Functionalized Nanocarriers for Drug delivery: Amalgam of Biopolymers and Lipids

Mallesh Kurakula[1]*; Devang B Patel[2]; Bhaumik Patel[3]; Shashank Gorityala[4]; Pratap Basim[5]

[1]Department of Biomedical Engineering, The University of Memphis, Memphis, TN-38152, USA.

[2]Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, Brooklyn, NY 11201, USA.

[3]Product Development Department, Cure Pharmaceutical Corporation, Los Angeles, CA 90025, USA.

[4]Department of Bioanalytical Chemistry, Covance Laboratories, Madison, WI 53704, USA.

[5]Thermo Fisher Scientific, Cincinnati, OH 45237, USA.

*Corresponding Author(s): Mallesh Kurakula

Department of Biomedical Engineering, The Herff College of Engineering, University of Memphis, TN-38152, USA.

Email: mkrakula@memphis.edu

Abstract

Biopolymer–lipid nanocarriers as hybrids are upcoming and have been most assuring frontiers in both pharmaceutical and biomedical research areas. In last decade, great focus is oriented in the development of functionalized nanocarriers by amalgamation of biopolymer and lipids with inherit specific properties of organic, inorganic nanocarriers and the lipid structured particles (liposome, lipoprotein, solid lipid nanoparticle, and nanoemulsion, nanocrystals) for specialized properties and functions. By combining polymer-lipid composites these, functionalized nanocarriers gain futuristic properties that have a potential to numerous drug delivery and biomedical application ranging from stimuli/pH-triggered drug release, photothermal therapy, bioimaging and magnetic delivery). The presence of various nanoparticles within the polymer or lipid assemblies determines the final the properties and functions of the hybrid nanocarriers. Further can be classified as liposomes with surface-bound nanoparticles or liposomes with bilayered nanoparticles, and even liposomes with core-encapsulated nanoparticle. The present review discusses various hybrid nanocarriers prepared and reported till date for drug delivery and biomedical applications. The properties of each hybrid nanocarrier from their rational design up to delivery are discussed. Future prospectus and the scope of hybrid nanocarriers are also covered.

Introduction

Biopolymer-lipid systems provide a plethora of applications in the biomedical and pharmaceutical fields. Materials meant for biomedical/pharmaceutical applications like tissue engineering, wound healing, drug delivery, and gene delivery should possess certain properties like biocompatibility, biodegradation, low toxicity, low antigenicity, high bio-activity, processability, and appropriate mechanical strength. Based on a specific application the materials are supposed to have a specific property. For example, during tissue regeneration, the material should support cell growth and proliferation.

Characterization studies for prepared hybrid systems are size analysis using zeta sizer, rheological studies using cone and plate rheometer, structural lamellarity studies using cryo-TEM, and drug release studies using vial and fluorescence microplate reader. The advantages noticed with such a hybrid system include:

➢ Nanocarriers embedded in biopolymer gel are more stable to the external environmental stimuli.

➢ The encapsulated drug faces two-level transport resistance, primarily from bilayer shell and secondarily from the biopolymeric gel, thereby allowing the drug release for a prolonged duration.

➢ Such a constructive mechanism can avoid the problem of burst release seen generally with the individual systems that lead to toxicity.

➢ Biopolymer gel matrix provides localization of the product at the administered area and the combined network permits sustained drug delivery thereby offering prolonged therapy at the targeted site.

➢ Cytotoxicity studies of doxorubicin were also reported with promising results in addition to the sustained effect.

Hence, it can be observed that the combination of appropriate properties of Nanocarriers with the biopolymers leads to beneficial applications with enhanced performance of the lipid carrier system in biomedical and pharmaceutical fields. Scientists have reported multiple works stating that Nanocarriers and biopolymers have promising applications in drug delivery, gene delivery, and the biomedical field. At the same time, it is also well noted that neither the Nanocarriers nor the biopolymers provide all the desired properties like carrier stability, encapsulated component stability like DNA, prolonged delivery of encapsulated agents, etc. Hence, it is a necessary step to combine the unique features of both lipid systems and biopolymers to achieve the desired goals. Even in the case of drugs with a narrow therapeutic index, the prolonged treatment can be provided by modulating the pharmacokinetics and biodistribution of the drug substances using a suitable hybrid system of biopolymer functionalized lipid systems.

Nanocarriers formed by functionalisation of biopolymer-lipids

Nanoparticle

Nanoparticles in biomedical and pharmaceutical fields area revolutionary success for healthcare management. Nanoparticles, which are of the nanometric size range, made up of biopolymers are of prime importance in drug delivery and targeted drug release. Nanoparticles got their importance in biological signalling pathways for intracellular and cellular targets, even crossing through blood-brain barriers. Their success rate in therapeutics and easy entry followed by circulation in the body is owed to their small particle size. The advantages of biopolymer-based nanoparticulate drug delivery have dragged the attention of researchers. The modulations brought with the use of biopolymers in nanoparticles have contributed a lot to their efficiency. Biopolymers used in nanoparticle fabrication have paved paths for the surface immobilization of many bioactive like proteins, peptides, enzymes, immunomodulating agents, nucleotides (e.g., DNA) resulting in the formation of nanoparticle-biomolecular conjugates [1-3].

