Whites Science
A Scientific Erudition

ROLE OF NANOCOMPOSITES IN DRUG DELIVERY – A REVIEW

Kapoor D[1]*, Vyas RB[1], Lad C[1], Patel M[1], Lal B[2]

[1]Dr. Dayaram Patel Pharmacy College, Sardar baug, Station Road, Bardoli, Dist – Surat, Gujarat, India, Pin-394601

[2]Sun Pharmaceuticals Limited, Haridwar, Uttarakhand.

ABSTRACT

Nanotechnology is one approach to overcome challenges of conventional drug delivery systems based on the development and fabrication of nanostructures. Some challenges associated with the technology as it relates to drug effectiveness, toxicity, stability, pharmacokinetics and drug regulatory control are discussed in this review. Clearly, nanotechnology is a welcome development that is set to transform drug delivery and drug supply chain management, if optimally developed. Electrospinning is a very simple and versatile process by which polymer nanofibers with di-ameters ranging from a few nanometers to sev-eral micrometers can be produced using an electrostatically driven jet of polymer solution or polymer melt. Significant progress has been made in this process throughout the past few years and electrospinning has advanced its ap-plications in many fields, including pharmaceu-tics. The limitations associated with the conventional therapeutics have intended the use of controlled drug delivery systems. In recent years, the hydrogel technology has been an integral part of human health care. The pharmaceutical industry has been developing hydrogel based drug delivery system in an advanced manner by tuning the structure, shape and surface modifications of the biopolymers. In the large field of nanotechnology, polymer matrix based nanocomposites have become a prominent area of current research and development. Exfoliated clay-based nanocomposites have dominated the polymer literature but there are a large number of other significant areas of current and emerging interest. This review will detail the technology involved with exfoliated clay-based nanocomposites and also include other important areas including barrier properties, flammability resistance, biomedical applications, electrical/electronic/optoelectronic applications and fuel cell interests.

KEYWORDS: Hydrogels, Drug delivery, Biomaterials, Electrospinning, Nanofibers Nanocomposites, Exfoliated clay.

INTRODUCTION

In the recent decades, polymers are extensively used as biomaterials due to their encouraging properties such as good biocompatibility, uncomplicated design and preparation, a diversity of structures and interesting bio-mimetic character. Especially in the field of elegant drug delivery, polymer played a noteworthy role because it can send therapeutic agents directly into the intended site of action, with better efficacy. The ideal requirements for designing nano-particulate delivery system are to effectively be controlled particle size, surface character; enhance permeation, flexibility, solubility and release of therapeutically active agents in order to attain the target and specific activity at a predetermined rate and time. The most of the polymeric nanoparticles with surfactants offer stability of various forms of active drugs and have useful to smart release properties. There are numerous biological applications have been reported for the nano-scale to micro-scale sized particles, such as site-targeted, controlled, and enhanced bioavailability of hydrophobic drugs. [1, 2, 3, 4]

Corresponding author:

Email: dev7200@gmail.com

In the area of nanotechnology, polymer matrix based nanocomposites have generated a important amount of attention in the recent literature. This area emerged with the acknowledgment that exfoliated clays could yield significant mechanical property advantages as a modification of polymeric systems. [5, 6] Polymers or microparticle-based hydrogels have been applied in dentistry and

periodontics in specific until now, which can affect the rate of release because of their structure, and so the development of more refined means of delivering medications at therapeutic levels to specific sites is an important clinical issue. [7, 8]

