

Review Article

## ANTIBACTERIAL POTENTIALS OF CLARITHROMYCIN-LOADED POLYMERIC NANOCARRIERS

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### ABSTRACT

Clarithromycin (CTM) is a semisynthetic derivative of erythromycin that have been reported to exhibit potential antibiotic activities mostly against the gram-negative and gram-positive bacteria, lower/upper respiratory tract and skin infection causing pathogens. It is widely used for the prevention and management of infections due to *Mycobacterium avium* complexes and peptic ulcers due to *Helicobacter pylori*. Various marketed formulation of CTM in the form of tablets, capsules and other conventional dosage forms is available as anti-infective, however the drug itself has several limitations. These limitations include low oral bioavailability, rapid metabolism, poor targeting to infected sites and toxicity to normal cells/tissues. Also, the CTM-based therapy has been reported for several gastrointestinal adverse effects, including diarrhea, stomach upset, gastric distress, atypical taste and others. Thus, to overcome these issue, various novel strategies including nanotechnology or nanocarrier-based approaches have showed significant effects and have been immensely considered worldwide. In recent years, the various nanocarriers or nanocarrier-based delivery systems, particularly the polymeric nanocarrier have played significant role in effective drug targeting. Thus, in this review, the various polymeric nanocarrier-based delivery systems of CTM that effective reduced the dosing frequency, improved the patient compliance and potentially enhanced the therapeutic efficiency of CTM has been summarized.

### 1. INTRODUCTION

Clarithromycin (CTM), being an antibiotic of semi-synthetic macrolide category, is widely used for the prevention and management of numerous infections including infections in lower and upper respiratory tracts, ear, dermal, and others affected by diverse categories of bacteria. Figure 1 represents the chemical configuration of CTM. The CTM has been reported to have stability in acidic conditions, has short half-life of 3–4 hours and poor systemic bioavailability, which hinders its therapeutic efficiency against intracellular contagions. However, a higher

dose of CTM for a longer period could help to attain a therapeutic outcome, but this causes adverse and toxicity in system [1,2]. The major mechanism behind the CTM is that when it gets metabolized in the human body, 14-hydroxy clarithromycin (14-H/CTM) (microbiologically active metabolite of CTM) is originated. The 14-H/CTM significantly contributes a synergistic effect to the activity of CTM against the pathogens (mainly bacteria). CTM has been reported to exhibit antibiotic activity mostly against the pathogens causing infections in stomach regions [3].

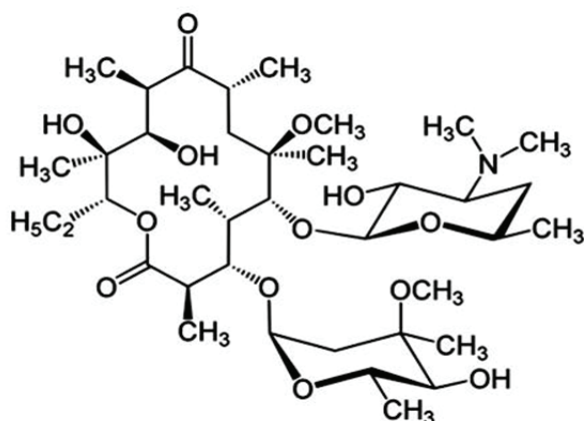


Fig. 1 Chemical configuration of Clarithromycin

Oral administration is one of the easiest and appropriate route for the delivery of most drug regimens. However, futile targeting due to various biological barriers is one of the major issue associated with orally directed drugs or drug delivery systems 4. Similarly, being a BCS class II drug, CTM also has a major limitation of bioavailability and permeability, thus to overcome these issue nanocarrier-mediated delivery systems has been established to mimic the systemic processess 5. Generally, the nanocarrier vary in size between 10-1000 nanometers (nm) and are usually considered to be in range of 100-500 nm for biomedical applications [4,5]. In particular, the polymeric nanocarrier have been widely used for the effective delivery of poorly soluble drugs like CTM, also with the alterations in its properties, they could be fabricated into smart delivery systems for effective targeting. the polymeric nanocarriers could efficiently deliver the drug at specific sites and improve sustained release pattern of drug [6,7]. Thus, the polymeric nanocarriers have exhibited various advantages, including improved drug stability, bioavailability, biodistribution and pharmacokinetics and simultaneously have reduced the adverse effects and toxicity. So, the polymeric nanocarriers could effectively assist CTM to overcome its limitations [8,9]. In this review, we have summarized the various polymeric nanocarriers of clarithromycin applicable in the prevention and management of bacterial infections.