In the development of particulate systems, the selection of a specific biopolymer depends on important factors like:

➢ Particulate system properties: Size, shape, charge, polarity, permeability, loading capacity (entrapment efficiency) degradability, release rate, etc.

➢ Biopolymer properties: Solubility, hydrophobicity, charge, polarity, etc.

➢ Active ingredient (drug/bioactive) properties: stability, solubility, polarity, charge, dose, permeability, etc.

Nanoparticles have been conceptually developed as a merged form of lipid polymer hybrid nanoparticles for meeting the desired goals of oncology treatment, delivery of DNA/RNA materials, and imaging/diagnostic agent [4]. Polymeric nanoparticles developed by self-assemblage of biodegradable amphiphilic block copolymers are applicable for systemic administration. They can encapsulate the drugs and also can be decorated with ligands on the surface for targeted drug delivery [4,5].

Lipid-polymer hybrid nanoparticles

To overcome the drawbacks of individual carrier systems, liposomes, and nanoparticles, a new offspring of delivery system has been evolved which is termed as lipid-polymer hybrid nanoparticles (Figure 1) [6]. The hybrid composite can have increased encapsulation efficiency, improved stability, defined kinetics for controlled release, and specifically targeted release profile. Lipid-polymer hybrid nanoparticles have 3 sections, an inner polymer core (which encapsulate the drug), a middle lipid monolayer (surrounding the polymer core, which provides control over drug release), and an outer lipid-polymer layer (for steric stabilization, which provides prolonged systemic circulation avoiding the clearance from the immune system) [6-9]. These hybrid systems are useful in encapsulation/adsorption/covalent bonding of molecules like drugs, proteins, genes, vaccines, imaging agents, and ligands for a target [10-14].
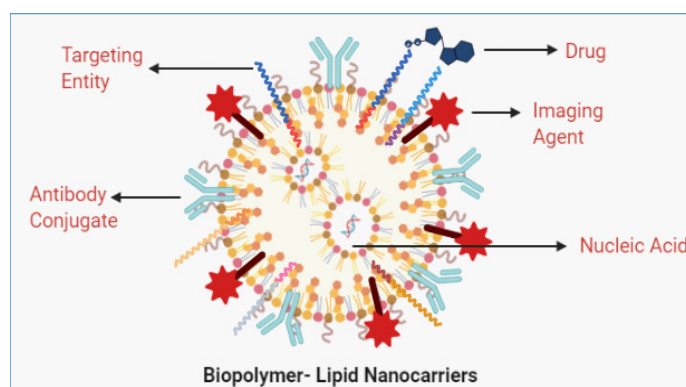

Figure 1: Depicts functionalised biopolymer-lipid nanocarriers with multifunctional components.

Types of lipid-polymer hybrid nanoparticle systems

Preparation techniques of lipid-polymer hybrid nanoparticles have been depicted in **Figure 2**. Based on the assembling of lipids and polymers, these hybrid systems can be further classified into different types [15].

a) Polymer core lipid shell

The simplest form of the lipid-polymer hybrid nanoparticle is the presence of a polymer core which entraps the drug sur-

rounded by the single or double layer of lipid shell further covered by the lipid-PEG layer or else incorporated within the shell. The combined features, the biomimetic property of lipids, and the structural integrity of polymer make this type of system as a promising delivery system for different types of therapeutic agents [16].

b) Double shell hybrid nanoparticles

This type of core-shell lipid polymer-lipid hybrid nanoparticles has a hollow inner polymer core surrounded by the lipid coating which is in turn coated by a polymeric material and finally coated with lipid shell (lipid-PEG mixture). In these systems, a bilayer or multilayers of lipids are present around the polymer core surface. They combine the properties of liposomes and polymeric materials. The gaps are filled with aqueous buffer. In some cases, the cationic or zwitterion phospholipids were incorporated to prepare the covering of lipoparticles through electrostatic interactions with the oppositely charged polymers [17-18].

c) Polymeric nanoparticles concealed by erythrocyte membrane

These polymeric nanoparticles attained biomimetic nature with the camouflaging caused by the erythrocyte membrane. They physically represent the vesicles that mimic the typical surface chemistry of the erythrocyte [19]. Such hybrid nanoparticles can cross the biological membrane easily and provide longer circulation periods in the bloodstream.

d) Monolithic lipid-polymer hybrid nanoparticles

These systems also called mixed lipid-polymer hybrid nanoparticles, are something like in reverse structure of the above-discussed systems, because the external layer is comprised of the polymer matrix in which the lipid or lipid-PEG molecules are distributed. The outer polymer matrix, surrounding the lipoid shell, is loaded with drug molecules [20].

e) Polymer caged liposomes

These include the self-possession of polymers smeared at the liposome surface providing the stability [21-23].
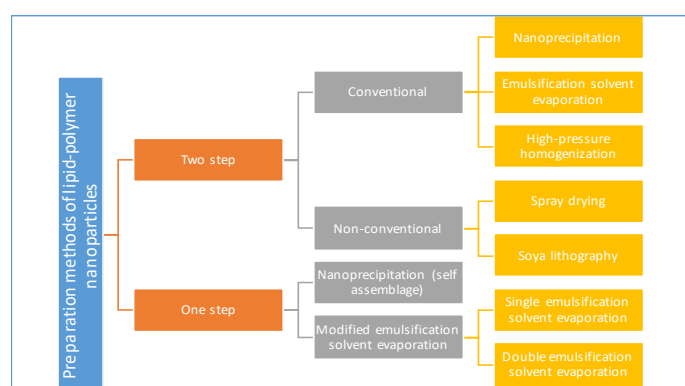

Figure 2: Different methods of preparation of lipid-polymer hybrid nanoparticles [21-22].

