Chapter 9
Biodegradable Nanoparticles for Drug Delivery and Targeting

Viroj Wiwanitkit

Abstract The application of nano-biotechnology in pharmacology is very interesting. The nano-biotechnology can be applied in many steps including drug delivery and targeting. Several new nanoparticles are developed to serve those purposes. In this specific chapter, the author will focus on the biodegradable nanoparticles which can be automatic degraded. The application of biodegradable nanoparticles for drug delivery and targeting will be summarized and presented in this article. Summary on important reports on this topic is also provided in this article.

Keywords Nano-biotechnology · Pharmacology · Biodegradable nanoparticle Drug · Delivery · Targeting

1 Introduction

Nano-biotechnology is the novel biotechnology dealing with extremely small scale at nano-level (10^{-9}). The application of nano-biotechnology in pharmacology is very interesting. The basic concept is based on the biophysical property of the nanomaterials. In general, nanomaterials are usually very small. The extremely small size, at nanoscale, results in several specific properties of nanoparticles. The increased interaction surface and change in biophysical properties (such as electrical charge) can be observed. In addition, the extremely small size also implies the increased chance for passing to the passage. It is no doubt that the nanoparticles can pass or penetrate thorough many cellular pores and enter into the intracellular environment. There are many early evidences in nano-medicine studies confirming that nanoparticle can enter into several human cells such as leukocyte [1], lymphocyte

V. Wiwanitkit (✉)
DY Patil University, Pune, India

Joseph Ayobabalola University, Ilara-Mokin, Nigeria

Faculty of Medicine, University of Nis, Nis, Serbia

Hainan Medical University, Haikou, China

Y. V Pathak (ed.), *Surface Modification of Nanoparticles for Targeted Drug Delivery*, https://doi.org/10.1007/978-3-030-06115-9_9

[2], or renal cells [3]. As a consequence, the change of the mentioned cells after the invasion of the nanoparticle is also observable [1–3].

This means the nanoparticles can have effect within cells. Hence, if the nanoparticle is a kind of drug having pharmacological properties, it can be used as a very effective drug for management of illness in medicine. To achieve this purpose, the construction of the drug at the nano-level is the important step. This becomes the new area for pharmacological research and development. In general, the nanobiotechnology can be applied in many steps including drug delivery and targeting. Several new nanoparticles are developed to serve those purposes. In this specific chapter, the author will focus on the biodegradable nanoparticles which can be automatic degraded. The application of biodegradable nanoparticles for drug delivery and targeting will be summarized and presented in this article. Summary on important reports on this topic is also provided in this article.

2 How Can a Biodegradable Nanoparticle Act as Drug and Has Pharmacological Effect?

An important basic question in nano-medicine is "How can a nanoparticle be used as drug?" This question might be answered according to the already mentioned concept. First, there must be the drug molecule. This means there must be a specific nanoparticle that posed specific biochemical property that can be useful in disorder prevention or management. Then that specific nanoparticle will be called a nanodrug. The nanodrug usually has a very small size, and this very small molecular usually has more effectiveness in acting on cells. The second step that requires for completing the usage of nanoparticle as drug is the administration of the drug into the body. In general pharmacology, drug will not be useful if it is not administered into the body. For usage in human, there are many ways for administrations of drug such as intake by ingestion, inhalation, absorption via skin after dermatological application, absorption after dropping into the eye or ear, suppository into anal or vaginal canals, implantation, or injection (into blood vessel, subcutaneous fat, muscle, vertebral canal, or ocular cavity). This is also the necessary steps for using nanodrug. Nanodrug will be useless if it is not administered into the body. Hence, an important consideration of any newly developed nanodrug is the feasibility of administration. The specific method of administration of different drug is usually different. Focusing on nanodrug, the administration is usually not problematic. Due to the fact that nanodrug is very small, it can naturally be absorbed via normal skin barrier or directly inhaled and passed thorough lung alveoli.

The next step is similar to other drugs. The concern is usually on the bioavailability, pharmacostatics, pharmacokinetics, and pharmacodynamics. The general considerations on the newly available nanodrugs are on drug distribution and drug entering into the target cells. This is according to standard concept in pharmacology. A good nanodrug must be easily administered, absorbed, delivered into the target

cell, and induced desired pharmacological reaction. The described simple principles are applicable for any nanodrug including the specific nanodrug that is produced from biodegradable nanomaterial.

3 What Is a Biodegradable Nanomaterial?

Before, a further discussion on using biodegradable nanodrug, the details about degradable nanomaterial should be mentioned. Generally, degradable substance means a substance that can be degraded. The degrading can result in change of molecule. Erosion of the molecular structure during degradation and change of molecular property occur. Change in size, change and strength occur during degradation process. Finally, the complete disappearance of the molecule might be expected. A nanomaterial that can be degraded will be called a degradable nanomaterial. Automatic degradation is the expected property in using any degradable substance including to degradable nanosubstance. As already mentioned, the degradable process is similar to the catabolism in metabolic pathway. It will result in downing of the molecule and can finally result in ending of existence. Hence, the degradable nanomaterial will disappear without leftover; hence, it might be considered environmental-friendly substance.

