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An overview on oral drug delivery via nano-based formulations

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ABSTRACT

Oral drug administration is used for a large number of medications, intended to create a systemic effect in the body. Over the recent years, an increasing attention has been directed by pharmacists toward the development of successful formulations for oral drug delivery. However, this issue is still controversial in pharmaceutical technology with many limitations due to the numerous barriers against the absorption and permeability in the gastrointestinal tract. On the other hand, drug carriers play an important role in providing prolonged release and delivery and overcome the multiple barriers of maintaining appropriate bioavailability. Nano scaling of the particles, carriers, and polymers has also provided the capability to characterize and control materials in order to produce unique pharmaceutical components and structures. Furthermore, personalized healthcare, rational drug design, and site-specific targeted drug delivery are some of the profits gained from a nano-based formulation approach. This review aimed to evaluate the evidence on some different types of nanoscaled drug delivery systems, which allow for the delivery of small-molecule drugs and facilitate the merging of larger particles, such as nucleic acids, peptides, and proteins. The delivery of these molecules to the exact target areas inside the body can be accomplished, which would decrease systemic adverse effects and allow for more effective application of the pharmaceutical preparations.

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Introduction

Oral route has been known as the most appropriate, easily applicable, inexpensive, convenient, and preferred way for drug administration. However, the majority of available pharmaceutical preparations have shown poor absorption and permeability through gastrointestinal barriers. This failure, due to the structural properties, such as molecular size and hydrophilicity, would be followed by a decrease in bioavailability, resulting in the non-fulfillment of the expected pharmaceutical effect. Furthermore, the bioavailability of therapeutic nanoparticles, peptides, and proteins via the oral administration route is almost nil as a result of proteolytic degradation, mucosal barriers, and intestinal efflux pumps. Meanwhile, the enhancement of the absorption and bioavailability of the so-called pharmaceuticals is quiet a fundamental challenge (1-3). Buoyant nanotechnology, as a novel promising approach, offers several innovations to elucidate the supposed complication (4, 5). This nanotechnology has been also used for pharmaceutical purposes, which is resulted in the enhancement of the bioavailability of the oral medications (6, 7). This may happen through a size reduction from 1 to 100 nanometer scale, which considerably results in higher surface area, dissolution, and absorption of the particles (8, 9). Nano-based formulations cover liposomes, lipohydrogel nanocarriers, and inorganic/metallic nanoparticles. Novel approaches and applications, such as nanosuspension coating technique, have been generated in this regard (10, 11). On the other hand, the assessment of the stability of the aforementioned nanoparticles is of similar importance in this domain (12, 13). Moreover, the unique properties and side effects of nanomaterials on the human body have become a subject of extreme interest. These unique effects are due to the high surface area and the consequent reactive surface chemistries of the named particles. Biocompatibility and capability of the nanoparticles, which may depend on their size, shape, and charge, should be assessed in order to prepare novel formulations and polymers (14, 15). Nanoparticles, having a rapid intestinal uptake, can accumulate, and consequently become toxic for the cells of different organs (e.g., liver, kidney, or lungs) if administered for prolonged periods. This is an unavoidable characteristic of these particles that should be concerned for in vivo applications (16, 17). The aim of this study was to investigate the evidence on the current nanoparticle-based formulations and their applications in the oral route of drug delivery. The focus of the study was on different nanoparticulate formulations, stability, bioavailability, biocompatibility, toxicity, and morphology to facilitate the efficient application of these medications.

Oral Drug Delivery

Drug administration via oral route allows for the achievement of both local and systemic effects; therefore,

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it is highly preferred by the patients. Moreover, this route of drug administration entails the advantages of being easy and painless. In addition, this route of delivery can be utilized for the administration of different time-release forms, including slow-, sustained-, or delayed-release, of medical preparations, thereby fulfilling the need of a wide scope of the drug delivery market (1, 13). In conventional oral drug delivery systems, including solid (e.g., tablets and capsules) and liquid (e.g., solutions and suspensions) dosage forms, there is very little control over the release of drug (18). Conventional oral formulations have some drawbacks. In this regard, the delivery of effective concentrations of these formulations to the target site can be achieved by the recurrent administration of high doses, which in most of the cases results in overdosing or continuously changing, irregular, random, and often sub-therapeutic plasma concentrations, thereby inducing considerable side effects (19, 20). This issue has underscored the urgent need for performing studies targeted toward the enhancement of oral absorption in the recent years where nanostructured preparations may be a key component.