Lipid nanoparticles

These are colloidal lipophilic systems differentiated from the liposomes for having a lipid core stabilized in aqueous media and covered by a single layer of surfactants e.g., phospholipids. There are 3 such types of Lipid Nanoparticles (LNPs) namely, Solid Lipid Nanoparticles (SLNs), Lipid Nano-Emulsions (LNEs),

and Nanostructured Lipid Carriers (NLCs). SLNs have a solid lipid core, LNEs have liquid lipid core, and NLCs have a combination of both solid and liquid lipids in the core [24-26]. The lipids used for the fabrication of lipid nanoparticles are FDA (Food and Drug Administration) and EMA (European Medicines Agency) approved and hence found to be non-toxic and biodegradable representing the lipophilic physiological molecules. The size range of thus obtained lipid nanoparticles is in the nanometer range [27-29]. LNPs have gained importance for their applications in drug delivery, enhancement of bioavailability of hydrophobic drugs, and stabilization of hydrophobic active molecules. The inner lipid core of the LNPs encapsulates the hydrophobic active molecules whereas the outer surfactant membrane comprising of surfactants/phospholipids ensures the stability of LNPs in the external aqueous milieu. LNPs are well known for their transdermal drug delivery by forming a monolayer film over the skin thereby limiting the evaporation of water and improving the hydration of the skin. [30-32]

Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles are nanometric micelle structured spheres comprising of a solid hydrophobic lipid core surrounded by amphiphilic surfactants or phospholipids (e.g., triglycerides, fatty acids, polysorbates as components). Comparing with liposomes, the SLNs can encapsulate more quantity of hydrophobic drugs in its core due to the availability of a large volume of lipid core. These SLNs are gaining interesting applications in biomedical and pharmaceutical fields [33-36]. They can penetrate the brain parenchyma through absorption mediated transcytosis which involves the adsorption of the polysorbate of SLN on to the brain endothelial cell membrane followed by particle internalization followed by subsequent excretion from endothelial cells of the brain into the brain parenchyma. Jose et al. have studied the delivery of anticancer drugs, resveratrol into the brain tumor cells [37]. Jos et al. developed SLNs loaded with resveratrol, an anticancer drug, for delivery to the brain tumor. SLNs are made up of triglyceride trimyristin with a drug-lipid ratio of 1:10 and surface covered with polysorbate 80 and polyvinyl alcohol. With the large volume of a hydrophobic core, around 30% of resveratrol was encapsulated into the SLNs providing high therapeutic efficacy with minimal systemic toxicity [38-40].
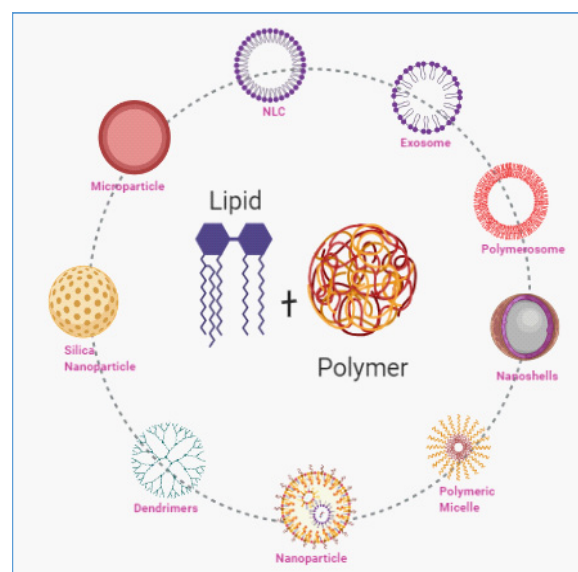

Figure 3: Depicting various nanocarriers formulated by amalgam of biopolymer and lipids.

Nanostructured lipid carriers

These NLCs are comprised of core structure with a blend of solid and liquid lipids with a surrounding shell of amphiphilic surfactants or phospholipids. They have the potential to load higher amounts of active molecules in addition to control the drug release at a better level [41-45]. For better physical stability and therapeutic efficiency, LNPs are administered as aqueous dispersions through hydrogel formulations (Figure 3) [45-50].