There are many ways that a substance can undergo degradation. The mechanical degradation, the chemical degradation, or the biological degradation are the common types of degradation. The nanomaterials might be degraded by one the mentioned type of degradation. Nevertheless, in biological condition in the body, the spontaneous biological degradation is the most preferable type of degradation. This process is termed biodegradation. In biomedicine, biodegradation is a useful process that helps biotransform, recycle, and detoxify; hence, the substance with biodegradable property is more preferable than that one without this property. The biodegradation might be generated by enzymatic system within the body or by the microbial (such as bacteria and fungi) reaction. The proper might be aerobic and anaerobic condition, and it might occur intracellularly or extracellularly. In pharmacological use of nanomaterial, the autobiodegradation by the intracellular enzymatic process is the most preferable biodegradation. In cellular level, the interference of external factors such as temperature, water, or oxygen level is usually controlled, and the smooth biodegradation bioprocess can occur. This specific degradation is considered safe and does usually not induce any unwanted adverse effect.

The important consideration of biological degradation of a nanodrug is the time and place that the biodegradation occurs. A too early or tool late biodegradation is not preferable. In addition, the biodegradation must occur at the mot proper place, the target pathological site for allowing pharmacological reaction against the medical problem.

The degradability of the nanomaterial might be helpful in controlling of the releasing of the nanomaterial. In case that the nanodrug is designed in shell form, the degradability of the external shell core can be useful in controlling of the

releasing of the druggable part inside [4]. This is a very useful concept for new nanodrug design. The use of degradable nanocarrier is proven helpful in pharmaceutical process. How to prepare a good biodegradable nanomaterial is a basic question in nano-biotechnology. There are many factors that affect the preparation of degradable nanomaterials. Those factors include size of desired resulted nanoparticle, functionality and surface properties, releasing property of the outcome product, biocompatibility and degradability degree, and delivery material property [5].

4 Preparation of Biodegradable Nanomaterials for Use as Nanodrug

In preparation of degradable nanomaterials should focus on absorption, pharmacokinetics, and disposition [5–8]. The good absorption is usually the target. The preparation should result in the outcome with a favorable pharmacokinetics properties [5–8]. A less mentioned consideration in biodegradable nanomaterial preparation is on the toxicity. Jian et al. noted that biodegradable nanoscale preparations were commonly done at present, and there should be the concern on the toxicity [9]. The toxicity in nanoscale preparations is possible and strongly related to the preparation methodology [9]. Jian et al. concluded that there very many factors determining the toxicity of the biodegradable nanoscale preparations including to the particle size, shape, and surface structure [9]. The examples of the presently widely prepared degradable nanomaterials are liposome, micelle, and solid lipid nanoparticle (SLN) (Table 9.1).

Table 9.1 Some widely prepared degradable nanomaterials and details regarding preparation

Nanomaterials	Details
Liposome	Liposome is widely used nanomaterial at present. A liposome molecule has spherical shape and appears as a vesicle with at least one lipid bilayer. A liposome has a hydrophilic head group and hydrophobic hydrocarbon tail, hence, presents both hydrophobic and hydrophilic properties [10]. This bi-property helps ease distribution of liposome. It is considered as a useful soft nanocarrier. Barani and Montazer noted that the best character of liposomes was energy saving due to reduction in temperature of process [10]. Also, I considered the liposome environmental friendly since it is a degradable nanomaterial
SLN	SLN has a sufficient affinity with the biomembranes that can improve absorption by several administration routes (oral, transdermal, pulmonary, nasal, ocular, rectal, etc.) [8]. Qi et al. concluded that SLN was food for colloidal drug delivery systems due to the fact that SLN posed the nature of both the “soft” carriers (such as emulsions and liposomes) and non-soft polymeric nanoparticles [8]. Qi et al. noted that an oral SLN could enhance lymphatic absorption by either the chylomicron-association pathway or the M cell uptaking pathway [8]

As earlier mentioned, the preparation of biodegradable is complex and has many considerations during preparation. Due to the desired property, degradability, several biodegradable nanomaterials are produced and used in pharmacology at present. Dhiman et al. noted that different preparation techniques for biodegradable nanomaterials have different advantages and disadvantages [11]. Dhiman et al. found that biodegradable polymer usually had uncertainty in the absorption pathway in gastrointestinal tract [11]. Dhiman et al. also noted that there might be some harmful toxic by-products after metabolism occurred [11]. Dhiman et al. suggested that the use of synthetic or semisynthetic polymeric nanoparticles which had a defined structure might resolve the problem due to the molecule that was still in intact form till absorption in gastrointestinal tract [11]. Concerning the toxicity, the preparation of degradable nanomaterials with lipid composition might help decrease then problem [12]. The lipid nanoparticle is usually considered bioacceptable, and the high biodegradable nature results in little toxicity [12].

There are many interesting reports on preparation of biodegradable nanomaterials for using as nanodrugs. The important reports will be hereby summarized.

