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REVIEW

Mechanical properties of nanoparticles in the drug delivery kinetics

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Abstract: Nanoparticle formulation is a recently developed drug delivery technology with enhanced targeting potential. Nanoparticles encapsulate the drug of choice and delivers it to the target via a targeting molecules (ex. antigen) located on the nanoparticle surface. Nanoparticles can even be targeted to deeply penetrating tissue and can be modeled to deliver drugs through the blood brain barrier. These advancements are providing better disease targeting such as to cancer and Alzheimer's. Various polymers can be manufactured into nanoparticles. The polymers examined in this paper are polycaprolactone (PCL), poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), and poly(glycolic acid) (PGA). The purpose of this study is to analyze the mechanical properties of these polymers to establish drug delivery trends and model pharmacokinetics and biotransport. We found that, in general, as the melting point, elastic modulus and tensile strength increases, the degradation rate also increases. PLA composite material may be an ideal polymer for drug delivery due to its good control of degradation.

Keywords: nanoparticles, polymers, PCL, PLA, PLGA, PGA, melting point, modulus, kinetics

1 Introduction

Biomaterials play an important role in our healthcare system including diagnostic equipment, medical devices, prosthetics, drug delivery and tissue engineering [1]. Biomaterials play an equally important role in drug delivery, controlling molecular interactions, biocompatibility, release rate, degradation, host interactions and targeting. Earlier drug delivery studies via the gastrointestinal tract examined the effective absorption of drugs into the blood stream and half life analysis due to different stresses. The methods for delivery were crude involving simple macromolecular degradation and release of drug, causing the half life of the drug to be relatively short ($<$ 30 minuets) [2]. With improvements in scientific technology and understanding, drug delivery became more dynamic and controllable including improved release rate and degradation times. Complexity of the drug increased to include microparticles, and with improved techniques and polymers the field of nanomedicine was developed [3].

2 Nanoparticle characteristics

Nanoparticles are nanoscale objects between 10ηm and 1000ηm in size [4]. the small size improves transport between biological tissue. Nanoparticles have a large surface area which improves reactivity, absorption, higher solubility and lower melting temperature. Particles smaller than 10ηm can have unique quantum physical effects [5]. Cargos used in research include therapeutics such as DNA or RNA, chemotherapeutics an Alzheimer's medication. Nanoparticles include a targeting molecule attached to the surface, and are often coated with particles to subvert immunologic interactions [6]. (see Figure 1)

There are various types of nanoparticles used in drug delivery including liposome, polymeric, gold, iron, and unique formations of carbon (see Figure 2). These nanoparticles can be synthesized using chemical methods or biological methods which use microorganisms, enzymes, fungi or plants [7, 8]. We will be focusing on polymeric nanoparticles in this paper. Polymeric nanoparticles are commonly used as carriers in therapeutics. There is a lot of research and interest on producing a polymeric nanoparticle with optimal drug delivery attributes [7, 9].

Polymeric nanoparticles form via spontaneous self-assembly. The core is usually hydrophobic and the outside is hydrophilic which helps to maintain a barrier between the drug on the inside and the host until the drug is delivered to its target. Drugs that are incorporated into the nanoparticle can be either hydrophobic or hydrophilic. Polymeric nanoparticles used for drug

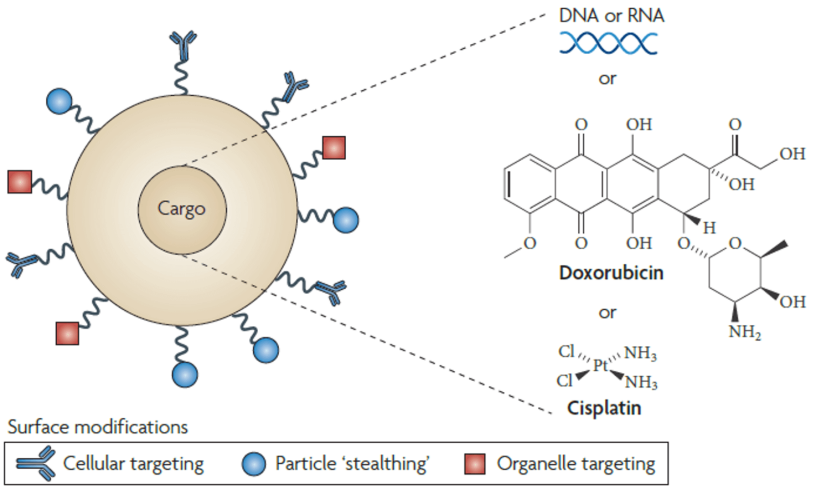

Figure 1 Nanoparticle composition [6]