Electrospinning, firstly reported in 1934, has been used for more than 60 years, and yet is under developed in studying the fabrication of continuous nanofibers. The term "electrospinning", derived from "electrostatic spinning", was coined relatively recently. Since 1980s and especially in recent years, the electrospinning process has regained more awareness most likely due in part to a surging importance in nanotechnology, as ultrafine fibers or fibrous structures of various polymers with diameters in the submicron/nanometer range can be easily fabricated using this process. A schematic diagram demonstrating the process of electrospinning of polymer nanofibers is shown in Figure 1. There are basically three components: a high voltage supplier, a capillary tube with a pipette or needle of small diameter, and a metal collecting screen. In electrospinning a high voltage is used to create an electrically charged jet of polymer solution or melt out of the pipette. Before reaching the collecting screen, the solution jet evaporates or solidifies, and is collected as an interconnected web of small fibers. [9-14]

CLASSIFICATION OF HYDROGELS

The important parameters opted for the classification of hydrogels is the structure of hydrogels, route of synthesis, types of crosslink's. The differences in the properties are the consequences of the variation in any of the defined characteristics. Firstly, on the basis of route of their synthesis can be classified as:

- Homopolymer hydrogels (made up of only one type of hydrophilic monomer)
- Copolymer hydrogels or network gels (composed of two types of monomers)
- Mutipolymer hydrogels (made up of three types of monomers or inter penetrating polymeric network)

PREPARATION OF NANOPARTICLES

Nanocomposite hydrogels are synthesized as replica systems for in situ cured local drug delivery devices for the management of periodontal infections. The composite include the following components: nanoparticles, a matrix gel and the suitable antibacterial drug. The nanoparticles were obtained by free radical initiated copolymerization of monomers, 2- hydroxy methymethacrylate (HEMA) and polyethyleneglycoldimethacrylate in aqueous solution. The same monomers were used to prepare crosslinked matrices by photopolymerization. Nanocomposite hydrogels were obtained by mixing nanoparticles, monomers and the drug in aqueous solution then crosslinked by photopolymerization. These nanoparticles are suitable for incorporation into a hydrogel matrix and to design new drug delivery devices for dental and periodontal application.

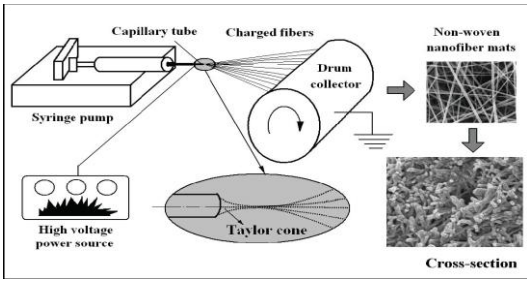

Figure 1: The process of electrospinning

Advantages of nanocomposites: [15]

- Highly dispersible in aqueous medium
- Uniform distribution of the active agent over an extended period of time
- Controlled release of the drug
- Reduces frequency of administration
- Augmented stability
- Penetrate regions inaccessible to other delivery systems

IMPORTANCE OF HYDROGELS AS DRUG DELIVERY SYSTEM

The word smart polymers originated from the ability of hydrogels to reproduce the non-linear response of DNA and Proteins. Above all the characteristic features of hydrogels, their behavior to adapt structural changes in response to various physical or chemical trigger and make them clever candidates for drug delivery system. The present drug delivery systems are grievous, unproductive and meddlesome. The discovery of Micro/ Nano Hydrogels provided insightful means of sustained drug delivery systems that unfold the above obstacles. Furthermore, the drug release kinetics may be submissive by modifying the shape, size and drug distribution of the hydrogels during assembling process. [16]

Antimicrobial enzyme:

Sathish kumar et al developed a system using hens' egg lysozyme (antimicrobial enzyme) which is attached to two types of polystyrene latex nanoparticles: positively charged, containing aliphatic amines surface groups and negatively charged, containing sulphate and chloromethyl surface group. These particles showed lower activity when compared to free enzymes, but can be explored for targeted antimicrobial activity.