Hydrogels

Hydrogels, a promising area for drug delivery and tissue engineering has been utilizing biopolymers for better efficiency and advanced applications. Polysaccharide or protein-based natural hydrogels are useful in several biomedical applications like cardiovascular/orthopedic implantation, intravascular/urinary tract catheters, wound dressing, tissue engineering, biosensors, controlled release systems, etc [51-56]. Since the hydrogels alone are not able to handle the delivery of lipophilic drugs and are not well stabilized in the hydrophilic matrix, undergoes precipitation or aggregation or shows uncontrolled burst release, there is an advancement of merging the hydrogel with lipid nanoparticles to provide better encapsulation, stability and controlled release of lipophilic drugs [57]. Biopolymers, particularly polysaccharides are of special interest in the synthesis of hydrogels for biomedical applications. As they are naturally abundant, biodegradable, biocompatible, mucoadhesive, hydrophilic, accessible for modulation, polysaccharides are quite interesting in the development of hydrogels. However, hydrogels made of polysaccharides alone suffer from poor mechanical properties showing brittleness/fragility/degradation at physiological pH. As one alternative, the hydrogels are combined with LNPs to develop LNP polysaccharide-based hydrogel systems for the efficient delivery of drug molecules. It was reported that the most used biopolymers for the fabrication of LNP-polysaccharide hydrogels include chitosan, cellulose, xanthan gum, dextran, and alginate [58-60].

Liposomes

Liposomes are self-assembled vesicular bilayer systems prepared by using natural or synthetic lipids with hydrophobic nature within the bilayer and hydrophilic nature in the core. Liposomes can incorporate both the hydrophobic and hydrophilic drugs. Hydrophobic drugs can be loaded in the bilayer shell whereas the hydrophilic drugs can be loaded in the aqueous core [61-63]. On administration, the encapsulated drug(s) or bioactive(s) slowly come out of the bilayer into the surrounding environment thereby producing the sustained release of the agents [64-69]. Liposomes have plenty of advantages like they are suitable to load both hydrophobic and hydrophilic drugs, suitable for targeted drug delivery unlike conventional therapies causing adverse effects. Liposomes show better biodistribution of potent drugs at the site of action. They are promising carriers for several antibiotics increasing the uptake by resistant extracellular/intracellular pathogens. Improved pharmacokinetics has been achieved with the introduction of liposomes in drug delivery. The sustained-release rate of drugs is made possible with liposomes. Due to the usage of phospholipids, the biocompatibility and non-immunogenicity features are the positive factors for liposomes. Liposomes are also used as biomimicking models for cell membranes to do in vitro cell culture and in vivo model experiments which are found to be cost-effective alternatives. With all these interesting characteristics, liposomes are now a real commercialized carrier for drugs in the treatment of cancer, chronic bacterial/fungal infections, resistant lung infections, etc. [70]. However, scientists have observed certain disadvantages with the liposomes which include, leakage of encapsulated drugs, burst release in certain unfavourable conditions, short biological half-life (short biodistribution), low entrapment efficiency, high production cost, lack of stability due to oxidation or hydrolysis of lipids, batch to batch variation and difficulty in scale-up or production [74].

To overcome some of the disadvantages and make use of the existing positive features along with the enhancement of functions, the combination of liposomes with polymeric networks has been initiated by scientists. Over the last two decades, it's been promising research with the liposome-polymer hybrid systems. Both natural and synthetic polymers have been incorporated in the development of liposomal carrier systems to achieve desired outcomes. Researchers have developed liposomes and embedded in a polymer gel matrix to combine the properties of both the systems within the same network [75]. The initial attempt of embedding liposomes in the polymer gel matrix has been performed by Weiner et al. using a collagen matrix. Here there are no active connections between the liposomes and polymer gel matrix. It is the simplest way of combining the liposomes with polymer gel. Such an attempt has shown that the hybrid gel has prolonged the release of encapsulated hormones. Later several experiments were reported in a similar line with the combination of liposomes in biopolymer gels like gelatin, xanthan gum, chitosan, carboxymethylcellulose, and also of synthetic polymer gels like poly(acrylic) acid. Injectable biomaterials gained importance for their site-specific drug delivery [76].

To be suitable for injection, the gel should be in low viscous nature before and while injecting, whereas it should rapidly convert into an elastic gel at the site of administration. Hence, shear-thinning injections have been designed and developed by researchers. Upon injection of the drug-loaded gel at the site of the tumor, the anti-cancer drug gets released only at that site, and due to the sustained release effect shown by the liposome, the cytotoxic drug will not reach high levels in other areas of the body. In this way, the hybrid system of liposomes with biopolymer gels has gained importance in reducing the toxicity at healthy tissues, providing targeted therapy, and also minimizing the need for repeated injections [77-79]. Lee et al. reported the application of biopolymer connected liposomes over conventional liposomes for delivery of the anti-cancer agent, doxorubicin [98]. For this, the researchers have used the hydrophobically modified chitosan to connect the liposomes into a gel network through hydrophobic interactions. Liposomes are made up of Dipalmitoylphosphatidyl-Choline (DPPC) and 1,2-distearoylsn-glycero-3-phospho-ethanolamine-N-[methoxy(polyethylene glycol)-2000] (DSPE-PEG2000). Liposomes were prepared by film formation, lyophilization, sonication, and size exclusion chromatography. The drug loading of doxorubicin was done by incubation. The developed drug-loaded liposomes were reported to be in a size range of 100-150 nm.