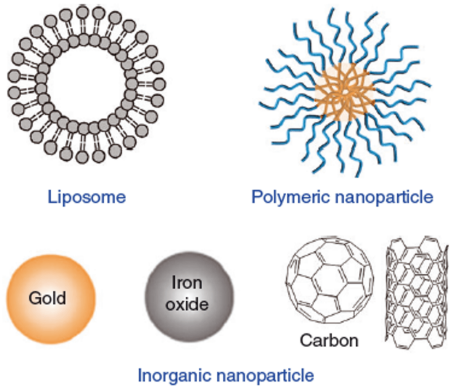

Figure 2 Different types of nanoparticles used for drug delivery [9]

delivery generally range from 10-100ηm but not more than 200ηm after drug encapsulation. Methods for synthesis of polymers for nanomedicine include ring opening, polycondensation, bulk synthesis, dehydrative coupling, and reaction of diketene acetals with diols [9, 10]. (see Figure 3)

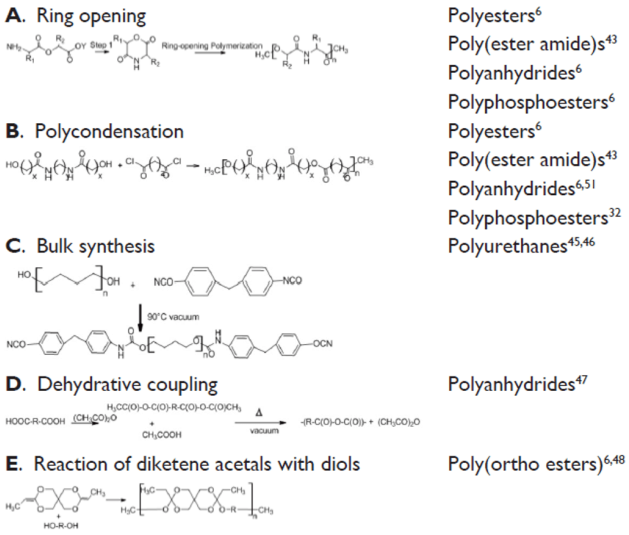

Figure 3 Common synthesis methods for nanoparticles [10]

2.1 Nanoparticle delivery

Nanoparticles can be administered in several different ways including local injection, intravenous, respiratory, and gastrointestinal pathways. The least invasive method is via the gastrointestinal pathway and is generally preferred and the most common method used. Delivery of the nanoparticles into the blood stream from gastrointestinal ingestion can be difficult due to factors such as poor solubility, stability issues related to the harsh gastrointestinal environment and mucosal lining on the intestines. Nanoparticles are susceptible to mucosal entrapment and shedding from the gastrointestinal tract. Nanoparticle drug carriers must be designed carefully to subvert these challenges [11].

Most nanoparticles that are orally administered are not retained, having no effect. A common attempt to improve drug uptake is mucoadhesion, however this has been proven detrimental in many cases as the drug ends up in the mucus and does not come into contact with the intestinal epithelium. For this reason it is important to examine the charge effect (electrostatic interactions, van der Waals forces, hydrophobic interactions, etc) on the nanoparticle in order to limit mucoadhesion. There are several systems however that optimize mucoadhesion to improve bioavailability, and have shown some success. Common particles used in mucoadhesive systems include PLA, PLGA, poly(sebacic acid) (PSA), and poly(acrylic acid) (PAA). An alternative is mucous penetrating systems (using mucolytics) which disrupt the mucosal membrane. This has the potential for improved drug delivery, however disrupting the mucosal membrane could have negative health related repercussions [12].