(a) Reports on in Oncology

The development of new nanodrug usually aims at management of presently untreatable diseases. The common focus is usually malignancy. The development of the degradable nanomaterial for management of cancer is widely done at present. Several newly developed biodegradables for use as new nanodrugs in oncology are proposed. For example, Cerqueira et al. developed biodegradable poly-lactic-co-glycolic acid (PLGA) nanoparticles surface engineered with hyaluronic acid for targeted delivery of paclitaxel to triple negative breast cancer cells [13]. Cerqueira et al. found that HA–PLGA nanoparticles could increase cellular uptake, when compared to non-coated PLGA nanoparticles, due to interaction of HA with CD44 receptors that result in a receptor-mediated endocytosis [13]. In another report by Zhang et al., the effect of autophagy inhibitors on drug delivery using biodegradable polymer nanoparticles in cancer treatment was investigated [14]. Zhang et al. found a new a new biological mechanism of malignant cells to have PLGA NPs captured and degraded by auto-lysosomes [14]. In another study, Kapoor et al. studied on intracellular delivery of peptide cargos using polyhydroxybutyrate-based biodegradable nanoparticles [15]. In this work, antitumor efficacy of BCL-2 converting peptide, NuBCP-9 was assessed, and it was concluded that this formulation might be a good alternative for tumor management [15]. In another recent publication, Aluri and Jayakannan reported on development of L-tyrosine-based enzyme-responsive amphiphilic poly(ester-urethane) nanocarriers for multiple drug delivery to neoplastic cells [16]. Aluri and Jayakannan mentioned for the specific advantage of this formulation that the drug-loaded L-tyrosine nanoparticles were stable extracellularly but enzymatic-biodegradable intracellular, which results in specific targeting on intracellular releasing of the drugs [16].

Based on the given examples, it might conclude that the biodegradable nanomaterials are effective option for cancer management. As concluded by

Zhao et al. [17], the biodegradable polymeric nanoparticles could be effectively used as a nanodrug delivery carrier [17]. The art on design of nanopolymer is the important determinant for the efficacy of the antitumor nanomolecule.

(b) Reports on in Ophthalmology

There are also some interesting reports on preparation of biodegradable nanomaterials as new nanodrugs in ophthalmology. For example, Bisht et al. reported on using nanoparticle-loaded biodegradable light-responsive in situ forming injectable implants for effective drug delivery to the posterior segment of the eye [18]. This study can confirm the usefulness of the degradable nanosubstance for help access to the hard-to-access part within the body. In another article, Salama et al. reported on success in using PLGA nanoparticles as subconjunctival injection for management of glaucoma in rabbit model [19]. In another report, Prakash and Dhesingh reported the success in using nanoparticle-modified drug-loaded biodegradable polymeric contact lenses for sustainable ocular drug delivery [20]. Finally, Salehi et al. recently reported the use of poly (glycerol sebacate)-poly (ε-caprolactone) (PEG–PCL) blend nanofibrous scaffold as intrinsic bio- and immunocompatible system for corneal repair [21]. These reports also confirm the usefulness of biodegradable nanomaterials in ocular disease management. Similar to the case of oncology, designing of a good nanopolymer is the important determinant for the success.

(c) Reports on in Neurology

There are also some interesting reports on preparation of biodegradable nanomaterials as new nanodrugs in neurology. For example, Mastorakos et al. reported on treatment of malignant brain tumor by biodegradable brain-penetrating DNA nanocomplexes [22]. This application is the same as the already mentioned one in the topic of clinical oncology. Ruan et al. reported another development on matrix metalloproteinase triggered size-shrinkable gelatin-gold fabricated nanoparticles for tumor microenvironment-sensitive penetration and diagnosis of glioma [23]. Similarly, this application is also the same as the already mentioned one in the topic of clinical oncology.

In fact, the application in non-oncology neurology is also reported in the medical literature. The good example is the report by Bi et al. on intranasal delivery of rotigotine to the brain with lactoferrin-modified PEG–PLGA nanoparticles for Parkinson's disease treatment [24]. The success use of same degradable nanomaterials in management of Parkinson's disease is also reported in another study by Hu et al. [25]. Focusing on another important neurodegenerative disorder, Alzheimer's disease, the role of degradable nanomaterials as nanodrugs is also reported [26–28]. A recent report by Sánchez-López et al. is the good example [26]. Sánchez-López et al. proposed for using pegylated biodegradable dexibuprofen nanospheres administration to APPswe/PS1dE9 as new potential strategies for Alzheimer's disease prevention [26]. Herran et al. also reported the observation on enhanced hippocampal neurogenesis in APP/Ps1 mouse model of Alzheimer's disease after implantation of VEGF-loaded PLGA nanospheres which implies the possible role of the mentioned nanomaterial in treatment of

Alzheimer's disease [27]. Finally, the development of PLGA-functionalized quercetin nanoparticles as possible effective nanomaterials for management of Alzheimer's disease is also reported by Sun et al. [28].

In fact, the use of degradable nanomaterials for management of degenerative neurological disorder is the new concept in clinical neurology. It is also the new hope to use degradable nanomaterials combining with gene therapy as an effective novel treatment of the previously untreatable neurodegenerative disorder [29, 30].

(d) Reports on in HIV Medicine

Human immunodeficiency virus (HIV) infection is still the global public health problem at present. There is still no effective treatment that can cure HIV infection. The use of nanomedical technology is the new hope for management of HIV. There are some interesting reports on using degradable nanomaterials in HIV medicine. For example, Mohideen et al. reported on development of degradable bioadhesive nanoparticles for prolonged intravaginal delivery and retention of elvitegravir [31]. In another study, Caizhen et al. reported on using zirconium phosphatidylcholine-based nanocapsules as an in vivo degradable drug delivery system of a momordica anti-HIV protein, MAP 30 [32].