Micelles

Lav et al. have developed solid phospholipid micelles containing bile salts and biopolymers for the improvement of oral bioavailability of the poorly soluble drug, cucurbitacin B, and also for its effective delivery. They developed the system as fast dissolving oral films using carboxymethyl chitosan or pullulan and PEG in different formulations. They have conducted the in vivo studies in rats and rabbits as animal models [80].

Applications in tissue engineering

Tissue engineering is meant for the regeneration of injured tissue and regeneration of a biologically valid articular surface [81-85]. The properties of the biomaterials used for such tissue engineering purpose shows a direct impact on the treatment strategies.

Future prospectus

With the existing reports and successful journey, there is a lot of scope for future progress utilizing the probabilities of a combination of biopolymer and lipid systems for better therapeutic efficiency with minimized or no adverse effects in treatment of gastric diseases. There is a need to understand the complete mechanism for the enhanced properties and optimization strategies. Applying the existing concepts in different routes of administration and different disease conditions has yet to be explored to identify the best-synchronized applications. Even with the high-end technologies available today, there is the least commercialization of the products which indicates that the research needs gear up in the right path that reaches the patient.

Conclusion

On their self-build properties, functionalized nanoparticles and lipid structures are readily adaptable systems those are tailored towards specific properties and functionalities. Basically, the combination of the two (biopolymer and lipid) systems into hybrid nanocarriers offer great design potentials for pharmaceutical and biomedical application. In the last ten years, the total studies based on the development of hybrid nanocarriers for pharmaceutical and biomedical purposes have grown exponentially and their outcomes are very helpful, lot more to be explored. Huge research is underway in the field of hybrid nanocarriers. Existing hybrid nanocarriers are even optimized for few clinical translations and with particular new nanomaterial fabricated, a hybrid nanocarrier designed with futuristic properties are outplayed. It is evident that hybrid nanocarriers would play key role in both the pharmaceutical and biomedicine in the coming years.

References

1. Gopi S, Amalraj A, Thomas S. Effective Drug Delivery System of Biopolymers Based On Nanomaterials and Hydrogels - A Review. Drug Des. 2016; 5: 129.

2. Rai M, Ingle AP, Gupta I, Brandelli A. Bioactivity of noble metal nanoparticles decorated with biopolymers and their application in drug delivery. International Journal of Pharmaceutics. 2015; 496: 159-172.

3. Crespilho FN, Lima FCA, da Silva ABF, Oliveira Jr ON, Zucolotto V. The origin of the molecular interaction between amino acids and gold nanoparticles: A theoretical and experimental investigation. Chemical Physics Letters. 2009; 469: 186-190.

4. Suresh T, Cheng FY, Su CH. Advancements in the Blood–Brain Barrier Penetrating Nanoplatforms for Brain Related Disease Diagnostics and Therapeutic Applications. Polymers. 2020; 12: 3055.

5. Naveen NR, Gopinath C, Kurakula M. Okra-thioglycolic acid conjugate-synthesis, characterization, and evaluation as a mucoadhesive polymer. Processes. 2020; 8; 316.

6. Anubhab Mukherjee, Ariana K Waters, Pranav Kalyan, Achal Singh Achrol, Santosh Kesari, Venkata Mahidhar Yenugonda. Lipid-polymer hybrid nanoparticles as a next-generation drug delivery platform: state of the art, emerging technologies, and perspectives. International Journal of Nanomedicine 2019:14, 1937-1952.

7. Farokhzad OC, Cheng J, Teply BA, et al. Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy in vivo. Proc Natl Acad Sci U S A. 2006; 103: 6315-6320.

8. Torchilin VP. Micellar nanocarriers: Pharmaceutical perspectives. Pharm Res. 2006; 24: 1-16.

9. Raghavendra Naveen N, Kurakula M, Gowthami B. Process optimization by response surface methodology for preparation and evaluation of methotrexate loaded chitosan nanoparticles. Materials Today: Proceedings. 2020.

10. Hosny KM, Alhakamy NA, Almodhwahi MA, Kurakula M, Almehmady AM, et al. Self-Nanoemulsifying System Loaded with Sildenafil Citrate and Incorporated within Oral Lyophilized Flash Tablets: Preparation, Optimization, and In Vivo Evaluation. Pharmaceutics. 2020; 12: 1124.

11. Zhang L, Chan JM, Gu FX, et al. Self-assembled lipid-polymer hybrid nanoparticles: A robust drug delivery platform. ACS Nano. 2008; 2: 1696-1702.

12. Kurakula M; Naveen NR. Electrospraying: A Facile Technology Unfolding the Chitosan based Drug Delivery and Biomedical Applications. European Polymer Journal. 2021; 110326.

13. Chan J, Zhang L, Yuet K, Liao G, Rhee J, et al. PLGA-lecithin-PEG coreshell nanoparticles for controlled drug delivery. Biomaterials. 2009; 30: 1627-1634.

14. Zhang L, Zhang L. Lipid polymer hybrid nanoparticles: synthesis, characterization, and applications. Nano Life. 2010; 1: 163-173.