2.2 Biocompatibility

Nanoparticle surface characteristics often result in an immunogenic reaction attributed to the reticuloendothelial system (RES) which includes monocytes, macrophages and other phagocytic cells in the liver and spleen. These cells are a white blood cell of the innate immune system that detect pathogen associated molecular patterns (PAMPs) and chemical properties of materials and nanoparticles such as composition, surface charge and structure [13]. Due to the RES the vast majority of nanoparticles are filtered out. In an attempt to improve nanoparticle retention, nanoparticles are often coated with some chemical altering the surface reactivity [14, 15]. (see Figure 4)

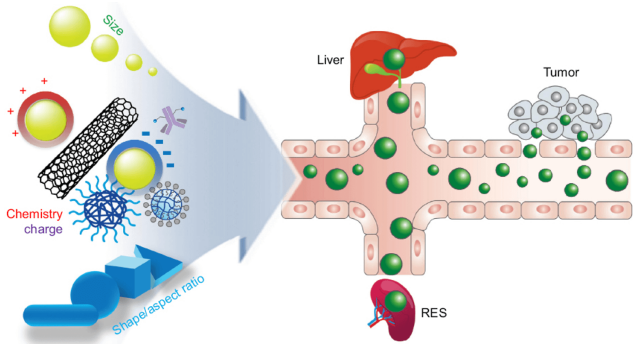

Figure 4 The reticuloendothelial system interaction with nanoparticle is affected by chemistry, surface charge, and shape characteristics. [15]

Polyethylene glycol (PEG) is a common nanoparticle compound used for surface coating to improve retention time of therapeutics. PEG is a water-soluble polymeric compound which is flexible and non-ionic that is able to decrease RES uptake considerably. PEGylation has been demonstrated to improve pharmacokinetics and the half-life of therapeutics thereby enhancing bioavailability of the drug [16]. PEG is able to improve drug retention and delivery in both non targeting nanoparticle formulations as well as targeted nanoparticle formulations, with the targeting ligand often attached directly to the PEG [17, 18]. (see Figure 5)

3 Biomaterials

There are several conditions that will affect the material properties of nanoparticles in addition to the intrinsic chemical properties and composition. A few of the most important ones are molecular weight, crystallinity, annealing temperature, crosslinking, addition of a plasticizer. The First step in developing a nanoparticle is understanding the chemical and mechanical properties associated with potential composite, then other parameters can be evaluated. In this

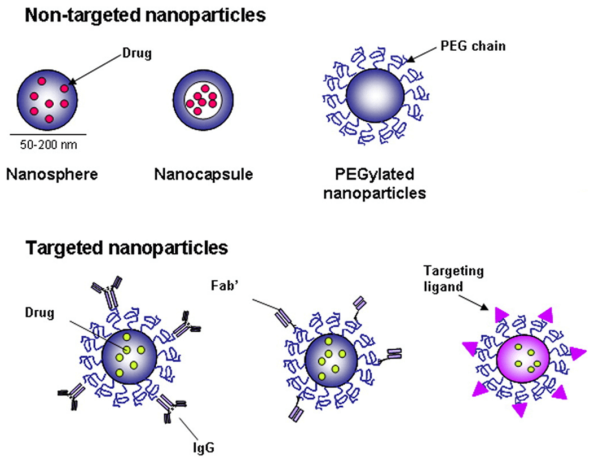

Figure 5 PEGylation of targeted and non-targeted nanoparticles [18]

paper the material properties of PCL, PGA, PLA and PLGA are examined how they determine drug delivery kinetics.