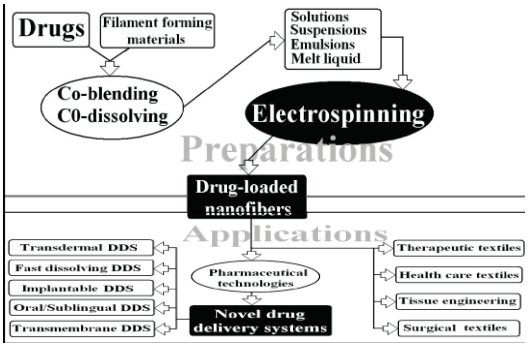

Figure 2: Preparation and application of electrospun drug loaded nanofibers

RECENT STATUS OF ELCTROSPUN NANOFIBRE BASED DRUG DELIVERY SYSTEM

Kenawy et al. Electrospun fiber mats were explored as drug delivery vehicles using tetracy-cline hydrochloride as a model drug. The mats were made either from poly (lactic acid) (PLA), poly (ethylenecovinyl acetate) (PEVA), or from a 50:50 blend of the two from chloroform solutions. Release profiles showed promising results when they were compared to a commercially available DDS--Actisite® (Alza Corpora-tion, Palo Alto, CA), as well as to the corresponding cast films. An early patent registered by Ignatious and Baldoni described electrospun polymer nanofibers for-pharmaceutical compositions, which can be designed to provide rapid, immediate, delayed, or modified dissolution, such as sustained and/or pulsatile release characteristics.[17, 18]

Tungprapa et al. prepared ultra-fine fiber mats of cellulose acetate (CA) for four different types of model drugs, i.e., naproxen (NAP), indomethacin (IND), ibuprofen (IBU), and su-lindac (SUL), from 16% w/v CA solutions in 2:1 v/v acetone/N,N-dimethylacetamide (DMAc) by electro-spinning. The amount of the drugs in the solutions was fixed at 20 wt% based on the weight of CA powder. No drug aggregates were observed on the surfaces of the fibers. The maximum release of the drugs from loaded fiber mats were ranked as follows: NAP>IBU>IND> SUL and this did not correspond to their solubility prop-erties. [19]

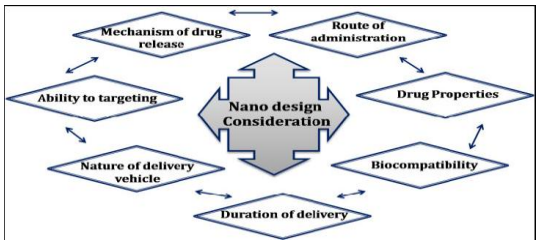

Figure 3. Requirements of several factors for simultaneous consideration to design a polymeric nanoparticle for the smart drug delivery system

Chew et al. investigated the feasibility of encapsu-lating human β-nerve growth factor (NGF) that was sta-bilized in the carrier protein, bovine serum albumin (BSA) in a copolymer of ε-caprolactone and ethyl eth-ylene phosphate. Partially aligned protein encapsulated fibers were obtained and the protein was found to be randomly dispersed throughout the electrospun fibrous mesh in an aggregated form. The sustained release of NGF by diffusion was obtained for at least 3 months. PC12 neurite outgrowth assay confirmed that the bioac-tivity of electrospun NGF was retained throughout the period of sustained release. [20]

Zhang et al. reported that degradable heparin-loaded poly (ε-caprolactone) fiber mats were successfully fabricated by electrospinning. The highly sulphated heparin hetropolymer remained homogenous in the spinning solution and was evenly distributed throughout the fab-ricated polymers. A sustained release of heparin could be achieved from the fibers over 14 days with the release diffusionally controlled over this period. The released heparin retained biological properties and functionality. [21]

The reward of employing electrospinning tech-nology to prepare drug delivery system are not as yet fully subjugated. Nanotechnology is now having a blow in biotechnology, pharmaceutical and medical diagnostics sciences. Nanodrugs are at the vanguard of bioengineering for diseases and symbolize the next generation of medical therapies that will bang worldwide markets and especially the healthcare industry. Furthermore electrospinning as noted before has gained more attention due in part

to a surging interest in nanotechnology, as ultrafine fibers or fibrous structures of various polymers with small diameters. On the other hand, electro-spinning should exert more influence on new DDS development through providing novel strategies for conceiving and fabricating them. [22, 23]

