International Journal of Advanced Pharmaceutical Sciences and Research (IJAPSR)
ISSN: 2582-7618 (Online), Volume-3 Issue-1, December 2022

Potentials of Polymeric Nanocarriers Loaded with Clarithromycin for Antibacterial Activity

Shivendra Misra, Vivekanand Prajapati, N T Pramathesh Mishra

***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.*

***Keywords**: CTM, Nanotechnology, Polymeric, Atypical Taste, Including Diarrhea, Stomach Upset,*

I. 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.

Manuscript received on 08 December 2022 | Revised Manuscript received on 13 December 2022 | Manuscript Accepted on 15 December 2022 | Manuscript published on 30 December 2022.

*Correspondence Author(s)
Shivendra Misra, Department of Pharmacy, Hygia College of Pharmacy, Dr. A. P. J. Abdul Kalam Technical University, Lucknow. (Utter Pradesh), India. ORCID ID: https://orcid.org/0009-0006-9605-9139
Vivekanand Prajapati, Department of Pharmacy, Hygia College of Pharmacy, Dr. A. P. J. Abdul Kalam Technical University, Lucknow. (Utter Pradesh), India. ORCID ID: https://orcid.org/0009-0008-2076-5357
Dr. N T Pramathesh Mishra*, Department of Pharmacy, Hygia College of Pharmacy, Dr. A. P. J. Abdul Kalam Technical University, Lucknow. (Utter Pradesh), India. E-mail: mishrant@hygia.in, ORCID ID: https://orcid.org/0000-0001-9268-841X

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]. Figure 1 Chemical configuration of Clarithromycin Oral administration is one of the easiest and appropriate routes for the delivery of most drug regimens. However, futile targeting due to various biological barriers is one of the major issues 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 processes [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. 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.

II. 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 approaches6. 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 swell ability 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 hydroxypropyl methylcellulose (HPMC) for the management of *H. pylori* infections. The tablet compositions and its mechanical strength showed significant effect over the drug release and floating behavior. 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 (CaCO3; 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, CaCO3 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 trating 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 [19]. Valizadeh et al. Similarly, in another study the potential antibacterial activity of PLGA-CTM-NPs was evaluated against different bacterial strains, inclusing *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 CTM4. 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.

III. RESULTS AND DISCUSSION

It 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 multiarticulate 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 was effectively loaded with all the drugs in a fixed proportions and exhibited a controlled release behavior. 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 characterictics 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].

IV. 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 must 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.

ACKNOWLEDGMENT

I would like to acknowledge Dr. N T Pramathesh Mishra and Mr. Vivekanand Prajapati for their valuable contributions to this article. Their expertise and insights have greatly enriched the content and helped to provide a comprehensive understanding of the subject matter. Thank you for your collaboration and support.

DECALARION

Funding/ Grants/ Financial Support	No, I did not receive.
Conflicts of Interest/ Competing Interests	No conflicts of interest to the best of our knowledge.
Ethical Approval and Consent to Participate	No, the article does not require ethical approval and consent to participate with evidence.
Availability of Data and Material/ Data Access Statement	Not relevant.
Authors Contributions	All authors have equal participation in this article.

