ejpmr, 2025, 12(2), 100-105

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

CHITOSAN NANOPARTICLES: VERSATILE CARRIERS FOR DRUG DELIVERY AND BEYOND

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Article Received on 12/12/2024 **Article Revised on 01/01/2025** **Article Accepted on 22/01/2025**

ABSTRACT

Chitosan nanoparticles have emerged as a promising platform for drug delivery due to their unique properties such as biocompatibility, biodegradability, and mucoadhesive nature. Derived from chitin, these nanoparticles offer significant advantages in improving drug solubility, permeability, and targeted delivery. By leveraging their ability to crosslink with anions and interact with cell membranes, CSNPs enable controlled and sustained drug release while enhancing therapeutic efficacy. Various synthesis methods, including ionic gelation and emulsification, have been explored to optimize their applications across diverse biomedical fields. This review delves into the preparation techniques, advantages over other systems, and their potential for site-specific drug delivery.

KEYWORDS: Chitosan nanoparticle, controlled release, drug delivery, biocompatibility, ionic gelation.

INTRODUCTION

Nanomedicine and nano delivery systems are rapidly evolving fields that involve the use of nanoscale materials as diagnostic tools or as carriers for therapeutic agents. These systems enable precise and controlled delivery of drugs to specific targeted sites within the body, enhancing both diagnosis andtreatment.[1] Various drug delivery systems have been developed and some of them under development with an aim to minimize drug degradation or loss, to prevent harmful side effects and to improve drug bioavailability and also to favour and facilitate the accumulation in required bio- zone (site). There are number of novel carries which have been established and documented to be useful for controlled and targeted drug delivery. It is important to critically evaluate different terms used under the different broad categories of novel drug delivery system.[2]

Different drug delivery and drug targeting systems are presently being developed in order to reduce drug degradation and loss, avoid negative side effects, boost drug bioavailability, and increase the percentage of the medication accumulating in the necessary zone. Soluble polymers, microparticles, nanoparticle composed of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles are a few examples of drug carriers. The carriers can be made slowly degradable, stimuli-reactive, and even targeted.[3]

NANOPARTICLE

"Solid colloidal particles with diameters ranging from 10 to 1000 nm and are superior to larger particles in biological applications due to their improved magnetic properties and better surface area-to-volume ratio are referred to as nanoparticle". Different nanosystems can be used to classify nanoparticles. They are receiving a lot of interest because of their potential in medicinal applications, particularly in medication delivery, together with nanomaterials. These tiny carriers can be designed to deliver medications to particular human areas or cells. Researchers can enhance their capacity to target diseased cells while avoiding healthy ones by altering the surface properties of nanoparticles. This could improve therapy efficacy and lessen adverse effects.[4,5]

CHITOSAN NANOPARTICLE

Chitosan, a non-toxic and biocompatible polymer, is widely used in drug delivery systems, especially for the absorption of hydrophilic macromolecular drugs. Derived from the natural polymer chitin, chitosan is composed of β-[1-4]-linked D-glucosamine and N-acetyl-D-glucosamine subunits. Its free amine groups allow it to be easily cross-linked with anions, improving its mucoadhesive and biocompatible properties for enhanced drug delivery. One of its key features is its ability to increase drug permeation across mucosal epithelia. When protonated at a pH of 6.5, chitosan interacts with tight junctions between epithelial cells, temporarily opening paracellular pathways, thus

facilitating drug transport across the epithelial barrier. Chitosan nanoparticles (CSNPs), which are more effective than chitosan solution alone, are often used for controlled and improved drug delivery. The positively charged CSNPs bind to negatively charged cell membranes, enhancing drug penetration and delivery by altering membrane elasticity, though the exact mechanism of cellular entry remains debated.[6,7]