(e) Reports on in Obstetrics and Gynecology

There are also some interesting reports on preparation of biodegradable nanomaterials as new nanodrugs in obstetrics and gynecology. For example, Luo et al. observed the efficient inhibition of ovarian cancer by degradable nanoparticle-delivered survivin T34A gene [33]. This application is also the same as the already mentioned one in the topic of clinical oncology. For non-oncology problem, the use of degradable nanomaterials to promote the efficacy of anti-HIV drug in HIV-infected mother as earlier mentioned is a good example.

(f) Reports on Infectious Medicine

There are also some interesting reports on preparation of biodegradable nanomaterials as new nanodrugs in infectious medicine. Apart from the already mentioned reports in HIV infection, the good example is the report by Zhang et al. Zhang et al. reported on the use of degradable polyphosphoester-based silver-loaded nanoparticles as therapeutics for bacterial lung infections in complicated case with underlying cystic fibrosis [34]. In another study, Wang et al. reported the development of an anti-infection nano-hydroxyapatite drug delivery microsphere and its drug release in vitro [35]. Wang et al. found favorable drug release and observed good efficacy of the nanoformulation in management of osteomyelitis, the deep bone infection [35].

Based on the mentioned application in clinical medicine, it can summarize that the present trend of using degradable nanomaterial preparation is for the management of the disease that is non-curable by presently available method or management of the pathology sit at hard-to-access position. The complex biodegradable is usually designed and prepared to serve the different specific needs in treatment of different clinical problems. This is the specific property of polymeric nanocomplex

that is superior to moneric nanocomplex in using as nanodrugs for management of clinical disorder in medicine. The use of advance nanotechnology for preparation or nanoformation of the drug is widely studied in the present day. Several new techniques are developed. The good example is the nanoprecipitation and nanoencapsulation techniques that help assemble the hydrophobic and hydrophilic compartments within molecule to form the final biodegradable nanomaterial product [36].

5 Drug Delivery by Biodegradable Nanoparticles

Drug delivery is an important step that determines the success of pharmacotherapy. The effective drug delivery is required for any treatment. Delivery of the drug should be focused since it is administered into the body until it reaches the target site. The issue on drug delivery by biodegradable nanomaterial substance is very interesting. The smooth delivery without any loss on the way transporting to the target site is the ideal concept. To achieve the successful delivery, the design of good nanodrug complex is very important. The good designed nanodrug should be small, easily transported in vivo, resistant to external insult during transportation, and nontoxic to the in vivo environment during the in vivo biotransportation process to the pharmacological target. The confirmation for these desirable properties of any newly developed nanomaterials is required.

The nanoformulation that is widely used for drug delivery includes the use of nanodisks, high-density lipoprotein (HDL) nanostructures, liposomes, and gold nanoparticles [37]. With the advancement in nanomaterial complex design, the next important step of modification in drug delivery is the integrating of other therapeutic stimulation systems such as such as triggered release, multicomponent therapies, theranostics, or gene delivery system [38]. The apparent advantages of nanoparticles for drug delivery are ability to carry delivery of water-insoluble substances, ability to target the pathological site, ability to co-deliver more than one drug for pharmacological combination therapy, and visualization of the drug delivery site by combining nanoimaging system [36]. Hence, the use of the nanodrug delivery system technology can increase the effectiveness of drug transportation to the pharmacological target with reduction on the loss of drug during the transportation pathway and can help solve the problem of multidrug resistance and increase drug targeting, which means increased efficacy and effectiveness of pharmacological treatment [37]. The research and development of the new nanocompositions and nanoformulation technology is useful for further development of new modalities for management of several untreatable medical disorders such as cancerous diseases, neurodegenerative disease, and HIV infection (Table 9.2).

Table 9.2 Some widely used compositions of nanomaterial polymer for drug delivery

Compositions	Details
PEG–PCL [38]	PEG–PCL can help increase drug accumulation at the site of therapeutic action; therefore, PEG–PCL use results in decreased off-target effects [38]. The example of drug delivery that this system is used is the delivery of doxorubicin [39]
PCL–PEG–PCL [40]	PCL–PEG–PCL is an important composition for forming core cross-linked micelle for drug delivery [40]. The example of drug delivery that this system is used is the delivery of doxorubicin [40] and honokiol [41]
PEG–PCL–PEG [40]	PEG–PCL–PEG or PECE is another important composition for forming core cross-linked micelle for drug delivery [40]. PECE is proven safe and can be used intravenously [40]. The PECE becomes the new composition for the new anticancerous drug development at present [40]
PEG-block-poly(D,L-lactic acid) (PEG-*b*-PLA) [42]	PEG-block-poly(D,L-lactic acid) (PEG-*b*-PLA) is another important composition for forming core cross-linked micelle for drug delivery aiming at transportation of poorly water-soluble drug [42]. It is presently used for development of anticancerous drug [42]
Poly(D,L-lactic-co-glycolic acid)-block-PEG-block-poly(D,L-lactic-co-glycolic acid) (PLGA-*b*-PEG-*b*-PLGA) [42]	PLGA-*b*-PEG-*b*-PLGA is another important composition for forming core cross-linked micelle for drug delivery aiming at transportation of both poorly water-soluble and water-soluble drugs [42]. The ability to deliver both water-soluble and water-non-soluble drug makes PLGA-*b*-PEG-*b*-PLGA superior to PEG-*b*-PLA [42, 43]. It is presently used for development of anticancerous drug [42]
Poly-lactic acid–PEG (PLA–PEG) [44]	Similar to PEG–PLC, PLA-PEG is another important composition that can help increase drug accumulation at the site of therapeutic action; therefore, PLA–PCL use results in decreased off-target effects [44]
PLA-D-α-tocopheryl polyethylene glycol 1000 succinate (PLA–TPGS) [44]	PLA–TPGS or PLA–vitamin E is another important composition that can help increase drug accumulation at the site of therapeutic action; therefore, PLA–TPGS use results in decreased off-target effects [44]
PCL–TPGS [45]	PCL–TPGS is another important composition that is under study regarding its efficacy in increased cytotoxic effect to the target malignant cells [45]