Oral route limitations in drug delivery

In the gastrointestinal tract (GI), the absorption, permeability, and finally bioavailability of the drug molecules would be reduced due to many barriers existing in this route (3, 21, 22). The barriers include wide pH range of the GI tract, enzymatic environment, degradation of especially proteinaceous drug molecules, and reduced absorption of these molecules. These challenges are produced due to either the enterocytes or the tight junctions of the intestinal cells. Generally, the GI tract is composed of a number of sections functioning together with mechanical and biochemical progressions to support converting foodstuff into energy. These molecules would have different ways to enter the bloodstream in which they face various barriers (23, 24). Figure 1 illustrates the schematic presentation of the obstructions existing in the GI tract, the different transcellular, paracellular, and active diffusion through receptor-mediated endocytosis, and carrier-mediated transport.

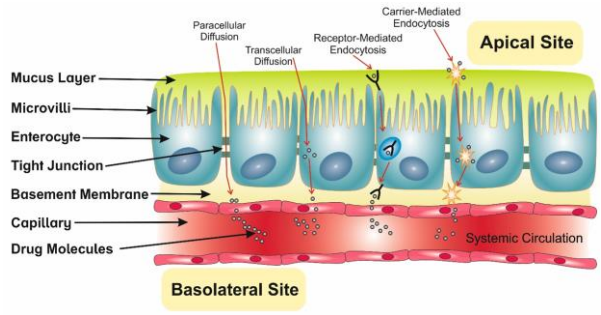

Figure1: Schematic summary of the transport pathways existing in the gastrointestinal tract for pharmaceutical molecules via the biological barriers (not to scale)

Table 1 summarizes information regarding GI tract barriers to proteinaceous absorption.

Stomach	Intestine		References
	Enzymes	Absorption	
Broad-spectrum enzymes (e. g., pepsin) Acidic environment	Pepsin Trypsin Chymotrypsin Carboxypeptidase A Carboxypeptidase B	Enterocytes or tight junctions of the intestinal cells	(25, 26)

Nano-based formulations

Nanomedicine could be well-defined as the knowledge of controlling, employing, studying, and manufacturing structures or carriers/devices in the “nanometer” scale and "nanoparticles". Nanoparticles stand for "particles in one billionth" in its wide-ranging explanation and is defined as particles with size ranges of 10-1000 nanometers. Nanoparticles have been recognized as a unique and promising approach due to retaining very high surface area to volume ratios. In addition, this approach has addressed the limitations of the currently available methods in order to enhance the dissolution rates of poorly water-soluble drugs . It was also shown to be more stable than other colloidal preparations in the GI tract. Moreover, they are capable of being manipulated easily owing to their physical and chemical characteristics, drug-release profile, and biological behavior. These particles are able to adsorb and/or encapsulate a drug, thereby protecting it contrary to chemical and enzymatic degradation (15, 27, 28). Many different formulations have been introduced by nanomedicine, such as inorganic/metallic nanoparticles, polymeric nanoparticles, liposomes, and lipohydrogel nanocarriers, which approve absorption through the intestinal epithelium (29, 30). The schematic presentation of drug incorporation within these nanoparticles is depicted in Figure 2. Nanoparticles possess a wide variety of applications in medical field. Table 2 presents some orally administered nanomaterials reported in different studies.