In comparison to other polymeric carriers, chitosan has a number of benefits, including biodegradability, biocompatibility, and simpler, less toxic formulation methods. Since chitosan nanoparticles dissolve in acidic aqueous solutions, they eliminate the need for hazardous organic solvents. Chitosan's cationic properties enhance crosslinking with multivalent anions. For the treatment of inflammatory bowel disease (IBD), microparticulates of several medications and prodrugs, such as salazosulfapyridine, prednisolone, and sulfasalazine have been effectively developed.[8]

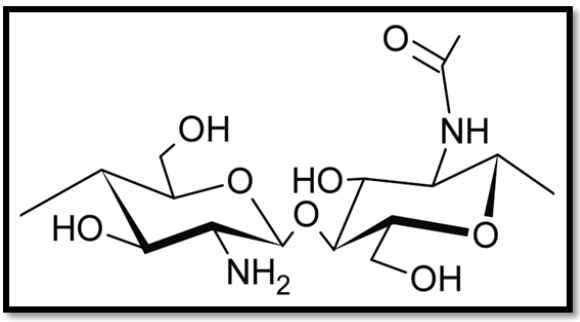

Figure 1: Structure of Chitosan.[9]

PREPARATION METHODS OF CHITOSAN NANOPARTICLE

Synthesis Techniques

Several techniques have been employed to prepare chitosan nanoparticles, each offering distinct advantages.

1. Ionic gelation method

The process starts by dissolving positively charged chitosan in acetic acid at room temperature, followed by magnetic stirring for about an hour. In a separate solution, tripolyphosphate (TPP), a polyanion, is dissolved in deionized water (DI) to act as an ionic cross-linker.

When TPP is added to the chitosan solution, nanoparticles begin forming immediately due to electrostatic interactions between the positively charged chitosan and negatively charged TPP. The solution transitions through three stages: starting as clear (chitosan solution), becoming opalescent or milky (upon adding TPP), and then aggregating with more TPP, indicating the formation of CNPs. Mild stirring for 10 minutes stabilizes the nanoparticles.

To separate the CNPs from unreacted materials, the suspension is centrifuged. The collected nanoparticles are then thoroughly washed with water and dried for further use. This method offers scalable and effective approach to prepare CNPs for various drug delivery applications.[10,11]

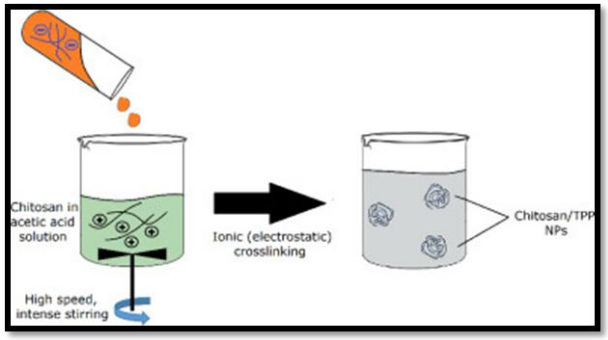

Figure 2: Ionic Gelation Method.[12]

2. Emulsification Solvent Diffusion Method

In this method, an emulsion is formed by adding an organic phase to a chitosan solution containing a stabilizing agent (e.g., poloxamer). The mixture is mechanically stirred and homogenized under pressure. Upon dilution with water, polymer precipitation occurs, forming nanoparticles. The diffusion of the organic solvent into the aqueous phase is the key mechanism. This method has limitations due to high shear forces and the use of organic solvents.[13]

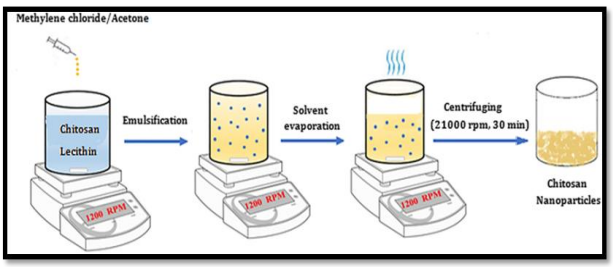

Figure 3: Emulsification Solvent Diffusion Method.[14]