REFERENCES

1. Van Nuffel, A.M.; Sukhatme, V.; Pantziarka, P.; Meheus, L.; Sukhatme, V.P.; Bouche, G. Repurposing drugs in oncology (ReDO)-clarithromycin as an anti-cancer agent. E Cancer. Med. Sci. 2015, 9, 1–26. [CrossRef]
2. Lebel, M. Pharmacokinetic properties of clarithromycin: A comparison with erythromycin and azithromycin. Can. J. Infect. Dis. 1993, 4, 148–152. [CrossRef]
3. Hardy, D.J.; Swanson, R.N.; Rode, R.A.; Marsh, K.; Shipkowitz, N.L. Enhancement of the in vitro and in vivo activities of clarithromycin against Haemophilus influenzae by 14-hydroxy-clarithromycin, its major metabolite in humans. Clement JJ Antimicrob Agents Chemother. 1990, 34(7):1407-13. [CrossRef]
4. Valizadeh, H.; Mohammadi, G.; Ehyaei, R.; Milani, M.; Azhdarzadeh, M.; Zakeri-Milani, P.; Lotfipour, F. Antibacterial activity of clarithromycin loaded PLGA nanoparticles. Die Pharmazie, 2012, 67(1), 63–68.
5. Zakeri-Milani, P.; Islambulchilar, Z.; Majidpour, F.; Jannatabadi, E.; Lotfipour, F.; Valizadeh, H. A study on enhanced intestinal permeability of clarithromycin nanoparticles. Braz. J. Pharm. Sci. 2014, 50, 121–129. [CrossRef]
6. Das, S.S.; Bharadwaj, P.; Bilal, M.; Barani, M.; Rahdar, A.; Taboada, P.; Bungau, S.; Kyzas, G.Z. Stimuli-Responsive Polymeric Nanocarriers for Drug Delivery, Imaging, and Theragnosis. Polymers **2020**, 12, 1397. [CrossRef]
7. Rizvi, S.A.A.; Saleh, A.M. Applications of nanoparticle systems in drug delivery technology. Saudi. Pharm. J. 2018, 26, 64–70. [CrossRef]
8. Öztürk, A.A.; Yenilmez, E.; ¸Senel, B.; Arslan, R.; Yazan, Y. Dexketoprofen trometamol-loaded Kollidon® SR and Eudragit® RS 100 polymeric nanoparticles: Formulation and in vitro-in vivo evaluation. Lat. Am. J. Pharm. 2017, 36, 2153–2165.
9. Bamrungsap, S.; Zhao, Z.; Chen, T.; Wang, L.; Li, C.; Fu, T.; Tan, W. A Focus on nanoparticles as a drug delivery system. Nanomedicine 2012, 7, 1253–1271. [CrossRef]
10. Majithiya, R. J., Murthy, R. S. Chitosan-based mucoadhesive microspheres of clarithromycin as a delivery system for antibiotic to stomach. Current drug delivery, 2005, 2(3), 235–242. [CrossRef]
11. Nostro, A., Cellini, L., Di Bartolomeo, S., Cannatelli, M. A., Di Campli, E., Procopio, F., Grande, R., Marzio, L., Alonzo, V. (2006). Effects of combining extracts (from propolis or Zingiber officinale) with clarithromycin on Helicobacter pylori. Phytotherapy research : PTR, 20(3), 187–190. [CrossRef]
12. Patel, S. S., Ray, S., Thakur, R. S. (2006). Formualtion and evaluation of floating drug delivery system containing clarithromycin for Helicobacter pylori. Acta poloniae pharmaceutica, 63(1), 53–61.
13. Nama, M., Gonugunta, C. S., Reddy Veerareddy, P. (2008). Formulation and evaluation of gastroretentive dosage forms of Clarithromycin. AAPS PharmSciTech, 9(1), 231–237. [CrossRef]
14. Rajinikanth, P. S., Mishra, B. (2008). Floating in situ gelling system for stomach

site-specific delivery of clarithromycin to eradicate H. pylori. Journal of controlled release : official journal of the Controlled Release Society, 125(1), 33–41. [CrossRef]
15. Rajinikanth, P. S., Mishra, B. (2009). Stomach-site specific drug delivery system of clarithromycin for eradication of Helicobacter pylori. Chemical & pharmaceutical bulletin, 57(10), 1068–1075. [CrossRef]
16. Jain, S. K., Jangdey, M. S. (2009). Lectin conjugated gastroretentive multiparticulate delivery system of clarithromycin for the effective treatment of Helicobacter pylori. Molecular pharmaceutics, 6(1), 295–304. Patel, S. S., Ray, S., & Thakur, R. S. (2006). Formualtion and evaluation of floating drug delivery system containing clarithromycin for Helicobacter pylori. Acta poloniae pharmaceutica, 63(1), 53–61. [CrossRef]
17. Gattani, S. G., Savaliya, P. J., Belgamwar, V. S. (2010). Floating-mucoadhesive beads of clarithromycin for the treatment of Helicobacter pylori infection. Chemical & pharmaceutical bulletin, 58(6), 782–787. [CrossRef]
18. Vaghani, S. S., Patel, M. M. (2011). pH-sensitive hydrogels based on semi-interpenetrating network (semi-IPN) of chitosan and polyvinyl pyrrolidone for clarithromycin release. Drug development and industrial pharmacy, 37(10), 1160–1169. [CrossRef]
19. Mohammadi, G., Nokhodchi, A., Barzegar-Jalali, M., Lotfipour, F., Adibkia, K., Ehyaei, N., Valizadeh, H. (2011). Physicochemical and anti-bacterial performance characterization of clarithromycin nanoparticles as colloidal drug delivery system. Colloids and surfaces. B, Biointerfaces, 88(1), 39–44. [CrossRef]
20. Pereira, J. M., Mejia-Ariza, R., Ilevbare, G. A., McGettigan, H. E., Sriranganathan, N., Taylor, L. S., Davis, R. M., Edgar, K. J. (2013). Interplay of degradation, dissolution and stabilization of clarithromycin and its amorphous solid dispersions. Molecular pharmaceutics, 10(12), 4640–4653. [CrossRef]
21. Rose, W. E., Otto, D. P., Aucamp, M. E., Miller, Z., de Villiers, M. M. (2015). Prevention of biofilm formation by methacrylate-based copolymer films loaded with rifampin, clarithromycin, doxycycline alone or in combination. Pharmaceutical research, 32(1), 61–73. [CrossRef]
22. Li, Y., Su, T., Zhang, Y., Huang, X., Li, J., Li, C. (2015). Liposomal co-delivery of daptomycin and clarithromycin at an optimized ratio for treatment of methicillin-resistant Staphylococcus aureus infection. Drug delivery, 22(5), 627–637. [CrossRef]
23. Cong, Y., Geng, J., Wang, H., Su, J., Arif, M., Dong, Q., Chi, Z., Liu, C. (2019). Ureido-modified carboxymethyl chitosan-graft-stearic acid polymeric nano-micelles as a targeted delivering carrier of clarithromycin for Helicobacter pylori: Preparation and in vitro evaluation. International journal of biological macromolecules, 129, 686–692. [CrossRef]
24. Soisuwan, S., Teeranachaideekul, V., Wongrakpanich, A., Langguth, P., Junyaprasert, V. B. (2019). Impact of uncharged and charged stabilizers on in vitro drug performances of clarithromycin nanocrystals. European journal of pharmaceutics and biopharmaceutics: official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, 137, 68–76. [CrossRef]