15. Abdelhady S, Honsy KM, Kurakula M. Electro Spun-Nanofibrous Mats: A Modern Wound Dressing Matrix with a Potential of Drug Delivery and Therapeutics. Journal of Engineered Fibers and Fabrics. 2015; 10: 155892501501000.

16. Dave V, Tak K, Sohgaura A, Gupta A, Sadhu V, et al. Lipid-polymer hybrid nanoparticles: Synthesis strategies and biomedical Applications. Journal of Microbiological Methods. 2019; 160: 130-142

17. Kurakula M, Basim P. Biopolymer-Lipid Hybrid Composites and their Advances in Bio-imaging and Drug Delivery. J Radiol Med Imaging. 2021; 4: 1041.

18. Ahmed OAA, Kurakula M, Banjar ZM, Afouna MI, Zidan AS. Quality by design coupled with near infrared in formulation of transdermal glimepiride liposomal films. Journal of Pharmaceutical Sciences. 2015; 104: 2062–2075.

19. Alessandra L, Vitiello G. Understanding the nano-bio interfaces: Lipid-coatings for inorganic nanoparticles as promising strategy for biomedical applications." Frontiers in chemistry. 2019; 7: 343.

20. Moon JJ, Suh H, Polhemus ME, Ockenhouse CF, Yadava A.et al. Antigen-displaying lipid-enveloped PLGA nanoparticles as delivery agents for a plasmodium vivax malaria vaccine. PLoS One. 2012; 7: 1-9.

21. Alhakamy NA, Ahmed OAA, Kurakula M, Caruso G, Caraci F.et al. Chitosan-based microparticles enhance ellagic acid's colon targeting and proapoptotic activity. Pharmaceutics. 2020; 12: 1–14.

22. Mieszawska AJ, Gianella A, Cormode DP, Zhao Y, Meijerink A, et al. Engineering of lipid-coated PLGA nanoparticles with a tunable payload of diagnostically active nanocrystals for medical imaging. Chem. Commun. 2012; 48: 5835-5837.

23. Thevenot J, Troutier AL, Putaux JL, Delair T, Ladaviere C. Effect of the polymer nature on the structural organization of lipid/polymer particle assemblies. J Phys. Chem. 2008; 112: 13812-13822.

24. Alhakamy NA, Fahmy UA, Ahmed OAA, Caruso G, Caraci F, et al. Chitosan coated microparticles enhance simvastatin colon targeting and pro-apoptotic activity. Marine Drugs. 2020; 18: 226.

25. Pratap B, Haware RV, Dave RH. Tablet capping predictions of model materials using multivariate approach. International journal of pharmaceutics. 2019; 569: 118548.

26. Shi J, Xiao Z, Votruba AR, Vilos C, Farokhzad OC. Differentially charged hollow core/shell lipid-polymer-lipid hybrid nanoparticles for small interfering RNA delivery. Angew. Chem. Int. Ed. Eng. 2011; 123: 7165-7169.

27. Hasnain MS, Kiran V, Kurakula M, Rao GK, Tabish, M et al. Use of alginates for drug delivery in dentistry. In Alginates in Drug Delivery. 2020; 387–404.

28. Hu CMJ, Zhang L, Aryal S, Cheung C, Fang RH. Erythrocyte membrane camouflaged polymeric nanoparticles as a biomimetic delivery platform. Proc. Natl. Acad. Sci. 2011; 108: 10980-10985.

29. Siewert Christian D, Haas H, Cornet V, Nogueira SS, Nawroth T, et al. "Hybrid biopolymer and lipid nanoparticles with improved transfection efficacy for mRNA. 2020; 9: 2034.

30. Hasnain MS, Nayak AK, Kurakula M, Hoda MN. Alginate nanoparticles in drug delivery. In Alginates in Drug Delivery. 2020; 129–152.

31. Hosny KM, Aldawsari HM, Bahmdan RH, Sindi AM, Kurakula M, et al. Preparation, Optimization, and Evaluation of Hyaluronic Acid-Based Hydrogel Loaded with Miconazole Self-Nanoemulsion for the Treatment of Oral Thrush. AAPS PharmSciTech. 2019; 20: 297.

32. Lee SM, Chen H, Dettmer CM, O'Halloran TV, Nguyen SBT. Polymer caged liposomes: a pH-responsive delivery system with high stability. J. Am. Chem. Soc. 2007; 129: 15096-15097.

33. Murali VP, Fujiwara T, Gallop C, Wang Y, Wilson JA, et al. Modified electrospun chitosan membranes for controlled release of simvastatin. International Journal of Pharmaceutics. 2020; 584: 119438.

34. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery-A review of the state of the art. Eur. J Pharm. Biopharm. 2000; 50: 161-177.

35. Müller RH, Radtke M, Wissing SA. Nanostructured lipid matrices for improved microencapsulation of drugs. Int. J. Pharm. 2002; 242: 121-128.

36. Kurakula M, A Ahmed, T. Co-Delivery of Atorvastatin Nanocrystals in PLGA based in situ Gel for Anti-Hyperlipidemic Efficacy. Current Drug Delivery. 2015; 13: 211–220.