3. Emulsification and Cross-Linking Method

This method involves the formation of a water-in-oil (W/O) emulsion followed by the addition of a cross-linking agent, such as glutaraldehyde, which covalently bonds with the amino groups of chitosan. This process leads to the formation of hardened droplets, resulting in CNPs suitable for drug delivery applications.[15]

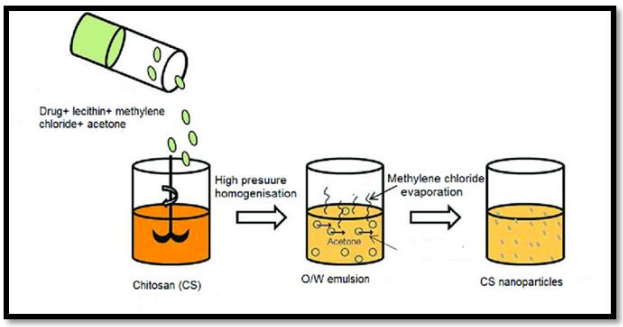

Figure 4: Emulsification and Cross-Linking Method.[16]

4. Emulsion Droplet Coalescence

Chitosan and drug are dissolved together, and the mixture is added to liquid paraffin with Span 80 to form a W/O emulsion. A second emulsion is created by adding sodium hydroxide to liquid paraffin. Mixing both emulsions via high-speed homogenization causes droplet coalescence, where sodium hydroxide acts as a precipitating agent for chitosan. The particles are then washed and centrifuged.[17]

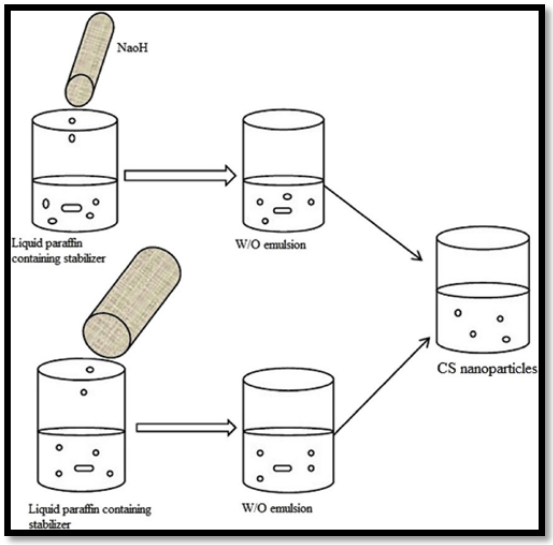

Figure 5: Emulsion Droplet Coalescence Method.[18]

5. Reverse Micellization

In this method, reverse micelles form a W/O system by adding a lipophilic surfactant (e.g., cetyl triethyl ammonium bromide or sodium bis(ethylhexyl) sulfosuccinate) to an organic solvent like n-hexane. Chitosan, drug, and glutaraldehyde are dissolved in water and added to the organic phase. The nanoparticles are extracted after solvent evaporation. This method achieves uniform particle size and is suitable for hydrophobic drugs.[19]

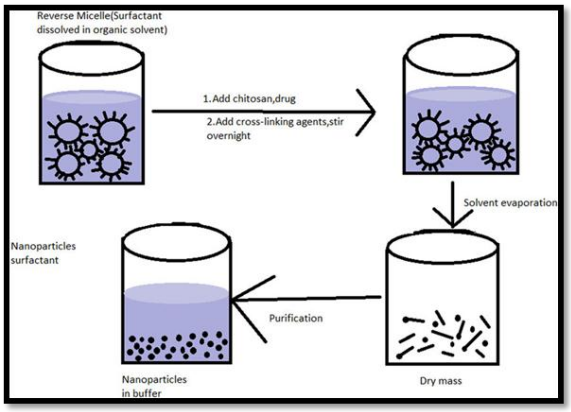

Figure 6: Reverse Micellization.[20]

