vesicular and particulate) like liposomes, transfer some, niosomes, solid lipid nanoparticles, microspheres, micelles, dendrimers etc. are broadly used nowadays for their antimicrobial property in nanomaterial. A list of important nanocarriers used for delivering antimicrobials has been depicted in table 2.

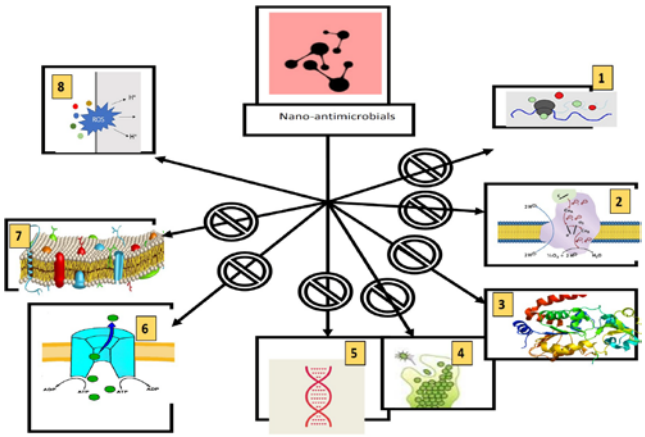

Fig. 3: Nano anti-microbials and their different mode of actions, (1-Attachment to 30s ribosome subunits; 2-Damage/disruption of proton pumps; 3-Protein damage; 4-Prevention of Biofilm formation; 5-DNA damage; 6-Disruption of electron transport chain; 7-Disruption of microbial cell membrane; 8* Generation of ROS) [23]

Nanoparticles

Antimicrobial nanoparticles now in use are metal, metal oxide, and organic nanoparticles type. They show a diversity of intrinsic and modified chemical composition properties. Silver and gold metal nanoparticles are established for their antimicrobial efficacy. Polymeric nanoparticles destroy microorganisms either by releasing the entrapped antimicrobial agents or by direct contacting with cationic surfaces such as quaternary ammonium compounds to the negatively charged bacterial cell [24].

Liposomes

These are defined as microscopic (unilamellar or multilamellar vesicles) and are composed of phospholipids, cholesterol and long chain fatty acids. The advantages of liposomes include non-toxic, biocompatible, non-immunogenic, biodegradable and able to protect the encapsulated material. Liposomes have been employed to deliver many antimicrobials to the lungs. They provide an excellent control release of drug in the lungs and is stable. Many liposomal preparations of antimicrobials like Arikace® (liposomal amikacin) and Pulmaquin® (liposomal ciprofloxacin) have reached to advance phases of the clinical trials [25, 26].

Niosomes

These are non–ionic surfactant-based liposomes i.e. microscopic lamellar structures obtained on the hydration of non-ionic surfactant, cholesterol and other lipids. These are cheaper to prepare than liposomes and are highly resistant to oxidation. It comprises both hydrophobic and hydrophilic moiety and these were developed for reducing systemic toxicity by encapsulating the drug and minimize the clearance of its release slowly in the body. In a study, cephalexin-loaded niosomal formulations were made using span 60 and tween 60. The developed formulation exhibits an enhanced in antibiotic activity against *E. coli* and *S. aureus* as compared to free drug. Moreover, the niosomal formulation was stable and exhibited slight cytotoxicity in HepG2 cells, measured by MTT assay [27].

Polymeric microspheres

These are made of solid polymeric spherical particles (1-1000 µm) in which the drug is distributed through the matrix containing polymer. These are effective for delivering therapeutic substances to the target site in a sustained and controlled manner. The main advantages of this system are to protect the unchangeable drug before and after administration and thus improve the bioavailability, reduces the incidence or intensity of adverse effects, provide extended therapeutic effects and improve patient compliance. In a study, Thaya *et al.* developed a chitosan-alginate microsphere with high antifilm and antimicrobial activity against bacteria of public health relevance [28]. Similarly, Adebisi *et al.* also formulated clarithromycin-loaded ethylcellulose/chitosan microspheres for treatment of *H. pylori* for the treatment of peptic ulcer [29].