37. Puglia C, Bonina F. Lipid nanoparticles as novel delivery systems for cosmetics and dermal pharmaceuticals. Expert Opin. Drug Deliv. 2012; 9: 429-441.

38. Kurakula M, Rao GK, Yadav KS. Fabrication and characterization of polycaprolactone-based green materials for drug delivery. In Applications of Advanced Green Materials. 2021; 395-423.

39. Maleki AA, Dolati S, Ahmadi M, Baghbanzhadeh A, Asadi M, et al. Nanoparticles and cancer therapy: Perspectives for application of nanoparticles in the treatment of cancers. J Cell Physiol. 2019; 1-11.

40. Kurakula M, Ahmed OAA, Fahmy UA, Ahmed TA. Solid lipid nanoparticles for transdermal delivery of avanafil: Optimization, formulation, in-vitro and ex-vivo studies. Journal of Liposome Research. 2016; 26: 288–296.

41. Kim J, Ahn SI, Kim YT. Nanotherapeutics engineered to cross the blood-brain barrier for advanced drug delivery to the central nervous system, J. Ind. Eng. Chem. 2019; 73: 8-18.

42. Kurakula M, Gorityala S, Basim P. Rationalizing Nanodeliverables for Effective L-Asparaginase Delivery in Chemotherapy: Update 2020." Cancer Sci Res. 2021; 4: : 1-7.

43. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC) in cosmetic and dermatological preparations. Adv. Drug Deliv. Rev. 2002; 54: S131-S155.

44. Kurakula M, El-Helw AM, Sobahi TR, Abdelaal MY. Chitosan based atorvastatin nanocrystals: Effect of cationic charge on particle size, formulation stability, and in-vivo efficacy. International Journal of Nanomedicine. 2015; 10: 321–334.

45. Souto EB, Wissing SA, Barbosa CM, Müller RH. Evaluation of the physical stability of SLN and NLC before and after incorporation into hydrogel formulations. Eur. J Pharm. Biopharm. 2004; 58: 83-90.

46. Ghada Hussein N, Al-Hazmi FE, Kurakula M, Al-Dharrab AA, Mohamed Hosny K, et al. Zein coated zinc oxide nanoparticles: Fabrication and antimicrobial evaluation as dental aid. International Journal of Pharmacology. 2018; 14: 1051–1059.

47. Bhaskar K, Mohan CK, Lingam M, Mohan SJ, Venkateswarlu V, et al. Development of SLN and NLC Enriched Hydrogels for Transdermal Delivery of Nitrendipine: In Vitro and In Vivo Characteristics. Drug Dev. Ind. Pharm. 2009; 35: 98-113.

48. Kurakula M, Koteswara Rao GSN. Moving polyvinyl pyrrolidone electrospun nanofibers and bioprinted scaffolds toward multidisciplinary biomedical applications. European Polymer Journal. 2020; 136: 109919.

49. Salerno A, Pascual CD. Bio-based polymers, supercritical fluids and tissue engineering. Process Biochemistry. 2015; 50: 826-838.

50. Sadeghi M. Synthesis and swelling behaviors of graft copolymer based on chitosan-g-poly (AA-co-HEMA). International Journal of Chemical Engineering and Applications. 2010; 1: 352-354.

51. Kurakula M, Rao GK. Probiotics in Lung Cancer: An Emerging Field of Multifarious Potential and Opportunities. InProbiotic Research in Therapeutics. Springer, Singapore. 125-158.

52. Lee JH, Oh H, Baxa U, Raghavan SR, Blumenthal R. Biopolymer-Connected Liposome Networks as Injectable Biomaterials Capable of Sustained Local Drug Delivery. Biomacromolecules. 2012; 13: 3388–3394.

53. Kurakula M, Naveen NR, Yadav KS. Formulations for Polymer Coatings. Polymer Coatings. 2020; 415–443.

54. Torchilin VP. Nat. Rev. Drug Discovery. 2005: 4: 145–160.

55. Kurakula, M, Rao GK. Probiotics in Lung Cancer: An Emerging Field of Multifarious Potential and Opportunities. In Probiotic Research in Therapeutics. Springer, Singapore. 2021; 125-128.

56. Bangham AD, Hill MW, Miller NGA. Preparation and use of liposomes as models of biological membranes. Methods Membr Biol. 1973; 1: 1-68.

57. Kurakula M, Raghavendra Naveen N. In situ gel loaded with chitosan-coated simvastatin nanoparticles: Promising delivery for effective anti-proliferative activity against tongue carcinoma. Marine Drugs. 2020; 18: 201.

58. Lasic DD. Liposomes: from Physics to Applications. Amsterdam: Elsevier. 1993: 1-575.

59. Kono, K. Adv. Drug Delivery Rev. 2001; 53: 307–319.

60. Ruiz MA, Arias JL, Clares B, Morales ME, Gallardo V. Curr. Drug Targets. 2011; 12: 1151–1165.

61. Kurakula M, Rao GK, Kiran V, Hasnain MS, Nayak AK. Alginate-based hydrogel systems for drug releasing in wound healing. In Alginates in Drug Delivery. Elsevier. 2020; 323-358.