6. Precipitation Method

Chitosan nanoparticles are produced by blowing a chitosan solution into an alkaline solution of sodium hydroxide or methanol. The coacervate particles are washed with hot air and cold water before filtration. The process is simple, but the resulting nanoparticles may have weak mechanical strength and irregular morphology, affected by factors like air pressure and chitosan concentration.[21]

7. Microemulsion Method

In this method, reverse micelles are used to synthesize CNPs by mixing a surfactant into an organic solvent. The mixture is then added to an acidic chitosan solution. Glutaraldehyde is used as a cross-linker to react with the free amine groups of chitosan. The nanoparticles formed through this method range from 30 to 110 nm and exhibit size uniformity. It is effective for synthesizing nanoparticles with controlled size based on the degree of cross-linking.[10]

COMPARISON OF CHITOSAN NANOPARTICLE WITH OTHER NANOPARTICLE SYSTEMS

Chitosan nanoparticles (CS-NPs) are often compared with other nanoparticle systems such as liposomes, dendrimers, and polymeric nanoparticles due to their unique properties and versatile applications. Each system has distinct advantages and limitations, making them suitable for specific purposes in drug delivery and biomedical applications.

1. Liposomes vs. Chitosan Nanoparticles

Liposomes, phospholipid-based vesicles, are widely used for encapsulating both hydrophilic and hydrophobic drugs. They offer excellent biocompatibility and the ability to target specific tissues by modifying their surface with ligands. However, liposomes are prone to leakage and have limited stability in biological environments. In contrast, CS-NPs provide higher stability due to their rigid structure and better mucoadhesive properties, which enhance drug residence time at mucosal surfaces. Additionally, chitosan's intrinsic antimicrobial activity provides an advantage in applications requiring bacterial suppression.[22,23]

2. Dendrimers vs. Chitosan Nanoparticles

Dendrimers are highly branched, synthetic macromolecules with a precise architecture and multiple functional groups for drug conjugation. While they offer high drug-loading capacity and excellent solubility, dendrimers can exhibit cytotoxicity due to their synthetic nature and strong cationic charges at high generations. CS-NPs, being naturally derived, are less cytotoxic and more biocompatible, making them a safer alternative for long-term therapeutic applications.[24]

3. Polymeric Nanoparticles vs. Chitosan Nanoparticles

Polymeric nanoparticles, such as those made from PLGA (poly(lactic-co-glycolic acid)), provide controlled drug release and excellent biocompatibility. However, their biodegradation products, such as lactic acid, may cause localized tissue irritation. CS-NPs offer a similar controlled release profile but with added mucoadhesion

and pH responsiveness, making them particularly effective for site-specific drug delivery, such as in gastrointestinal or respiratory systems. Furthermore, CS-NPs are easier to functionalize for targeted delivery than most polymeric systems.[25,26]

4. Metallic Nanoparticles vs. Chitosan Nanoparticles

Metallic nanoparticles, including gold and silver nanoparticles, have gained popularity for their plasmonic properties and applications in imaging, diagnostics, and antimicrobial therapies. However, their long-term safety and biodegradability remain concerns. CS-NPs, being fully biodegradable, avoid accumulation in tissues and offer a safer alternative for drug delivery purposes. Moreover, combining chitosan with metallic nanoparticles can synergistically enhance their antimicrobial and imaging properties.[27,28]

Chitosan nanoparticle synthesized by different researchers along with their composition and preparation technique were depicted in table 1.

Table 1: Chitosan nanoparticle synthesized by different researchers.