BIOENGINEERED MATERIALS

Nanoengines of drug delivery systems

Engineered materials have been utilized for developing smart drug delivery systems. Design and multi-functionalities fabricate of efficient smart drug delivery systems are vitally necessary for medicine and healthcare development. In the material science field provides biodegradable, biocompatible, environment-responsive, and highly effective novel polymeric system for targeted delivery. Nanotechnology provides bottom-up and top-down nanofabrication with size controlled and multi-functionality of particulate for targeted delivery. New materials invention and advanced technology have been synergistically achieved in drug delivery so far.

DIFFERENT TYPES OF NANOSTRUCTURES

Metallic nanoparticles

Metallic nanoparticles include iron oxide, gold, silver, gadolinium and nickel which have been studied for targeted cellular delivery. Gold exhibits favourable optical and chemical properties at nanoscale for biomedical imaging and therapeutic applications. It can be manipulated to obtain the desired size in the range of 0.8 to 200nm. The surface can be modified with different functional groups for gene transfection, modified into gene delivery vector by conjugation and also modified to target proteins and peptides to the cell nucleus. Gadolinium has been studied for enhanced tumour targeted delivery by modification of the nanoparticles with folate, thiamine and poly (ethylene glycol). Modification with folate was reported to enhance the recognition, internalization and retention of gadolinium nanoparticles in tumour cells. [25, 26, 27]

Carbon nanomaterials

These include carbon nanotubes and fullerenes. Fullerenes are carbon allotrope made up of 60 or more carbon atoms with a polygonal structure. Nanotubes have been used for their high electrical conductivity and excellent strength. These materials are being studied for therapeutic applications.

Ceramic nanoparticles

Ceramic nanoparticles are particles fabricated from inorganic compounds with porous characteristics such as silica, alumina and titania. They can be prepared with the desired size, shape and porosity. Their sizes are less than 100nm and are able to avoid uptake by the reticulo-endothelial system as foreign bodies. Entrapped molecules such as drugs, proteins and enzymes are protected from denaturation at physiological pH and temperature as neither swelling nor change in porosity occurs. [28]

Polymeric micelles

Micelles are formed when amphiphilic surfactant or polymeric molecules spontaneously associate in aqueous medium to form core-shell structures or vesicles. Polymeric micelles are formed from amphiphilic block copolymers, such as poly (ethylene oxide)-poly (benzyl-Laspartate) and poly (N-isopropylacrylamide) polystyrene, and are more stable than surfactant micelles in physiological solutions. They were first proposed as drug carriers about 24 years ago. The inner core of a micelle is hydrophobic which is surrounded by a shell of hydrophilic polymers such as poly ethylene glycol. Their hydrophobic core enables incorporation of poorly water soluble and amphiphilic drugs while their hydrophilic shell and size prolong their circulation time in the blood and increase accumulation in tumoural tissues. [29, 30]

FUTURE PERSPECTIVE

In the polymeric nanoparticle based drug therapy has to be improved by incorporating by the amalgamation therapies, Smart delivery has been achieved effectively in the case of cancer, but need to be concentrating more on other pathologies, also several challenges remain. From the material viewpoint, most of the elegant delivery systems mechanism do well in vitro studies but flops the in vivo studies. So the research has to be reconsidering to come up with uncomplicated, straightforward, well-organized and reasonably precise preparations with broadly applicable strategies, the pharmacologically active agent targeting to pathological sites, for the development of smart drug delivery systems. In technology vice the research has to spotlight into the fusion technologies. Although several specific specialized

technologies have been shown to in polymer synthesis, fictionalization, analysis, in vitro and in vivo study in the field of polymer science, the combinations of two or more techniques are regularly more effective than single technologies like a amalgamation of controlled radical polymerization with click chemistry. The fusion technologies can fulfill the various existing drawbacks of some individual technologies, and this has the high potentiality, synergistic enhancement in safest nanoparticle based drug delivery. Consider merging and adopting two or more right technologies for getting a high-throughput technology by selecting the right combinations is a fruitful area for research that is still largely unexplored.