3.1 Polycaprolactone (PCL)

PCL has been drawing increasing attention for tissue engineering applications. It works well as a healthcare biodegradable biomaterial for sutures, wound dressings and even bone regeneration. It is also used as a polymer and nanoparticle model for controlled delivery of therapeutics. PCL is a hydrophobic, semi crystalline linear aliphatic polyester that is biocompatible and has a slow degradation rate. PCL is synthesized by ring opening polymerization (ROP) of the ϵ-caprolactone using some catalyst (metallic, organic or enzymatic). PCL can not be digested by humans, it is degraded by microorganisms in the body [19]. (see Figure 6)

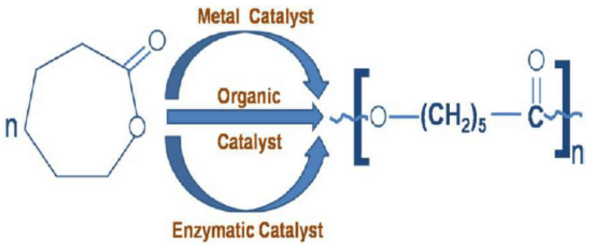

Figure 6 PCL synthesis [19]

3.2 Poly(lactic) acid (PLA)

PLA is a widely used nanoparticle due to its good biocompatibility and degradability into easily digested components. It is derived from renewable resources such as corn, sugar and potatoes making it a cost effective option for use. Mechanical characteristics are determined by factors such as temperature, molecular weight, and component isomers. PLA is a saturated poly-α-hydroxyl ester composed of lactic acid which degrades into lactic acid. Lactic acid is easily digested by our metabolism via the Krebs cycle with detrimental effect. The result of lactic acid digestion is water and carbon dioxide. There are generally 3 isomers of PLA, poly(D-lactic acid)(PDLA), poly(L-lactic acid)(PLLA), and racemic blend D,L-PLA (PDLLA). PLLA and PDLLA are semi crystalline while PDLA is amorphous. PDLLA is monophasic offering utility to drug delivery. Using differing composite ratios of these isomers we can control several material properties and degradation rate. Plasticizers such as glycerol and PEG can be used in combination with PLA to improve flexibility and other material properties. PLA is synthesized by direct polycondensation of lactic acid, and ring opening polymerization of lactic acid cyclic dimmer (lactide) [20, 21]. (see Figure 7)

3.3 Poly (glycolic acid) (PGA)

PGA is a semi crystalline polyester that is used in composite nanoparticles, but not often by itself (often PCL or PLA). It has good biocompatibility and is often used for sutures, bone tissue

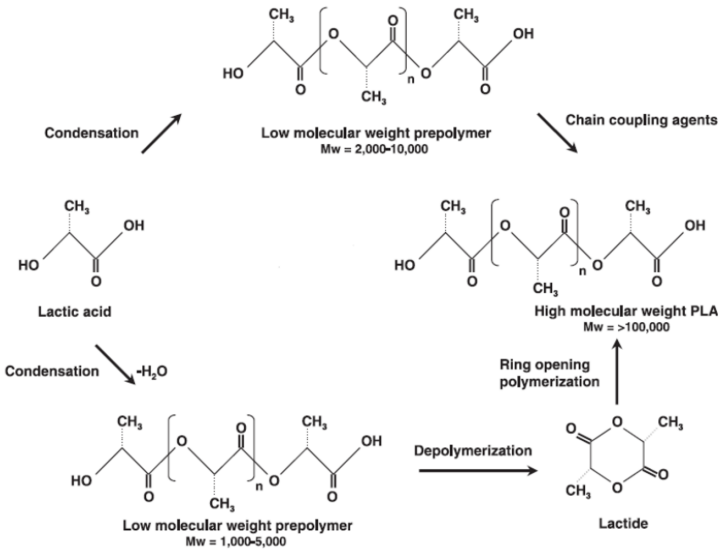

Figure 7 PLA synthesis [21]

engineering, and drug delivery. PGA degrades quickly in vivo due to metabolic hydrolysis. PGA can be synthesized by ring-opening polymerization [22, 23]. (see Figure 8)

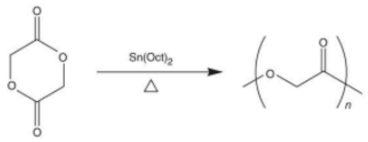

Figure 8 PGA synthesis (Ring opening polymerization) [22]