Drug	Composition other than chitosan	Method of Preparation	Researcher	Year
Risedronate	Tripoly phosphate, acetic acid, NaOH	Ionic gelation Method	Sandhya Pathak et al[29]	2024
Lidocaine	Glyceryl oleate, Isopropyl palmitate, Propylene carbonate, Gluconic acid, Caproic acid	Micro emulsion Method	Amnon C Sintov et al[30]	2024
Metronidazole	Borax, Tannic acid	Cross linking Method	Reena Nayak et al[31]	2024
Spironolactone	Palmitic acid, Oliec acid, Tween80, Acetic acid	Ultrasonication method	Majid saeedi et al[32]	2023
Montelukast	Tripoly phosphate, Tween 80, Hyaluronic acid, Leucine	Ionic gelation method	Faqir Ullah et al[33]	2022
Carbamazepine	TPP, Acetic acid	Ionotropic gelation method	Citra Ariani Edityaningrum et al[34]	2022
Measalamine	Pectin, Methanol	Nanoprecipitation method	Tejas Pachpute[35]	2019
Vancomycin	Tripolyphosphate, Acetic acid	Ionic gelation method	T Cerchiara et al[36]	2015
5 Fluro uracil	Poly Vinyl Alcohol, Acetic acid,Mannitol	Solvent emulsification evaporation technique	Shashank Tummala et al[37]	2014
Simvastatin	Sodium Tripolyphosphate	Ionotropic gelation method	A ahmed et al[38]	2014
5 Amino Salicylic Acid	Acetic acid, TPP,HCl	Ionotropic Gelation method	Pooja Mongia et al[39]	2014
Stavudine	Acetic acid,TPP	Ionotropic Gelation method	T Vyjayanthimala[40]	2013

REFERENCES

1. Patra, J.K., Das, G., Fraceto, L.F. *et al.* Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnol, 2018;* 16: 71. https://doi.org/10.1186/s12951-018-0392-8
2. Khan M. The novel drug delivery system. *World J Pharm Pharm Sci*, 2017; 6: 477- 87. doi: 10.20959/wjpps20177-
3. Manivannan rangasamy and Kugalur Ganesan Parthiban. Recent Advances in Novel Drug Delivery Systems. IJRAP, 2010; 1(2): 316- 26.
4. McNamara, K., & Tofail, S. A. M. (2016). Nanoparticles in biomedical applications. Advances in Physics: X, 2(1): 54 88. https://doi.org/10.1080/23746149.2016.1254570
5. Yusuf A, Almotairy ARZ, Henidi H, Alshehri OY, Aldughaim MS. Nanoparticles as Drug Delivery Systems: A Review of the Implication of Nanoparticles' Physicochemical Properties on Responses in Biological Systems. *Polymers*, 2023; 15(7): 1596. https://doi.org/10.3390/polym15071596
6. Subashini B, Inbakandan D. Molecular evaluation of chitosan nanoparticles mediated curcumin and quercetin delivery against pathogen induced oxidative stress in Litopenaeus vannamei, 2021. http://hdl.handle.net/10603/444963
7. Shaikh MS, Derle ND, Bhamber R. Permeability enhancement techniques for poorly permeable drugs: A review. Journal of Applied Pharmaceutical Science, 2012 Jul 30; 2(7): 34-9.
8. Kumar CP, Sharma GN. Formulation optimization and characterization of chitosan based nanoparticles containing sulfasalazine and methylprednisolone for the treatment of inflammatory bowel disease. Jaipur