Inorganic/metallic nanoparticles

Inorganic nanoparticles covering silver, iron oxide, and gold nanoparticles, as well as the quantum dots, which possess

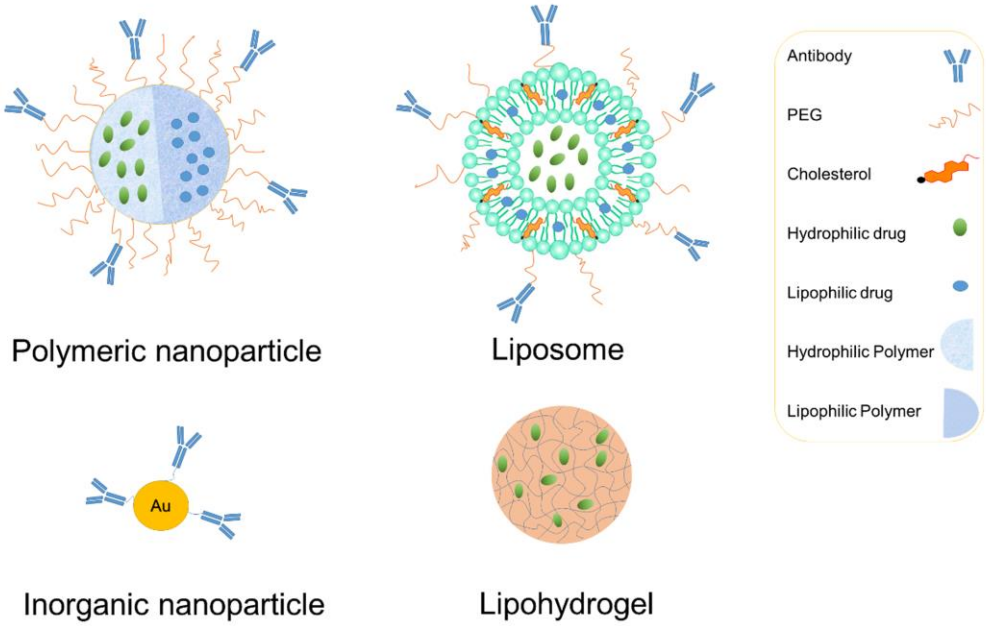

Figure 2: Schematic representation of different nanoscaled particles (Not to scale)

Table 2 Examples of the nanomaterials used via oral route of administration

Oral Nano-based Formulations	Type	Applications	References
Insulin loaded nanoparticles	Polymeric nanoparticle	Diabetes management	(31, 32)
Paclitaxel loaded SLNs with hydroxypropyl-b-cyclodextrin (HPCD)	Polymeric nanoparticle	Cancertherapy	(33, 34)
Nanosilver	Inorganic/metallic nanoparticle	Mouthwash, toothpaste, dental composites	(35, 36)
Nanogold	Inorganic/metallic nanoparticle	Oral cancer diagnosis	(37-39)

intrinsic magnetic, optical, and electrical properties, pave the way for the emergence of innovative technology. Accordingly, several recent efforts have been targetted toward the application of these nanoparticles in the biomedical field (40, 41). Metallic nanoparticles have a good capability of creating multifunctional nanoprobes for in vivo applications, both in imaging and therapeutic procedures, due to having excellent intrinsic physical assets and versatile surface. The use of these nanoparticles sequentially increase the need for the particles due to their biocompatibility, colloidal stability, and high efficacy (42). The inorganic nanoparticle-mediated probes have been exploited for biomedical purposes for many years. However, the investigation of the in vivo behavior of these nanoparticles, mainly the pharmacokinetics and unintendedly made protein corona, are still at a preliminary stage. They also attracted attention regarding their applicability in the enhancement of therapeutic efficacy (43).

Biocompatibility of nanoparticles has been achieved by either in situ coating throughout the synthesis or after surface modification via several ligands. A multi-targeting nanoparticle system, consisting of two or more targeting phases or stimuli-responsive targeting moieties, shows an encouraging targeting strategy. It can be also supposed that the eventual goal of developing nanomedicine is their clinical application. Therefore, it is essential to have sufficient supply of high-quality nanoparticles (33). Although a low number of these particles have been approved for clinical use, most of them still require overcoming potential toxicity problems. It would be predictable that some of the inorganic nanoparticles, such as gold colloids, will overcome these barriers and ultimately enter the clinical studies (44, 45).