AUTHORS PROFILE

Mr. Shivendra Misra holds a master's degree in pharmaceutics from Dr. A.P.J. Abdul Kalam Technical University in Lucknow, Uttar Pradesh. He has previous experience as an Assistant professor. He is skilled in the use of analytical tools and equipment such as UV-Vis Spectroscopy, HPLC, Dissolution apparatus, TLC, and others. In several international publications, he has published 3+ scholarly papers. In addition to participating in more than 20 conferences and symposiums both locally and internationally, he is a member of various professional organizations. He is now employed as an Assistant Professor in the department of pharmaceutics at Hygia College of Pharmacy, Dr. A.P.J. Abdul Kalam Technical University, Lucknow, Uttar Pradesh.

Mr. Vivekanand Prajapati holds a master's degree in pharmaceutics from Dr. A.P.J. Abdul Kalam Technical University in Lucknow, Uttar Pradesh, and is now enrolled in a PhD programme in pharmaceutics at Banasthali Vidyapeeth in Rajasthan. He has previous experience as an associate professor. He has been employed as a Quality Control Officer and Research Associate at MacLeod's Pharmaceuticals Ltd. and Jubilant Generics Ltd. (R&D-II) for a combined total of about four years. He is skilled in the use of analytical tools and equipment such as UV-Vis Spectroscopy, HPLC, Dissolution apparatus, TLC, UPLC, and others. He has five or more scientific publications published in a range of international journals. In addition to participating in more than 35 conferences and symposiums both locally and internationally, he is a member of various professional organizations. He is now employed as an associate professor in the department of pharmaceutics at Hygia College of Pharmacy, Dr. A.P.J. Abdul Kalam Technical University, Lucknow, Uttar Pradesh.

Dr. N T Pramathesh Mishra has experience as a research associate professor and has degrees in pharmacology, bioinformatics, molecular and structural biology, animal handling and management, molecular docking, 2D and 3D QSAR, clinical research, pharmacovigilance, medical writing, medical coding, and drug discovery and development. He is a member of several professional organizations and has participated as a delegate or invited speaker in more than 100 conferences both domestically and abroad. and has held a lot of national workshops. Among the honors bestowed upon Dr. Mishra are the Young Scientist 2017, Best Young Faculty 2019, HREA Annual Award 2020, Emerging Scientist 2020, Karma Veer Chakra, Global Youth Fellowship 2020-2021, Emerging Scientist Award 2020, Young Scientist Award 2017, Daniel Bovet Distinguished Young Scientist Award 2021, and Honorary Doctorate Awarded 2020, Pharmaceutical Sciences 2020 IMRF Young Scientist Award and Pharmacology 2020 HREA Annual Award He's a social worker and a journalist who has published 25+ scientific papers. At the Dr. APJ Abdul Kalam Technical University's Hygia College of Pharmacy in Lucknow, Uttar Pradesh, India, Dr. Mishra holds the position of Associate Professor in the Department of Pharmacology.