6 Targeting by Biodegradable Nanoparticles

The important step that determines the success of pharmacotherapy is the attacking to the problematic site. The ideal aim is the specific correctly hit to the pathological site. This means there must be both precision and accuracy in treatment. The targeting becomes the new concept in modern pharmacotherapy. Using the nanomedical technology, increasing accuracy and specificity of drug management can be expected.

The last step for finalizing the overall process is the biodegradation of the nanodrug within the target cell. The good nanodrug must be auto-degraded when it reaches the final destination in the pathological site. The favorable environmental-friendly degradation process is the biological process. This is usually a simple biochemical enzymatic reaction that occurs intracellularly. The biodegradation process should be simple, easily to occur and cause no toxic by-product or problematic adverse consequence. With the use of the new technology, the success for approach to hard-to-access areas such as central nervous system [12] and intraarticular area [46] is possible. The feasibility of approach of those mentioned site is usually due to the lipid composition of the newly designed biodegradable nanomaterials [12, 46]. The technology can help target and manage of difficult-to-treat medical diseases such as malignancies [47] and intracellular infections (e.g., toxoplasmosis [48]).

7 Presently Available Degradable Nanodrugs in Clinical Medicine

As already mentioned, the development of biodegradable nanomaterials as nanodrugs is useful in clinical medicine. Several attempts on clinical trials have been done for a few years, and there are already some success and available nanodrugs.

(a) Liposomal Amphotericin B

Liposomal amphotericin B is presently available antiparasitic drug that is indicated for treatment of leishmaniasis [49]. This drug is based on liposomal nanoformulation, which is a well-known technique for construction of biodegradable nanomaterials [50]. Carrillo-Muñoz et al. performed a comparative study and found that the liposomal amphotericin B was more effective than classical drug and increased the success in drug targeting [51].

(b) Liposomal Doxorubicin

Liposomal doxorubicin is presently available anticancerous drug that was recently developed based on liposomal technology [52]. Similar to liposomal amphotericin B, liposomal doxorubicin is based on liposomal nanoformulation, which is a well-known technique for construction of biodegradable nanomaterials [52]. This drug is presently available and commercially known as Caelyx(®)/Doxil(®). In clinical trial, it was proven and found that the liposomal doxorubicin was more effective than classical drug and increased the success in drug targeting [53].

(c) Liposomal Bupivacaine

Liposomal bupivacaine is presently available drug for anesthesiology purpose that was recently developed based on liposomal technology [54]. Similar to liposomal amphotericin B and liposomal doxorubicin, liposomal bupivacaine is based on liposomal nanoformulation, which is a well-known technique for construction of biodegradable nanomaterials. This drug is presently available and commercially known as Exparel(®). In clinical trial, it was proven that

found that the liposomal doxorubicin was more effective than classical drug and increased the success in drug targeting [54, 55]. However, the clinical trial showed an important adverse effect, cardiac side effect, of the new liposomal bupivacaine [55]. Viscusi et al. found that the side effect was observable in less than 1% and usually mild [55]. Nevertheless, this finding indicates the need for further improvement of the presently available bupivacaine drug.

8 Conclusion

The biodegradable nanomaterials can be used as nanodrugs for management of several medical problems. The design of biodegradable nanomaterials has to be carefully done, and there must be the concern on the desired product and possible toxicity. The effectivity of the nanoformulation starts from the nanodrug design thorough the nanodrug administration, nanodrug delivery, targeting, and pharmacological acting. The nanodrug becomes the hope for management of incurable disease (such as cancers) and effective approach to hard-to-access pathological sites (such as the brain, intraocular space, intraarticular space). The good biodegradable nanomaterials should be stable extracellular before reaching the final target and easily biologically degraded intracellularly at the target site. Several nanoformulations can be used for preparation of biodegradable nanomaterials. Different compositions of the new nanopolymer complexes are developed and proven differences in advantages. Some newly developed biodegradable nanomaterials are already registered as new commercially available drug for use in clinical practice [56]. Although there are many reports on the development and use of biodegradable nanomaterials in clinical medicine, further researches and developments in this area are still required. Finally, the diagram presenting biodegradable nanomaterials as nanodrugs for management of medical disorder in clinical medicine is shown in Fig. 9.1.