Hydrogels

These are a hydrophilic network of polymers, mainly of 3d structure, according to their ionic interaction and hydrogen bonding. The advantages include biocompatibility and their ability to bring changes of pH, temperature and other stimulation factors that can be easily injected and can absorb water, easily modify. Currently, hydrogels loaded with antimicrobial agents are a hotspot for research in the biomedical field. In the recent past, many advance hydrogels loaded with antibacterial have been developed, possessing qualities like high swellability, ease of drug loading and controlled drug release with a vast structural diversity [30].

Dendrimers

They are characterized as a 3D macromolecular structure with various branching units and multiple active terminal groups. The

drug can be administered both in the interior region, including the surface groups of the dendrimers. These provide miscellaneous advantages such as less susceptibility to uptake by the reticuloendothelial system, comfort of modification, targeting to a specific location in the body make sure generative, pharmacokinetic behavior [31].

Solid lipid nanoparticles

It contains a solid lipid core matrix that is used to solubilize lipophilic molecules. A greater quantity of surfactants is used to stabilize the lipid core. They are typically spherical and their size ranges from 10 to 1000 nm. Li C *et al.* developed a solid lipid nanoparticle (SLN) of enrofloxacin by a hot homogenization and ultrasonic emulsification method. The developed SLN exhibits good stability with an increased in area under the curve and mean retention time as compared to the pure drug. The SLN improved oral bioavailability, palatability, sustained-release performance and stability of enrofloxacin [32]. Jansook *et al.* formulated Amphotericin B-loaded SLN and studied the drug release profile, entrapment efficiency and biopharmaceutics of amphotericin B. They reported that the Amphotericin B-loaded SLN exhibit increased antifungal activity with a prolong release characteristic [33]. In a study, Chokshi *et al.* developed rifampicin-loaded SLN by employing a three-level, three-factor Box-Behnken design for the treatment of tuberculosis. The developed SLN exhibited the antilipolytic effect and *in vitro* gastrointestinal tract (GIT) stability studies (at pH 1.2, pH 4.5, pH 6.8, and pH 7.4) shows that the SLN can withstand various GIT media [34].

Micelles

Micelles are spherical amphiphilic structures that have a hydrophobic core and a hydrophilic shell. The main merits of these micelles are the biocompatibility, similar biological activity, sustained release of encapsulated materials, competence to act as long-circulating drug carriers, the elevated solubility of hydrophobic drugs and ability of therapeutic proteins to the target site. The above merits lead to the development of drug-loaded micelles in the delivery of antimicrobial agents. In a recent study, Zhou *et al.* developed tobramycin-embedded nanostructured pH-responsive micelles with efficient and sustained antibacterial properties [35].

Nanoemulsion

These are nano-sized emulsions. The main advantage of nanoemulsion is the loading of less amount of the drug so that it will show fewer side effects with a high dose of the drug and also help in the delivery of the poorly soluble drug into the bottom of the skin layer. The absorption rate increases when the drug particle size ranges from 10-200 nm. The main advantage is to provide the controlled release, sustained release of the drug to the target site and is easily reproducible [36].