Polymeric nanoparticles

Biodegradable polymeric nanoparticles have gained a great concern and considerable attention by means of being a potential drug delivery agent considering their applications in the controlled release of drugs and targeting particular biological ligands or targets. They have been also used in order to carry DNA in gene therapy processes and deliver proteins and peptides through the oral route (46).

Polymeric micelles are characterized by a core-shell structure. The viscosity of the micellar core may influence the physical stability of the micelles and drug release. The biodistribution of the micelle is mainly dictated by the nature of the shell, which is also responsible for micelle stabilization and interactions with plasma proteins and cell membranes. The micelles can contain functional groups at their surface for conjugation with a targeting moiety (47). Polymeric micelles are mostly small (10-100 nm). Pharmaceutical preparations should maintain their integrity for an adequate quantity of period after injection through the body for effectual delivery to their effective sites of action. Attachment of antibodies or sugars, or introduction of a polymer sensitive to variant temperatures or different pH points could also be valuable (48).

Liposomes

Liposomes are a form of vesicles that consist either of many, few, or just one phospholipid bilayers. The polar character of the liposomal core enables the polar drug molecules to be encapsulated. Amphiphilic and lipophilic molecules are solubilized within the phospholipid bilayer according to their affinity towards the phospholipids. They consists of small vesicles composed of unilamellar or multilamellar phospholipid bilayers surrounding one or several aqueous compartments (49). In addition, the charge, as well as lipid composition and size (ranging from 20 to 10,000 nm) of liposomes can vary. Many liposome formulations are rapidly taken up by macrophages. Cationic liposomes and lipoplexes have been extensively investigated for their application in non-viral vector-mediated gene therapy (15, 19, 49). The use of molecules, such as polyethylene glycol, to prevent liposome recognition by phagocytic cells led to the development of the so called 'stealth' liposomes with longer circulation times and increased distribution to peripheral tissues in the body (50). Moreover, targeting device or homing ligand can be included at the external surface of the liposome in order to obtain target cell specificity (50, 51). Another approach is the design of target-sensitive liposomes or fusogenic liposomes that become destabilized after binding and/or internalization to/into the target cells (49, 52). Liposomes possess the advantages of intact delivery to tissues and cells (enabling site-specific and targeted drug delivery), ability to be used for both lipophilic and hydrophilic drugs, and decreased toxicity to other tissues and cells. Furthermore, the size, charge, and other characteristics of the liposomes can be altered (49, 50, 52, 53). On the other hand, some disadvantages of using these spherical vesicle in drug delivery systems include the tendency to be taken up by the cells of RES and slow release of drug when absorbed by phagocytes (50, 54).

Lipohydrogel nanocarriers

Hydrogels are three-dimensional, hydrophilic, and polymeric networks that are capable of absorbing large amounts of water or biological fluids. These systems are composed of homopolymers or copolymers and are insoluble due to the existence of chemical crosslinks (tie-points, junctions) or physical crosslinks, such as entanglements or crystallites. Hydrogels display a thermodynamic compatibility with water, which permits them to swell in aqueous media. They are utilized in the regulation of drug release in reservoir-based, controlled release systems or as carriers in swellable and swelling-controlled release strategies. Hydrogels as enviro-intelligent and stimuli-sensitive gel systems modulate release in response to pH, temperature, ionic strength, electric field, or specific analyte concentration differences.

In these systems, release can be designed to occur within the specific areas of the body (e.g., within a certain pH of the digestive tract) or also via specific sites (adhesive or cell-receptor specific gels via tethered chains from the hydrogel surface) (15, 53).

Bioavailability

Water solubility, dissolution, and GI permeability are the most important factors that control the speed and amount of the finally absorbed drug, and consequently its bioavailability (55). The main objective of nanoparticulate forming of the medical preparations is to overcome the intestinal barriers and enhance the bioavailability (56). Integration of the drug molecules in different nanostructured carriers offers immense advantages by facilitating a better biodistribution of active compounds, protection against degradation,

targeting, expulsion, and more efficacious communication with biological barriers. Due to the small size of the nanoparticles, they can pass through the blood-brain barrier and function at cellular dimensions (57, 58).