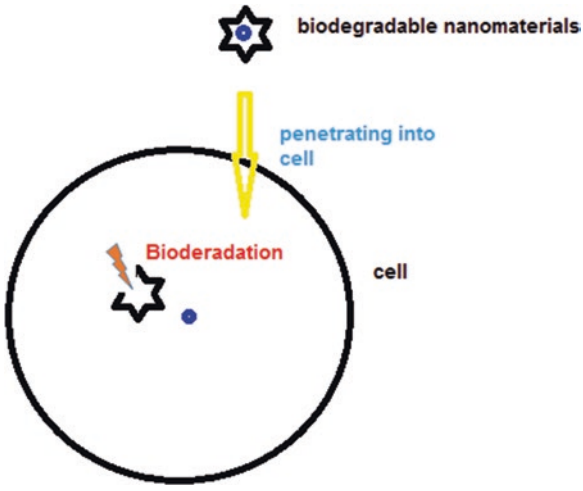

Fig. 9.1 The diagram presenting biodegradable nanomaterials as nanodrugs for management of medical disorder in clinical medicine (graphic drawing by Wiwanitkit V, 2018)

Conflict of Interest None.

References

1. Wiwanitkit, V., Sereemaspun, A., & Rojanathanes, R. (2009). Effect of gold nanoparticle on the microscopic morphology of white blood cell. *Cytopathology, 20*(2), 109–110.
2. Wiwanitkit, V., Sereemaspun, A., & Rojanathanes, R. (2009). Identification of gold nanoparticle in lymphocytes: A confirmation of direct intracellular penetration effect. *Turkish Journal of Haematology, 26*(1), 29–30.
3. Sereemaspun, A., Rojanathanes, R., & Wiwanitkit, V. (2008). Effect of gold nanoparticle on renal cell: An implication for exposure risk. *Renal Failure, 30*(3), 323–325.
4. Wan, W. K., Yang, L., & Padavan, D. T. (2007). Use of degradable and nondegradable nanomaterials for controlled release. *Nanomedicine (London, England), 2*(4), 483–509.
5. Wang, C., Wang, J., Chen, T., Luo, Z., Yang, X., Pan, X., et al. (2012). Absorption, pharmacokinetics and disposition of biodegradable nanoscale preparations. *Current Drug Metabolism, 13*(4), 429–439.
6. Lin, Y., & Qian, Z. (2012). Absorption, pharmacokinetics and disposition of biodegradable nanoscale preparations. *Current Drug Metabolism, 13*(4), 337.
7. Lu, Y., Qi, J., & Wu, W. (2012). Absorption, disposition and pharmacokinetics of nanoemulsions. *Current Drug Metabolism, 13*(4), 396–417.
8. Qi, J., Lu, Y., & Wu, W. (2012). Absorption, disposition and pharmacokinetics of solid lipid nanoparticles. *Current Drug Metabolism, 13*(4), 418–428.
9. Jian, F., Zhang, Y., Wang, J., Ba, K., Mao, R., Lai, W., et al. (2012). Toxicity of biodegradable nanoscale preparations. *Current Drug Metabolism, 13*(4), 440–446.
10. Barani, H., & Montazer, M. (2008). A review on applications of liposomes in textile processing. *Journal of Liposome Research, 18*(3), 249–262.
11. Dhiman, B., Divtrannum, D. A., & Saini, S. (2017). An appraisal on various methods of nano particulate formulations. *Pharmaceutical Nanotechnology, 5*(4), 255–262.
12. Shankar, R., Joshi, M., & Pathak, K. (2018, June 10). Lipid nanoparticles: A novel approach for brain targeting. *Pharmaceutical Nanotechnology, 6*(2), 81–93. https://doi.org/10.2174/2211738506666180611100416. [Epub ahead of print].
13. Cerqueira, B. B. S., Lasham, A., Shelling, A. N., & Al-Kassas, R. (2017). Development of biodegradable PLGA nanoparticles surface engineered with hyaluronic acid for targeted delivery of paclitaxel to triple negative breast cancer cells. *Materials Science and Engineering. C, Materials for Biological Applications, 76*, 593–600.
14. Zhang, X., Dong, Y., Zeng, X., Liang, X., Li, X., Tao, W., et al. (2014). The effect of autophagy inhibitors on drug delivery using biodegradable polymer nanoparticles in cancer treatment. *Biomaterials, 35*(6), 1932–1943.
15. Kapoor, S., Gupta, D., Kumar, M., Sharma, S., Gupta, A. K., Misro, M. M., et al. (2016). Intracellular delivery of peptide cargos using polyhydroxybutyrate based biodegradable nanoparticles: Studies on antitumor efficacy of BCL-2 converting peptide, NuBCP-9. *International Journal of Pharmaceutics, 511*(2), 876–889.
16. Aluri, R., & Jayakannan, M. (2017). Development of l-tyrosine-based enzyme-responsive amphiphilic poly(ester-urethane) nanocarriers for multiple drug delivery to cancer cells. *Biomacromolecules, 18*(1), 189–200.
17. Zhao, K., Li, D., Shi, C., Ma, X., Rong, G., Kang, H., et al. (2016). Biodegradable polymeric nanoparticles as the delivery carrier for drug. *Current Drug Delivery, 13*(4), 494–499.
18. Bisht, R., Jaiswal, J. K., & Rupenthal, I. D. (2017). Nanoparticle-loaded biodegradable light-responsive in situ forming injectable implants for effective peptide delivery to the posterior segment of the eye. *Medical Hypotheses, 103*, 5–9.