Table 2: List of reported literature for nanocarrier of antibacterial drugs

Nanocarrier	Drug	Targeted pathogen	References
Liposomes	Azithromycin	*MAC, Pseudomonas. aeruginosa*	[37]
	Gentamicin	*Listeria monocytogenes, Salmonella* spp., *Brucella abortus, Pseudomonas aeruginosa*	[38, 39]
	Ampicillin	*Helicobacter pylori, Serovar Typhimurium, Salmonella enterica*	[40, 41]
	Ciprofloxacin	*Streptococcus aureus, Francisella tularensis, Pseudomonas aeruginosa*	[42-45]
Polymer nanoparticles	Vancomycin	*Enterococcus clinical isolates, Streptococcus aureus*	[46]
	Ampicillin	*Pseudomonas aeruginosa, Streptococcus aureus, Enterobacter aerogenes,*	[47]
	Penicillin	MRSA	[48]
	Azithromycin	*Haemophilus influenzae, Escherichia coli, Streptococcus pneumoniae, Chlamydia pneumoniae,*	[49-50]
	Isoniazid	*Mycobacterium* spp.	[51]
	Rifampicin	*Mycobacterium bovis, Chlamydia pneumoniae, Chlamydia trachomatis*	[52]
Solid lipid nanoparticles	Amikacin	Pulmonary infections and *Pseudomonas aeruginosa*	[53]
	Gatifloxacin	*Streptococcus aureus* (MRSA)	[54]
	Norfloxacin	*Escherichia coli*	[55]
Dendrimers	Rifampicin.	*Mycobacterium spp*	[56]
	Vancomycin	*Streptococcus aureus*	[57]
	Amoxicillin	*Escherichia coli, Streptococcus aureus*	[58]

MRSA: methicillin-resistant *Streptococcus aureus*; MAC: *Mycobacterium avium*

Cotrimoxazole loaded novel drug delivery systems

Usually, antimicrobial agents are administered by oral or parenteral route in the form of capsules/tablets and injections, correspondingly. Topical antimicrobial preparations like ointments, gels and creams are also employed for local or systemic function. Unfortunately, this systemic antimicrobial drug delivery is associated with numerous challenges. The common problem is body tissues getting exposed to high concentrations of potent drugs when administered orally or parenterally relatively than that required at the site of action. It means the delivery is non-specific and thus creates a large number of unwanted side effects and sometime potential toxicity (in case of anticancer). Other limitations are

1. It requires larger doses due to first-pass metabolism or enzymatic destruction

2. Antimicrobials destroy friendly bacteria naturally present in the gut and therefore create unwanted problems, including fatalities.

3. In some conditions like venous ulcers or infected diabetic foot, systemic administration is unsuccessful due to low blood circulation in the extremities, particularly in diabetics.

4. Unnecessary large dose through systemic administration is not rational in local infections where low local doses may be beneficial.

For these reasons, novel delivery systems of these antimicrobials have been explored to overcome the above-mentioned limitations of conventional antimicrobial delivery. Many of these novel delivery systems modify the conventional (oral and parenteral) drug delivery by controlled or sustained delivery systems. Therefore, allow long-lasting maintenance of therapeutic doses in the systemic circulation and evade from repeated doses. Some of this novel delivery approaches are discussed in this section.

In a study, Kumar *et al.*, prepared a hydrogel loaded with CTX for the wound healing activity. The formulation can simultaneously deliver TMP/SMX at the wound site and accelerated the healing process. They prepared chitosan loaded CTX nanoparticle by an ion gelation method with a size range of 209.8 nm. The hydrogels were prepared on the basis of the concentration of carbopol 940. The hydrogel exhibits a MIC of µg/ml and zone of inhibition 3.7±0.3 times more than the plain drug after 72 h. The hydrogel releases the CTX in a sustained release fashion. The *in vivo* study showed that the hydrogel can heal the wound 1.5 times faster than the conventional marketed formulation [59]. Similarly, Attama AA *et al.* prepared a CTX loaded mucoadhesive microparticle through emulsification method employing mucin and carbopol 941. They observed that the complexation of mucin with carbopol modified the physical property of carbopol. The microparticle exhibits good mucoadhesion property