CONCLUSION

The uses of biodegradable synthetic polymers have shown prominent results in drug delivery. Self assembled hydrogel and hydrogels for tumor targeting and imaging are to be explored at a greater pace. The valuable calculation of an efficient drug delivery systems in comparison to the development of newly found drug can profit both economically as well as drastically diminish the duration of time taken to develop a new drug in the pharmaceutical world. The key to improve the hydrogel technology is to direct the research on the design of efficient drug delivery systems with minimal limitations and easy route of administrations. Quite a lot of nanoparticle based drug delivery systems have been approved in clinical trials, some of them in under pre-clinical trial levels, this nanoparticle based system can provide the increased half-life, high biocompatibility, and minimum immunogenicity, site targeting and overcome the membrane barriers. Also the last era, major and new identifications have been significantly established in the smart material that alter its own structure and function in response to the environment. This performance has been used for the fabrication smart drug delivery systems, Smart polymer matrices release drugs by environment responses this system have been fruitfully achieved. In parallel the novel method of bottom-up and top-down nanofabrication technologies provided specifically controlled size and shaped nanoparticulate delivery system.

REFERENCES

1. Allemann, E., R. Gurny, E. Doelker, 1993. Drug-Loaded Nanoparticles: Preparation Methods and Drug Targeting Issues. European Journal of Pharmaceutics and Biopharmaceutics, 39(5):173-191.
2. Kawashima, Y., 2001. Nanoparticulate Systems for Improved Drug Delivery. Advanced Drug Delivery Reviews, 47(1):1-2.
3. Soppimath, K.S., T.M. Aminabhavi, A.R. Kulkarni, W.E. Rudzinski, 2001. Biodegradable Polymeric Nanoparticles as Drug Delivery Devices. Journal of Controlled Release, 70(1-2):1-20.
4. Panyam, J., V. Labhasetwar, 2003. Biodegradable Nanoparticle from Drug and Gene Delivery to Cells and Tissue. Advanced Drug Delivery Reviews, 55(3):329-347.
5. Brigger I., C. Dubernet, P. Couvreur, 2002. Nanoparticles in Cancer Therapy and Diagnosis. Advanced Drug Delivery Reviews, 54(5):631-651.
6. Cui, Z., R.J. Mumper, 2002. Plasmid DNA-Entrapped Nanoparticles Engineered from Microemulsion Precursors: In Vitro and In Vivo Evaluation. Bioconjugate Chemistry, 13(6):1319-1327.
7. Levy B.M., 1986. Is periodontitis a disease of the aged? *Gerodontology*, 5:101-107.
8. Page R.C., 1984.. Periodontal disease in the elderly: a critical evaluation of current information. Gerodontology, 3:63-70.
9. Doshi, J. and D.H. Reneker, 1995. Electrospinning process and applications of electrospun fibers, Electro-statics, 35:151-160.
10. Huang, Z.M., Y.Z. Zhang, M. Kotaki, S. Ramakrishna, 2003. A review on polymer nanofibers by electro-spinning applications in nanocomposites, Composites Science Technology, 63:2223-2253.
11. McKee, M.G., J.M. Layman, M.P. Cashion, E.L. Timothy, 2006. Phospholipid nonwoven electrospun mem-branes, Science, 311:353-355.
12. Kenawy, E.R., G.L. Bowlin, K. Mansfield, J. Layman, D.G. Simpson, E.H. Sanders,and G.E. Wnek, 2002. Release of tetracycline hydrochloride from electrospun poly (ethylene-co-vinylacetate), poly (lactic acid), and a blend, Journal of Control. Release, 81:57-64.