## 2. POLYMERIC NANOCARRIERS OF CLARITHROMYCIN

Natural and synthetic polymers have gained much more considerations and thus have been used significantly in biomedical and pharmaceutical applications. The synthetic polymers have been widely used for the fabrication of biomedical structures and devices, whereas the natural polymers have been used for drug delivery approaches 6. The natural polymers play crucial role in the development of nanocarriers and delivery systems for effective delivery of drugs at the targeted sites with improved therapeutic efficacy.

In this context, Majithiya and Murthy developed CTM-incorporated chitosan-based microspheres (CTM-CS-MSs)

using emulsification method to improve the drug release and to manage stomach ulcers. The CTM-CS-MSs showed good mucoadhesiveness with percent entrapment efficiency (%EE) of 74%. Results showed that the swellability of the MSs decreased with an increase of glutaraldehyde (GA; cross-linker) amount. *In-vitro* studies showed that the CTM-CS-MSs improved the permeability of CTM, sustained release pattern and increased the accumulation of CTM in stomach as compared to free drug. *In-vivo* studies showed that, the bioavailability of CTM was increased by CTM-CS-MSs as compared free drug suspension and thus exhibited effective activities against stomach ulcers [10]. The synergistic therapeutic effects of CTM and extracts of propolis and *Zingiber officinale* (*Z. officinale*) was evaluated against *Helicobacter pylori* (*H. pylori*) strains The results demonstrated that the amalgamations of propolis extract + CTM and *Z. officinale* extract + CTM improved the inhibitory activity against *H. pylori* [11]. Patel and Thakur developed CTM-encapsulated floating tablets in the presence of hydroxypropylmethylcellulose (HPMC) for the management of *H. pylori* infections. The tablet compositions and its mechanical strength showed significant effect over the drug release and floating behaviour. The tablets exhibited sustained release, irregular diffusion patter and followed zero-order kinetics [12]. In another study, similar CTM-loaded floating tablets were prepared and its efficacy to prolong gastric residual with significant therapeutic effects against the management of *H. pylori* associated peptic ulcer was evaluated. The polymer (HPMC) based tablets improved the floating properties and sustain release of the tablets. The delivery system also showed significant therapeutic activities as compared to pure drug[13]. The research related to floating properties was reported in a study, in which CTM-loaded *in-situ* gelling systems comprised of gellan (gelling polymer) and calcium carbonate ( $\text{CaCO}_3$ ; floating agent). Afterwards, sucralfate was added to the system which showed significant activities. The gelling systems exhibited potent anti-infective activities against the *H. pylori* as compared to CTM suspensions. Also, the CTM-loaded gelling systems with sucralfate repressed *H. pylori* more efficiently than the formulation deprived of sucralfate[14].

The gellan gum was applied as a potent polymer for the development of floating beads encapsulated with CTM. The floating beads were developed by using ionotropic gelation technique and were evaluated for their anti-bacterial activity against *H. pylori*. The beads were found to be sphere-shaped with irregularities in the exterior surface. The various parameters such as amount of gellan gum,  $\text{CaCO}_3$  and drug significantly affected the *in-vitro* drug release properties of the beads. The developed beads exhibited superior anti-bacterial properties against the *H. pylori* strain. Also, the floating efficacy of the beads showed improved behaviour when evaluated through *in-vivo* studies in rabbits [15]. Jain and Jangdey developed and characterized CTM-loaded concanavalin-A (CVA) based gastro-retentive multiparticulate system (CTM-CVA-GRMS) for the management of colonization of *H. pylori*. The CTM-CVA-GRMS was formulated in the presence of ethylcellulose (EC) using emulsification or evaporation process. CTM-CVA-GRMS were regular, spherical and showed good mucoadhesiveness. The