3.4 Poly(lactic-co-glycolic acid) (PLGA)

PLGA has been approved for and is widely used in healthcare and drug delivery due to its good biocompatibility. PLGA degrades into lactic acid and glycolic acid which are easily metabolized in the human body via the Krebs cycle. There are several nanoparticle preparation techniques that can be used to create PLGA nanoparticles, the most common being solvent evaporation. This technique is good for encapsulation of hydrophobic drugs. Synthesis of PLGA occurs via copolymerization method of lactide and glycolide [24, 25]. (see Figure 9, Table 1)

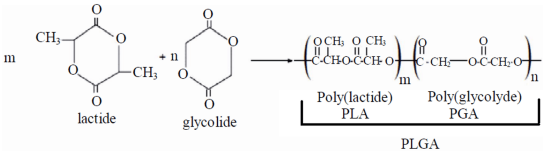

Figure 9 PLGA synthesis (Copolymerization) [25]

Data may be summarized from higher order to lower from left to right for melting point, degradation time, elastic modulus and ultimate tensile strength.

Melting Point:	PCL < PLGA < PLA < PGA
Degredation Time:	PLGA < PGA < PLA < PCL
Elastic Modulus:	PCL < PLGA < PLA < PGA
Ultimate Tensile Strength:	PCL < PLGA < PGA < PLA

PCL takes the longest time to degrade. We know this is because it is not digested metabolically and relies on bacteria. It also has the lowest melting point, elastic modulus, and ultimate tensile strength making it a very malleable material. This may be combined with other biomaterials to improve plasticity. PGA has the highest melting point and elastic modulus making it a brittle material by comparison. It also has a high ultimate tensile strength, but it degrades more quickly than PLA and PCL. PLA has a low ultimate tensile strength but fairly high elastic modulus, degradation time and melting point. PLGA has very low values over-all, with a very quick degradation time, low melting point, low elastic modulus and low ultimate tensile strength.

Table 1 Mechanical properties of nano/biomaterial compiled

Properties	PGA	PLA	PCL	PLGA
Melting Point [Tm]	225-230°C [5], >200°C [2]	175°C [2]; 130-180 [5]	58-63°C [5], 55-60°C [2]	150 [9]
Glass Transition Temp (Tg)	35-40°C [2], [5]; 40°C [11]	67C [11]; 40°C [11]; 55-60 [2]; 60-65 [5]	-60°C [5], -54°C [2]	50-55°C [5]; 50 [9]; 45-55 [17]
Half Life	slow cured = 5 months [13], fast cured = 0.85 months [13]	0.6 months		11-12 weeks [16]
Degradation Time (in vivo)	100% in 2-3 or 6-12 months [3], or 3-4 months [5]; 2.5-6 weeks [14]	50% in 1-2 years [3], 100% in 12-16months [3]	>24 months [5], 50% in 4 years [3]	100% in 50-100 Days [3], 100% in 1-2 months [2], Adjustable: 3-6months [5], 1-6 months [17]
Degradation Rate Constant (s-1)	0.091 wk-1 [14]	$6.6\times10\hat{}-9[s^{-1}]$		6.6x10^-9 [**?**]
Degradation by-products (pKa)	Glycolic acid(3.83) [3]	Lactic Acid (3.85) or (3.08) [3]	Caproic acid (4.88) [3]	Lactic Acid (3.85 or 3.08) [3], Glycolic Acid (3.83) [3]
Degradation mechanism	Both enzymatic and non-enzymatic hydrolysis [3]	Hydrolysis through the action of enzymes [3]	Hydrolytic degradation [3]	Hydrolysis through the action of enzymes [3]
Modulus of Elasticity	7-8.4 GPa [3], 12.5GPa [2], 5-7GPa [5]. 14GPa [11]; 6.5 [14]	14 Gpa [11]; 1.9-2.4 [2] [5]; 3.5-3.9GPa [6]; 3.31±0.22 GPa [1]; 3.5GPa [3]; 4.8 GPa [2]; 3.5-4.2 [6]	0.4-0.6GPa [5], 700 MPa [3]	2 GPa [3], 1.4-2.8 GPa [5]
Yield Stress (MPa)		44.3-78.9 [8]; 49-53 [6]; 51.3±1.0 MPa [1]; 63-70 [6]		
Breaking Stress		24.4-76.6 [8]; 45.5 ±0.7 MPa [1];		
Ultimate Strength	890 MPa [3] ; 1000MPa [11]	1000 Mpa [11], 1300-1870 MPa [8]; 40-44MPa [6]; 55 MPa [3] or 48-53 Mpa; 65.78±0.39 Mpa [7]; 47-66 [6]; 65-75 [7]	4-28 MPa [3], 23 MPa [2]	63.6 MPa [3]
Flexural Stiffness				0.5-2.2 GPa [9]
Flexural Strength (MPa)	60-120 [11]	60-120 [11]; 84-88 [6]; 64-106 [6]		4.14-54.6 MPa [9]
Elongation at Break %	30% [3]	5.23-230 [8]; 4.8-7.5 [6]; 8.91±0.44 [7], 30-240% [3], 1.3-8 [6]; 3.2-7.5 [7]	700-1000% [3]	3-10% [3]
Heat Deflection Temperature (°C)		50-51 [6]; 55-65 [6]		
Viscosity (dL/g)	1.1-1.7 [15]	0.88-1.73 [6]; .74-1.8 [6]		0.55-0.75
Shear Modulus	6GPa [12]			
Tensile Modulus	294 Gpa [12]	1.68±0.07 Gpa [7]; 1.7-2.0 [7]		3 MPa [10]