National University, 2020. http://hdl.handle.net/10603/343034
9. Teixeira-Costa BE, Andrade CT. Chitosan as a valuable biomolecule from seafood industry waste in the design of green food packaging. Biomolecules, 2021 Oct 28; 11(11): 1599.
10. Jha R, Mayanovic RA. A Review of the Preparation, Characterization, and Applications of Chitosan Nanoparticles in Nanomedicine. Nanomaterials (Basel), 2023 Apr 7; 13(8): 1302. doi: 10.3390/nano13081302. PMID: 37110887; PMCID: PMC10140956.
11. Carvalho, et al. Mucosal delivery of liposome-chitosan nanoparticle complexes.Methods Enzymol, 2009; 465: 289-312.
12. Yanat M, Schroën K. Preparation methods and applications of chitosan nanoparticles; with an outlook toward reinforcement of biodegradable packaging. Reactive and Functional Polymers, 2021 Apr 1; 161: 104849.
13. Jha R, Mayanovic RA. A Review of the Preparation, Characterization, and Applications of Chitosan Nanoparticles in Nanomedicine. Nanomaterials (Basel), 2023 Apr 7; 13(8): 1302. doi:10.3390/nano13081302. PMID: 37110887; PMCID: PMC10140956
14. Hassani FS, Hadizadeh M, Zare D, Mazinani S. Comparison of different methods for preparation of nanochitosan as anticancer agent. Polymer Bulletin, 2024 Jan; 81(1): 827-42.
15. Ohya Y, Shiratani M, Kobayashi H, Ouchi T. Release behavior of 5-fluorouracil from chitosan-gel nanospheres immobilizing 5-fluorouracil coated with polysaccharides and their cell specific cytotoxicity. J Macromol Sci, Part A., 1994; 31(5): 629-642.
16. Abdelkader H, Hussain SA, Abdullah N, Kmaruddin S. Review on micro-encapsulation with Chitosan for pharmaceuticals applications. MOJ Curr. Res. Rev, 2018 May; 1(2): 77-84.
17. Kannan C, Shering M, Suganeshwari M, Kumar K, Kumar V. Formulation of 5-fluorouracil loaded chitosan nanoparticles by emulsion droplet coalescence method for cancer therapy, 2011.
18. Naskar S, Kuotsu K, Sharma S. Chitosan-based nanoparticles as drug delivery systems: a review on two decades of research. Journal of drug targeting, 2019 Apr 21; 27(4): 379-93.
19. Pileni, M. P. (2006). Reverse micelles used as templates: a new understanding in nanocrystal growth. Journal of Experimental Nanoscience, 1(1): 13–27. https://doi.org/10.1080/17458080500462075
20. Chadha U, Bhardwaj P, Selvaraj SK, Kumari K, Isaac TS, Panjwani M, Kulkarni K, Mathew RM, Satheesh AM, Pal A, Gunreddy N. Retracted: Advances in chitosan biopolymer composite materials: from bioengineering, wastewater treatment to agricultural applications. Materials Research Express, 2022 May 6; 9(5): 052002.
21. Yanat, M., & Schroën, K. (2021). Preparation methods and applications of chitosan nanoparticles; with an outlook toward reinforcement of biodegradable.
22. Akbuga J, Durmaz G. Preparation and evaluation of cross-linked chitosan microspheres containing furosemide. Int J Pharm, 1994; 111(3): 217–22.
23. Rinaudo M. Chitin and chitosan: Properties and applications. Prog Polym Sci, 2006; 31(7): 603–32.
24. Stiriba SE, Frey H, Haag R. Dendritic polymers in biomedical applications: From potential to clinical use in diagnostics and therapy. Angew Chem Int Ed, 2002; 41(8): 1329–34.
25. Agnihotri SA, Mallikarjuna NN, Aminabhavi TM. Recent advances on chitosan-based micro- and nanoparticles in drug delivery. J Control Release, 2004; 100(1): 5–28.
26. Bhattarai N, Gunn J, Zhang M. Chitosan-based hydrogels for controlled, localized drug delivery. Adv Drug Deliv Rev, 2010; 62(1): 83–99.
27. Mody VV, Siwale R, Singh A, Mody HR. Introduction to metallic nanoparticles. J Pharm Bioallied Sci, 2010; 2(4): 282–9.
28. Sreekumar A, Thomas S, Rouxel D. Chitosan-based nanostructures for drug delivery applications. Adv Polym Nanocompos, 2016; 245–76.
29. Pathak S, Sahu P, Begum JS, Kashaw SK, Pandey A, Semwal P, Sharma R. Formulation and assessment of penetration potential of Risedronate chitosan nanoparticles loaded transdermal gel in the management of osteoporosis: In vitro and ex vivo screening. Carbohydrate Polymer Technologies and Applications, 2024 Jun 1; 7: 100440.
30. Sintov AC. The Distinctive Role of Gluconic Acid in Retarding Percutaneous Drug Permeation: Formulation of Lidocaine-Loaded Chitosan Nanoparticles. Pharmaceutics, 2024 Jun 19; 16(6): 831.
31. Nayak R, Halder J, Rajwar TK, Pradhan D, Dash P, Das C, Rai VK, Kar B, Ghosh G, Rath G. Design and evaluation of antibacterials crosslinked chitosan nanoparticle as a novel carrier for the delivery of metronidazole to treat bacterial vaginosis. Microbial Pathogenesis, 2024 Jan 1; 186: 106494.
32. Saeedi M, Morteza-Semnani K, Akbari J, Hajheydari Z, Goodarzi A, Rostamkalaei SS, Hashemi SMH, Rahimnia SM. Green Formulation of Spironolactone Loaded Chitosan-Coated Nano Lipid Carrier for Treatment of Acne Vulgaris: A Randomized Double-Blind Clinical Trial. Adv Pharm Bull, 2024 Mar; 14(1): 161-175. doi: 10.34172/apb.2024.011. Epub 2023 Sep 23. PMID: 38585452; PMCID: PMC10997933.
33. Ullah F, Shah KU, Shah SU, Nawaz A, Nawaz T, Khan KA, Alserihi RF, Tayeb HH, Tabrez S, Alfatama M. Synthesis, characterization and in vitro evaluation of chitosan nanoparticles physically admixed with lactose microspheres for pulmonary delivery of montelukast. Polymers, 2022 Aug 29; 14(17): 3564.