CTM-CVA-GRMS showed improved micromeritics properties. The drug release from the CTM-CVA-GRMS was prolonged and efficiently treated the *H. pylori* colonization [16]. Gattani et al. developed CTM-encapsulated alginate (AG)/HPMC based floating-CTM-AG/HPMC beads for providing effective prolonged release of drug at the for the management of stomach ulcer. The floating-CTM-AG/HPMC beads showed improved floating efficiency, increased therapeutic efficacy in the albino rats and thus were found to be a potential agent for treating peptic ulcers [17]. Vaghani and Patel produced a pH-responsive CS/polyvinyl pyrrolidone (PVP) based hydrogels with effective controlled release behaviour of CTM. The hydrogels were developed using cross-linking method in the presence GA (cross-linker). The hydrogels exhibited improved drug loading (~97%). As compared to alkaline conditions, the hydrogels showed good swelling index and mucoadhesiveness in the acidic conditions. *In-vitro* release studies showed improvement in extent of drug release and followed non-Fickian diffusion mechanism [18]. Mohammadi et al. prepared PLGA coated CTM-loaded nanoparticles (PLGA-CTM-NPs) and evaluated its anti-bacterial activity against *Staphylococcus aureus* (*S. aureus*). Results showed that the polymeric NPs exhibited descent particle size, a negative zeta potential and were showed more anti-bacterial than the blank CTM-suspensions [18, 19]. Valizadeh et al. Similarly, in another study the potential antibacterial activity of PLGA-CTM-NPs was evaluated against different bacterial strains, including *Escherichia coli*, *Haemophilus influenzae*, *Salmonella typhi*, *S. aureus* and *Streptococcus pneumonia*. The results specified that the zone of inhibition of was found to be more in cell treated with PLGA-CTM-NPs as compared to untreated CTM [4]. Pereira et al. developed amorphous solid dispersion of CTM, in presence of carboxylated cellulose, to improve the solubility and oral bioavailability of drug in the body. Results showed that CTM-ALDs significantly protected the drug in the neutral pH medium of the body and thus increased the drug residual time as well as release was prolonged with improved anti-bacterial activities [20].

Rose et al. developed a multiparticulate drug (rifampin, doxycycline and CTM) loaded films of poly- (styrene-co-methyl methacrylate) and evaluated their anti-biotic effects in biofilm prevention. The results showed that the film were effectively loaded with all the drugs in a fixed proportions and exhibited a controlled release behaviour. The anti-biotic films potentially inhibited the resettling of biofilms [21]. Li et al. developed polyethylene glycol-coated liposomal formulation of antibiotic agents (daptomycin, CTM or both) and evaluated their antibacterial potential against *S. aureus* strains. Results showed that as compared to daptomycin-loaded liposomes, the PEGylated daptomycin/CTM loaded liposomes exhibited superior anti-bacterial activity against *S. aureus* [22]. Cong et al. fabricated CTM-incorporated polymeric nano-micelles composed of carboxymethyl CS (CMCS) and were further modified with stearic acid and urea. The nano-micelles appeared as spherical particles in a range of approximately 200 nm. The nano-micelles exhibited cytotoxicity against AGS cells, and thus maintained stability in particle size for 6 hours in the

simulated gastric fluid and for 24h in phosphate buffer saline medium. Pleasingly, the polymeric backbones due to CMCS provided immense structural support to the nano-micelles and thus helped to improve the drug retention time in the stomach and so effectively targeted the *H. Pylori* induced infections [23]. Soisuwan et al. assessed the influence of charge on the *in-vitro* drug characteristics of CTM-loaded nanocrystals (CTM-NCs). In this context, the uncharged CTM-NCs were developed using poloxamer 407, and the negatively as well as positively charged CTM-NCs were steadied using a blend of poloxamer 407 with cetyltrimethylammonium bromide and sodium lauryl sulfate (SLS), respectively. Results showed that the particle size of the negatively and positively charged CTM-NCs were smaller as compared to the uncharged CTM-NCs. Also, the positively charged CTM-NCs exhibited greater mucoadhesive properties as compared to the uncharged and negatively charged CTM-NCs. Moreover, the permeability of CTM against NCI-N87 and Caco-2 cell monolayers were comparatively more in both charged CTM-NCs than the uncharged CTM-NCs [24].

### 3. CONCLUSIONS

In summary, the polymer-based nanocarriers including polymeric nanoparticles, films, liposomes, micelles, floating tablets and others could offer frequent advantages to improve the therapeutic potentials of clarithromycin, including reduced toxicity, improved aqueous solubility, oral bioavailability and biocompatibility. However, various oral dosage forms of CTM, including sustained/controlled release tablets and others, are available in the market as conventional dosage form, yet the major issues related with CTM could effectively resolved using polymeric nanocarriers-based delivery systems. Also, the various *in-vivo* animal studies and clinical trials has to be performed more accurately to improve the efficacy of the nanocarrier-mediated systems. In future, the various aspects of these nanocarrier-based delivery systems of CTM needs to be evaluated for its substantial anti-bacterial mechanism against significant pathogens to establish targeted therapies with greater anti-infective potentials.

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