4 Conclusions

PLGA and PLA are the most studied nanoparticles with several formulations and synthesis techniques available making them an ideal choice. However, PCL would be a good polymer with increased plasticity, especially with pure PLA which can be brittle, or PGA if that was chosen. PCL, PLA and PLGA all degrade via metabolic processes making them more ideal compared to PCL which could have a prolonged impact. PLGA and PGA quickly degrade in vivo so they would be best used with another polymer such as PLA or PCL. The problem with PCL is that it is left behind and takes time to degrade. Another option to improve degradation rate is incorporation of an inorganic biocompatible molecule which has a controllable degradation rate. Therefore, the degradation rate is a function of mechanical properties such as melting temperature, elastic modulus and tensile strength.

References

[1] More RB, Haubold AD and Bokros JC. Biomaterials Science: An Introduction to Materials in Medicine. San Diego: Academic Press, 1996.

[2] Langer R. Bioavailability of macromolecular drugs and its control in controlled drug bioavailability. Bioavailab. Control Drug Delivery System Design, Vol. 3, 1985.

[3] Langer R. Biomaterials in Drug Delivery and Tissue Engineering: One Laboratory's Experience. Accounts of Chemical Research, 2000, **33**(2): 94-101. https://doi.org/10.1021/ar9800993

[4] Mohanraj VJ and Chen Y. Nanoparticles-a review. Tropical Journal of Pharmaceutical Research, 2006, **5**(1): 561-573. https://doi.org/10.4314/tjpr.v5i1.14634

[5] Pokropivny V. Ed., Introduction to nanomaterials and nanotechnology. Tartu: Tartu University Press, 2007.

[6] Petros RA and Desimone JM. Strategies in the design of nanoparticles for therapeutic applications. Nature reviews. Drug discovery, 2018, **9**(8): 615-627. https://doi.org/10.1038/nrd2591

[7] Hasan S. A review on nanoparticles: Their synthesis and types. Research Journal of Recent Sciences, 2015, **4**: 1-3.

[8] Sharma D, Kanchi S and Bisetty K. Biogenic synthesis of nanoparticles: A review. Arabian Journal of Chemistry, 2015, **12**(8): 3576-3600. https://doi.org/10.1016/j.arabjc.2015.11.002

[9] Park W and Na K. Advances in the synthesis and application of nanoparticles for drug delivery. Wiley Interdisciplinary Reviews Nanomedicine & Nanobiotechnology, 2015, **7**(4): 494-508. https://doi.org/10.1002/wnan.1325

[10] Marin E, MI Briceño and Caballero-George C. Critical evaluation of biodegradable polymers used in nanodrugs. International Journal of Nanomedicine, 2013, **8**: 3071-3091. https://doi.org/10.2147/IJN.S47186