62. Basim P, Gorityala S, Kurakula M. Advances in Functionalized Hybrid Biopolymer Augmented Lipid-based Systems: A Spotlight on Their Role in Design of Gastro Retentive Delivery Systems. Biopolymers. 2021; 3: 4.

63. Webb SJ, Liem KP, Mart RJ. J. Am. Chem Soc. 2007; 129: 12080-12081.

64. Kurakula M, Rao GSNK. Pharmaceutical assessment of polyvinyl-pyrrolidone (PVP): As excipient from conventional to controlled delivery systems with a spotlight on COVID-19 inhibition. Journal of Drug Delivery Science and Technology. 2020; 60: 102046.

65. Plank C, Pradhan P, Giri J, Rieken F, Koch C, et al. Controlled Release. 2010; 142: 108–121.

66. Kurakula M, Sobahi TR, El-Helw A, Abdelaal MY. Development and validation of a RP-HPLC method for assay of atorvastatin and its application in dissolution studies on thermosensitive hydrogel-based nanocrystals. Tropical Journal of Pharmaceutical Research. 2014; 13: 1681–1687.

67. Kohane DS, Timko BP, Dvir T. Adv. Mater. 2010; 22: 4925–4943.

68. Alipour M, Omri A, Suntres ZE. Liposome-Entrapped Antibiotics: Recent Progress and Clinical Applications. In: Nanomedical Device and Systems Design: Challenges, Possibilities, Visions. Editors: Frank Boehm. 2013; 12.

69. Kurakula M, Srinivas C, Kasturi N, Diwan PV. Formulation and Evaluation of Prednisolone Proliposomal Gel for Effective Topical Pharmacotherapy. International Journal of Pharmaceutical Sciences and Drug Research. 2012; 4: 35.

70. Yadav D, Sandeep K, Pandey D, Dutta RK. Liposomes for Drug Delivery. J Biotechnol Biomater. 2017; 7: 276.

71. Weiner AL, Carpentergreen SS, Soehngen EC, Lenk RP, Popescu MC. J. Pharm. Sci. 1985; 74: 922–925.

72. Mallesh K, Pasula N, Kumar Ranjith CP. Piroxicam proliposomal gel: A novel approach for tropical delivery. Journal of Pharmacy Research. 2012; 5: 1755–1763.

73. Gabrijelcic V, Sentjurc M. Int. J. Pharm. 1995; 118: 207–212.

74. Pavelic Z, Skalko-Basnet N, Schubert R, Jalsenjak I. Methods Enzymol. 2004; 387: 287–299.

75. Kurakula M, Mohd AB, Rao PA, Diwan PV. Estimation of piroxicam in proliposomal formulation using RPHPLC method. Int. J. Chem. Anal. Sci. 2011; 2: 1193. 2011;1196.

76. DiTizio V, Karlgard C, Lilge L, Khoury AE, Mittelman MW, DiCosmo FJ. Biomed. Mater. Res. 2000; 51: 96–106.

77. Kurakula M, Naveen NR. Prospection of recent chitosan biomedical trends: Evidence from patent analysis (2009–2020). International Journal of Biological Macromolecules. 2020.

78. Pavelic Z, Skalko-Basnet N, Schubert R. Int. J. Pharm. 2001; 219: 139–149.

79. Gutowska A, Jeong B, Jasionowski M. Anat. Rec. 2001; 263: 342–349.

80. Venkatesh M, Mallesh, K. Self-Nano Emulsifying Drug Delivery System (Snedds) for Oral Delivery of Atorvastatin- Formulation and Bioavailability Studies. Journal of Drug Delivery and Therapeutics. 2013; 3: 131–140.

81. Popescu MT, Mourtas S, Pampalakis G, Antimisiaris SG, Tsitsilianis C. Biomacromolecules. 2011; 12: 3023–3030.

82. Kurakula M, Mohd AB, Samhuidrom AP, Diwan PV. Estimation of prednisolone in proliposomal formulation using RP HPLC method. Int. J. Res. Pharm. Biomed. Sci. 2011; 2: 663. 2011; 1669.

83. Luigi B, Gallarate M. Lipid nanoparticles: state of the art, new preparation methods and challenges in drug delivery." Expert opinion on drug delivery. 2012; 9: 2012: 497-508.

84. Wilczewska Agnieszka Z, Niemirowicz K, Markiewicz KH, Car H. Nanoparticles as drug delivery systems. Pharmacological reports. 2012; 64: 5: 1020-1037.

85. Anubhab M, Waters AK, Kalyan P, Achrol AS, Kesari S, aet al. Lipid–polymer hybrid nanoparticles as a next-generation drug delivery platform: state of the art, emerging technologies, and perspectives. International journal of nanomedicine. 2019; 14: 1937.

86. Beatriz GP, Porras-Alcalá C, Ortega-Rodríguez A, Sarabia F, Prados J, et al. Lipid-based nanoparticles: Application and recent advances in cancer treatment. Nanomaterials. 2019; 9: 638.