19. Salama, H. A., Ghorab, M., Mahmoud, A. A., & Abdel Hady, M. (2017). PLGA nanoparticles as subconjunctival injection for management of glaucoma. *AAPS PharmSciTech, 18*(7), 2517–2528.
20. Prakash, M., & Dhesingh, R. S. (2017). Nanoparticle modified drug loaded biodegradable polymeric contact lenses for sustainable ocular drug delivery. *Current Drug Delivery, 14*(4), 555–565.
21. Salehi, S., Czugala, M., Stafiej, P., Fathi, M., Bahners, T., Gutmann, J. S., et al. (2017). Poly (glycerol sebacate)-poly (ε-caprolactone) blend nanofibrous scaffold as intrinsic bio- and immunocompatible system for corneal repair. *Acta Biomaterialia, 50*, 370–380.
22. Mastorakos, P., Zhang, C., Song, E., Kim, Y. E., Park, H. W., Berry, S., et al. (2017). Biodegradable brain-penetrating DNA nanocomplexes and their use to treat malignant brain tumors. *Journal of Controlled Release, 262*, 37–46.
23. Ruan, S., He, Q., & Gao, H. (2015). Matrix metalloproteinase triggered size-shrinkable gelatin-gold fabricated nanoparticles for tumor microenvironment sensitive penetration and diagnosis of glioma. *Nanoscale, 7*(21), 9487–9496.
24. Bi, C., Wang, A., Chu, Y., Liu, S., Mu, H., Liu, W., et al. (2016). Intranasal delivery of rotigotine to the brain with lactoferrin-modified PEG-PLGA nanoparticles for Parkinson's disease treatment. *International Journal of Nanomedicine, 11*, 6547–6559.
25. Hu, K., Shi, Y., Jiang, W., Han, J., Huang, S., & Jiang, X. (2011). Lactoferrin conjugated PEG-PLGA nanoparticles for brain delivery: Preparation, characterization and efficacy in Parkinson's disease. *International Journal of Pharmaceutics, 415*(1–2), 273–283.
26. Sánchez-López, E., Ettcheto, M., Egea, M. A., Espina, M., Calpena, A. C., Folch, J., et al. (2017). New potential strategies for Alzheimer's disease prevention: Pegylated biodegradable dexibuprofen nanospheres administration to APPswe/PS1dE9. *Nanomedicine, 13*(3), 1171–1182.
27. Herran, E., Perez-Gonzalez, R., Igartua, M., Pedraz, J. L., Carro, E., & Hernandez, R. M. (2015). Enhanced hippocampal neurogenesis in APP/Ps1 mouse model of Alzheimer's disease after implantation of VEGF-loaded PLGA nanospheres. *Current Alzheimer Research, 12*(10), 932–940.
28. Sun, D., Li, N., Zhang, W., Zhao, Z., Mou, Z., Huang, D., et al. (2016). Design of PLGA-functionalized quercetin nanoparticles for potential use in Alzheimer's disease. *Colloids and Surfaces. B, Biointerfaces, 148*, 116–129.
29. Bangde, P., Atale, S., Dey, A., Pandit, A., Dandekar, P., & Jain, R. (2017). Potential gene therapy towards treating neurodegenerative diseases employing polymeric nanosystems. *Current Gene Therapy, 17*(2), 170–183.
30. Huang, R., Ma, H., Guo, Y., Liu, S., Kuang, Y., Shao, K., et al. (2013). Angiopep-conjugated nanoparticles for targeted long-term gene therapy of Parkinson's disease. *Pharmaceutical Research, 30*(10), 2549–2559.
31. Mohideen, M., Quijano, E., Song, E., Deng, Y., Panse, G., Zhang, W., et al. (2017). Degradable bioadhesive nanoparticles for prolonged intravaginal delivery and retention of elvitegravir. *Biomaterials, 144*, 144–154.
32. Caizhen, G., Yan, G., Ronron, C., Lirong, Y., Panpan, C., Xuemei, H., et al. (2015). Zirconium phosphatidylcholine-based nanocapsules as an in vivo degradable drug delivery system of MAP 30, a momordica anti-HIV protein. *International Journal of Pharmaceutics, 483*(1–2), 188–199.
33. Luo, L., Du, T., Zhang, J., Zhao, W., Cheng, H., Yang, Y., et al. (2016). Efficient inhibition of ovarian cancer by degradable nanoparticle-delivered survivin T34A gene. *International Journal of Nanomedicine, 11*, 501–512.
34. Zhang, F., Smolen, J. A., Zhang, S., Li, R., Shah, P. N., Cho, S., et al. (2015). Degradable polyphosphoester-based silver-loaded nanoparticles as therapeutics for bacterial lung infections. *Nanoscale, 7*(6), 2265–2270.
35. Wang, Y. F., Jin, A. M., Wei, K., Wang, X. D., Tang, S. H., & Min, S. X. (2006). Development of an anti-infection nano-hydroxyapatite drug delivery microsphere and its drug-release in vitro. *Nan Fang Yi Ke Da Xue Xue Bao, 26*(6), 754–756.