[11] Schenk M and Mueller C. The mucosal immune system at the gastrointestinal barrier. Best Practice & Research Clinical Gastroenterology, 2008, **22**(3): 391-409. https://doi.org/10.1016/j.bpg.2007.11.002

[12] Ensign LM,Cone R and Hanes J. Oral Drug Delivery with Polymeric Nanoparticles: The Gastrointestinal Mucus Barriers. Advanced Drug Delivery Reviews, 2012, **64**(6): 557-570. https://doi.org/10.1016/j.addr.2011.12.009

[13] Neus G, Sánchez Tilló E, Pujals Riatós S, *et al*. Inorganic Nanoparticles and the Immune System: Detection, Selective Activation and Tolerance. Society of Photo-Optical Instrumentation Engineers (SPIE) Conference Series, 2012. https://doi.org/10.1117/12.917327

[14] Li SD and Huang L. Nanoparticles evading the reticuloendothelial system: Role of the supported bilayer. Biochimica et Biophysica Acta, 2009, **1788**(10): 2259-2266. https://doi.org/10.1016/j.bbamem.2009.06.022

[15] Dongwoo K and Sang-Woo K. Multiple cues on the physiochemical, mesenchymal, and intracellular trafficking interactions with nanocarriers to maximize tumor target efficiency. International Journal of Nanomedicine, 2015, **10**:3 989-4008. https://doi.org/10.2147/IJN.S83951

[16] Thangaraja A, Savitha V and Jegatheesan K. Preparation and Characterization of Polyethylene Glycol Coated Silica Nanoparticles for Drug Delivery Application. International journal of nanotechnology and applications, 2014, **8**(1): 31-38.

[17] Mishra P, Nayak B and Dey RK. PEGylation in anti-cancer therapy: An overview. Asian Journal of Pharmaceutical Sciences, 2016, **11**(3): 337-348. https://doi.org/10.1016/j.ajps.2015.08.011

[18] Danhier F, Ansorena E, Silva JM, *et al*. PLGA-based nanoparticles: an overview of biomedical applications. Journal of Controlled Release, 2012, **161**(2): 505-522. https://doi.org/10.1016/j.jconrel.2012.01.043

[19] Mondal D, Griffith M and Venkatraman SS. Polycaprolactone-based biomaterials for tissue engineering and drug delivery: Current scenario and challenges. International Journal of Polymeric Materials & Polymeric Biomaterials, 2016, **65**(5): 255-265. https://doi.org/10.1080/00914037.2015.1103241

[20] Sha L, Chen Z, Zhou C, *et al*. Polylactic Acid Based Nanocomposites: Promising Safe and Biodegradable Materials in Biomedical Field. International Journal of Polymer Science, 2016, **2016**: 1-11. https://doi.org/10.1155/2016/6869154

[21] Lasprilla A, Martinez G, Lunelli BH, *et al*. Synthesis and Characterization of Poly (Lactic Acid) for Use in Biomedical Field. Chemical Engineering Transactions, 2011, **24**: 985. https://doi.org/10.3303/CET1124165

[22] Kaihara S, Matsumura S, Mikos AG, *et al*. Synthesis of poly(L-lactide) and polyglycolide by ring-opening polymerization. Nature Protocols, 2007, **2**(11): 2767-2771. https://doi.org/10.1038/nprot.2007.391

[23] Chujo K, Kobayashi H, Suzuki J, *et al*. Physical and chemical characteristics polyglycolide. Die Makromolekulare Chemie, 1967, **100**(1): 267-270. https://doi.org/10.1002/macp.1967.021000129

[24] Makadia HK and Siegel SJ. Poly Lactic-co-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier. Polymers, 2011, **3**(3): 1377. https://doi.org/10.3390/polym3031377

[25] Erbetta C. Synthesis and Characterization of Poly(D,L-Lactide-co-Glycolide) Copolymer. Journal of Biomaterials and Nanobiotechnology, 2012, **3**(2): 208-225. https://doi.org/10.4236/jbnb.2012.32027