34. Edityaningrum CA, Zulaechah AN, Putranti W, Arimurni DA. Formulation and Characterization of Carbamazepine Chitosan Nanoparticle. Pharmacy & Pharmaceutical Sciences Journal/Jurnal Farmasi Dan Ilmu Kefarmasian Indonesia, 2022 Aug 1; 9(2).
35. Tejas Pachpute et al. Formulation and Evaluation of Mesalamine Nanosphere Tablet. Journal of Drug Delivery and Therapeutics, 2019; 9(4s): 1045-1053.
36. Hajji S, Ktari N, Ben Salah R, Boufi S, Debeaufort F, Nasri M. Development of nanocomposite films based on chitosan and gelatin loaded with chitosan-tripolyphosphate nanoparticles: antioxidant potentials and applications in wound healing. Journal of Polymers and the Environment, 2022 Mar 1: 1-22.
37. Tummala S, Kumar MS, Prakash A. Formulation and characterization of 5-Fluorouracil enteric coated nanoparticles for sustained and localized release in treating colorectal cancer. Saudi Pharmaceutical Journal, 2015 Jul 1; 23(3): 308-14.
38. Ahmed A, Yadav HK, Manne N, Sureddy VL, Namburi NB, Shivakumar HG. Formulation and evaluation of enteric coated nanoparticulate system for poorly absorbable drug. Journal of Drug Delivery Science and Technology, 2014 Jan 1; 24(1): 50-6.
39. Mongia P, Khatik R, Raj R, Jain N, Pathak AK. PH-sensitive eudragit S-100 coated chitosan nanoparticles of 5-amino salicylic acid for colon delivery. Journal of Biomaterials and Tissue Engineering, 2014 Sep 1; 4(9): 738-43.
40. JB VK, Madhusudhan B. Synthesis, characterization and hemocompatibility evaluation of curcumin encapsulated chitosan nanoparticles for oral delivery. Int. J., 2015; 3(4): 604-11.