with drug entrapment and fluid sorption. They concluded that the optimized mucoadhesive microparticles having mucin and carbopol 941 in the ratio 1:1 shows a sustained release of CTX [60]. Amaral AC *et al.* tested the activity of peptide P10 (an immunomodulator) through a sustained delivery system in combination with TMP/SMX against paracoccidioidomycosis. In an animal model, the chronic form of paracoccidioidomycosis was induced in BALB/c mice with *Paracoccidioides brasiliensis*. The mice were treated with TMP/SMX alone or combination with peptide P10, either emulsified in Freund's adjuvant or loaded with poly (lactic acid-glycolic acid) (PLGA) nanoparticles. Quantitative level of cytokines and fungal burden in tissues was measured to assess the therapeutic efficacy of the treatments. The mice treated with PLGA nanoparticles presented a remarkable reduction in the fungal load in lungs as compared to the non-treated animals. Moreover, the PLGA nanoparticle was found to be more effective as compared to the emulsion form. Thus, they concluded that the PLGA nanoparticle loaded with TMP/SMX and P10 peptide demonstrated an increase activity against the fungus and reduce the degradation of P10 peptide [61]. In another study Bottari NB *et al.* investigate the synergistic effects of TMP/SMX and resveratrol inclusion complex nanoparticle on Toxoplasma gondii infected of mice. They divided 60 mice into 2 groups: uninfected (n = 24) and infected by T. gondii (n = 36) which was further subdivided into treated with resveratrol or TMP/SMX alone and co-administered with of TMP/SMX and resveratrol inclusion complex nanoparticle. They studied the behavioral test and various pathological changes including brain cyst count. They reported that the nanoparticle treated mice showed a reduced cyst in the brain and diminished lesion in the liver. The nanoparticle also increased the antioxidant level in the mice and prevent behavioral changes. Therefore, they concluded that the TMP/SMX and resveratrol inclusion complex nanoparticle shows an improved therapeutic effect with reduced oxidative stress, which results in liver protection and reduced cysts in the brain of *T. gondii* infected mice [62]. Mendes C *et al.* developed a supersaturating delivery system by solid dispersion technique containing TMP/SMX at fixed-dose combination (SMX: TMP 5:1 w/w). They proposed that the retention of supersaturation drugs in the intestinal lumen can result in higher bioavailability. The drug was made amorphous by spray drying and then solid dispersion was formulated with the help of Eudragit EPO polymer. The formulation containing 70% of Eudragit EPO maintains the supersaturation condition up to 24 h. Moreover, the formulation showed an improved antibacterial activity as compared to pure drugs alone. Thus, the developed formulation improves the bioavailability of drugs with reduce the dose and may be helpful in the prevention of antibiotic resistance emergence [63]. The SMX in CTX is a is insoluble in water, resulting in low bioavailability and limits its clinical use. Gurbuz MU *et al.* synthesis a surface-modified polyamidoamine (PAMAM) dendrimers loaded with SMX for enhancing the solubility. The results stated that the dendrimers increase the solubility of the SMX. Among various formulations, the NH_2 group containing PAMAM dendrimers exhibits highest aqueous solubility. In addition, in an *in vitro* drug release studies, the dendrimers exhibit a sustained release of SMX as compared to pure drug at the end of 2 h [64]. Similarly, Gokturk S, *et al.* also enhances the solubility of TMP/SMX by inclusion it in cyclodextrins (α-, β-, and γ-CDs) and anionic surfactant sodium dodecyl sulfate (SDS) [65]. Bodaghabadi *et al.*, formulated CTX and rifampicin loaded nanoparticles. Studies showed CTX efficiency didn't improve by stuffing into nanoparticles, the CTX ineffectiveness is expected not because of its insolubility or low penetration, and perhaps there are some other issues that persist to be making clear for the future investigations [66].

CONCLUSION

The review signifies that currently, numerous forms of nanocarrier based compounds tailored to meet up with various needs applications. The promising attributes for hydrogels primarily are as an outcome of its swelling under the contact of the aqueous environment. The review demonstrated literature pertaining to hydrogel classification on the basis of dissimilar bases, physic-chemical features of products along with technical likelihood over utilization. CTX is one of the potent antibiotics with a wide array of applications for treatment against numerous bacterial species for nearly two decades. However, there still appears that there exists no proper investigation pertaining to nanocarrier loaded CTX or in combination. It is quintessential to researchers in coming future towards synthesis of novel and efficacious CTX loaded nanocarriers to minimize its resistance problem and exploit its safe use.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

No conflict of interest.

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