36. Martínez Rivas, C. J., Tarhini, M., Badri, W., Miladi, K., Greige-Gerges, H., Nazari, Q. A., et al. (2017). Nanoprecipitation process: From encapsulation to drug delivery. *International Journal of Pharmaceutics, 532*(1), 66–81.
37. Ho, B. N., Pfeffer, C. M., & Singh, A. T. K. (2017). Update on nanotechnology-based drug delivery systems in cancer treatment. *Anticancer Research, 37*(11), 5975–5981.
38. Grossen, P., Witzigmann, D., Sieber, S., & Huwyler, J. (2017). PEG-PCL-based nanomedicines: A biodegradable drug delivery system and its application. *Journal of Controlled Release, 260*, 46–60.
39. Gou, M., Zheng, X., Men, K., Zhang, J., Zheng, L., Wang, X., et al. (2009). Poly(epsilon-caprolactone)/poly(ethylene glycol)/poly(epsilon-caprolactone) nanoparticles: Preparation, characterization, and application in doxorubicin delivery. *The Journal of Physical Chemistry. B, 113*(39), 12928–12933.
40. Zhang, J., Men, K., Gu, Y., Wang, X., Gou, M., Guo, G., et al. (2011). Preparation of core cross-linked PCL-PEG-PCL micelles for doxorubicin delivery in vitro. *Journal of Nanoscience and Nanotechnology, 11*(6), 5054–5061.
41. Gou, M., Zheng, L., Peng, X., Men, K., Zheng, X., Zeng, S., et al. (2009). Poly(epsilon-caprolactone)-poly(ethylene glycol)-poly(epsilon-caprolactone) (PCL-PEG-PCL) nanoparticles for honokiol delivery in vitro. *International Journal of Pharmaceutics, 375*(1–2), 170–176.
42. Cho, H., Gao, J., & Kwon, G. S. (2016). PEG-b-PLA micelles and PLGA-b-PEG-b-PLGA sol-gels for drug delivery. *Journal of Controlled Release, 240*, 191–201.
43. Cho, H., & Kwon, G. S. (2014). Thermosensitive poly-(d,l-lactide-co-glycolide)-block-poly(ethylene glycol)-block-poly-(d,l-lactide-co-glycolide) hydrogels for multi-drug delivery. *Journal of Drug Targeting, 22*(7), 669–677.
44. Vijayakumar, M. R., Muthu, M. S., & Singh, S. (2013). Copolymers of poly(lactic acid) and D-α-tocopheryl polyethylene glycol 1000 succinate-based nanomedicines: Versatile multifunctional platforms for cancer diagnosis and therapy. *Expert Opinion on Drug Delivery, 10*(4), 529–543.
45. Suksiriworapong, J., Phoca, K., Ngamsom, S., Sripha, K., Moongkarndi, P., & Junyaprasert, V. B. (2016). Comparison of poly(ε-caprolactone) chain lengths of poly(ε-caprolactone)-co-d-α-tocopheryl-poly(ethylene glycol) 1000 succinate nanoparticles for enhancement of quercetin delivery to SKBR3 breast cancer cells. *European Journal of Pharmaceutics and Biopharmaceutics, 101*, 15–24.
46. Chuang, S. Y., Lin, C. H., Huang, T. H., & Fang, J. Y. (2018). Lipid-based nanoparticles as a potential delivery approach in the treatment of rheumatoid arthritis. *Nanomaterials (Basel), 8*(1), E42.
47. Wang, Y., Li, P., Truong-Dinh Tran, T., Zhang, J., & Kong, L. (2016). Manufacturing techniques and surface engineering of polymer based nanoparticles for targeted drug delivery to cancer. *Nanomaterials (Basel), 6*(2), E26.
48. Aw, M. S., & Paniwnyk, L. (2017). Overcoming *T. gondii* infection and intracellular protein nanocapsules as biomaterials for ultrasonically controlled drug release. *Biomaterials Science, 5*(10), 1944–1961.
49. Wiwanitkit, V. (2012). Interest in paromomycin for the treatment of visceral leishmaniasis (kala-azar). *Therapeutics and Clinical Risk Management, 8*, 323–328.
50. Bricaire, F. (1998). Liposomes: Promising perspectives. *Presse Médicale, 27*(Suppl 5), 7–8.
51. Carrillo-Muñoz, A. J., Quindós, G., Tur, C., Ruesga, M., Alonso, R., del Valle, O., et al. (2000). Comparative in vitro antifungal activity of amphotericin B lipid complex, amphotericin B and fluconazole. *Chemotherapy, 46*(4), 235–244.
52. Pedrini, I., Gazzano, E., Chegaev, K., Rolando, B., Marengo, A., Kopecka, J., et al. (2014). Liposomal nitrooxy-doxorubicin: One step over caelyx in drug-resistant human cancer cells. *Molecular Pharmaceutics, 11*(9), 3068–3079.
53. Rom, J., Bechstein, S., Domschke, C., Golatta, M., Mayer, C., Heil, J., et al. (2014). Efficacy and toxicity profile of pegylated liposomal doxorubicin (Caelyx) in patients with advanced breast cancer. *Anti-Cancer Drugs, 25*(2), 219–224.

54. Tong, Y. C., Kaye, A. D., & Urman, R. D. (2014). Liposomal bupivacaine and clinical outcomes. *Best Practice and Research. Clinical Anaesthesiology, 28*(1), 15–27.
55. Viscusi, E. R., Sinatra, R., Onel, E., & Ramamoorthy, S. L. (2014). The safety of liposome bupivacaine, a novel local analgesic formulation. *The Clinical Journal of Pain, 30*(2), 102–110.
56. Gnacadja, G. (2017, December 6). An invitation to pharmacostatics. *Bulletin of Mathematical Biology*. https://doi.org/10.1007/s11538-017-0369-z. [Epub ahead of print].