13. Ignatious, F., J.M. Baldoni, 2001.Electrospun pharma-ceutical compositions, WO Pat 0154667.

14. Tungprapa S., I. Jangchud, and P. Supaphol, 2007. Release characteristics of four model drugs from drug- loaded electrospun cellulose acetate fiber mats, Polymer, 48:5030-5041.

15. Goodson, J.M. et al., 1983. Monolithic tetracycline-containing fibres for controlled delivery to periodontal pockets. Journal of Periodontol, 54:575-579.

16. Bartold, P.M., C.A.G. McCulloch, A.S. Narayanan, S. Pitaru, 2000. Tissue engineering: a new paradigm for periodontal regeneration based on molecular and cell biology. Periodontol 2000, 24:253-269.

17. Satish K., C.V. Mattaparthi, 2011. Nividh Lysozyme: A model protein for amyloid research. Adv in Protein Chemistry and structural Biology, Vol 84 *[Book Chapter]*

18. Kenawy, E.R., G.L. Bowlin, , K. Mansfield, , J. Layman, , D.G. Simpson, E.H. Sanders, G.E. Wnek, 2002. Release of tetracycline hydrochloride from electrospun poly (ethylene-co-vinylacetate), poly(lactic acid), and a blend, Journal of Control release, 81:57-64.

19. Ignatious, F., J.M. Baldoni, 2001. Electrospun pharma-ceutical compositions, WO Pat 0154667.

20. Tungprapa, S., I. Jangchud, P.Supaphol, 2007. Release characteristics of four model drugs from drug- loaded electrospun cellulose acetate fiber mats, Polymer, 48:5030-5041.

21. Chew, S.Y., J. Wen, E.K.F. Yim, K.W. Leong, 2005. Sustained release of proteins from electrospun biode-gradable fibers, Biomacromolecules, 6:2017-2024.

22. Ramakrishna, S. 2006. Coaxial electrospinning of fluo-rescein isothiocyanate – conjugated bovine serum albu-min)–encapsulated poly (ε-caprolactone) nanofibers for sustained release, Biomacromolecules, 7, 1049-1057.

23. Devalapally, H., A. Chakilam, and M.M. Amiji, 2007. Role of nanotechnology in pharmaceutical product development, Journal of Pharmaceutical Sciences, 96, 2547-2565.

24. Rutledge, G.C. and S.V. Fridrikh, 2007. Formation of fibers by electrospinning, Advanced Drug Delivery Reveiw, 59, 1384-1391.

25. Medina, C., M.J. Santos-Martinez, A. Radomski, O.I. Corrigan, M.W. Radomski, 2007. Nanoparticles: Pharmacological and toxicological significance. British Journal of Pharmacology, 150: 552-558.

26. Rawat, M., D. Singh, S. Saraf, S. Saraf, 2006. Nanocarriers: promising vehicle for bioactive drugs. Biology Pharmaceutical Bulletin, 29(9): 1790-1798.

27. Penn, S.C., I. He, M.J. Natan, 2003. Nanoparticle for bioanalysis. Current Opinion in Chemical Biology, 7: 609-615.

28. Orive, G., R.M. Hernández, A.R. Gascón, J.L. Pedraz, 2005. Micro and nano drug delivery systems in cancer therapy. Cancer Therapy, 3: 131-138.

29. Liu J., T. Gong, H. Fu, C. Wang, X. Wang, Q. Chien, Q. Zhang, Q. He, Z. Zhang, 2008. Solid lipid nanoparticles for pulmonary delivery of insulin. International Journal of Pharmacetics, 356: 333-344.

30. Jones, M.C., J.C. Leroux, 1999. Polymeric micelles-a new generation of colloidal drug carriers. European Journal of Pharmaceutical Biopharm, 48(2): 101-111.