Stability of nanoparticles

Evaluation of the stability of the nanoparticles is of paraamount importance in oral drug delivery approach and its pharmaceutical effects. This is accomplished through the assessment of the size, shape, surface, drug loading capacity, and physical appearance of these particles. (59, 60). Nanoparticles possess a faster and better drug-release profile and can cross the blood-brain barrier due to their particle size, compared to microparticles (61-63). Stability of nanoparticles is in close relation to their surface properties where the hydrophilicity/hydrophobicity balance, and the surface charge of the particles would change their final adsorbed extent by the immune proteins (2, 60).

Biocompatibility and toxicity concerns

Use of nanoparticles for biomedical purposes has been reported to have an exponential growth in the past few years. Although our knowledge of the safety of these nanoparticles has not yet reached a reliable grade, new drug delivery systems are brought to clinical application. Adverse side effects or desired outcomes related to these compounds could be investigated by preliminary and complementary animal studies (64). There are many factors affecting the toxicity of nanoparticles, including high surface area, particle size, coarseness, shape, surface charge, and surface coating molecules (65). The nanoparticles ought to be well designed to result in the lowest cell toxicity. The aforementioned parameters would also determine the biocompatibility of the nanoparticles and after reaching the systemic blood circulation, binding to plasma components (albumin) and degradation products for complex and novel co-polymers will be of utmost importance (66, 67). The different mechanisms of the toxicity of the nanoparticles include misfolding and protein fibrillation in the diseases of the central nervous system and chronic inflammation in the problems related to the respiratory system made by frustrated phagocytosis or reactive oxygen species (ROS) production (68).

Future prospect of nano-based formulation

As outlined in the various sections above, several types of nanoparticles can be used for the delivery of the pharmaceutical agents via oral drug administration route. Regarding this, the application of nanomedicine and nano-based formulations and systems is certainly the trend that will continue to be adopted as an important research area and development for the coming decades. However, it would be necessary to study and manipulate the long-lasting cytotoxicity of nanoparticles (69). Since nanoparticles are supposed to go through absorption by means of M-cells or enterocytes, it would be logical to consider the manner by which they will possibly interact at these sites. However, the progress of consistent tests with following technologies for nano-based formulations is still obligatory (70).

Conclusion

Polymeric nanoparticles possess various beneficial characteristics for the oral administration of peptides and proteins. These nanoparticles facilitate the achievemnt of the appropriate properties of prolonged release and protection from proteinaceous enzymatic environment. Nonetheless, many studies are still required to define the exact mechanism of the uptake and consequent elimination of nano-based formulations. As a final point, nano-based drug delivery offers a limitless and beneficial potential for oral preparations allowing better biomedical outcomes.

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Conflict of interests

The authors declare no conflict of interest or competing financial interest in the present study.

References

1. Tian C, Asghar S, Wu Y, Chen Z, Jin X, Yin L, et al. Improving intestinal absorption and oral bioavailability of curcumin via taurocholic acid-modified nanostructured lipid carriers. Int J Nanomed 2017;12:7897-911.
2. Batista P, Castro PM, Madureira AR, Sarmento B, Pintado M. Recent insights in the use of nanocarriers for the oral delivery of bioactive proteins and peptides. Peptides 2018;101:112-23.
3. Mohammadzadeh R, Baradaran B, Valizadeh H, Yousefi B, Zakeri-Milani P. Reduced ABCB1 Expression and Activity in the Presence of Acrylic Copolymers. Adv Pharm Bull 2014;4:219-24.
4. Mohammadzadeh R. Novel Agents for Antimicrobial Solutions. Eye Contact Lens 2016;42:401-2.
5. Chen YD, Liang ZY, Cen YY, Zhang H, Han MG, Tian YQ, et al. Development of oral dispersible tablets containing prednisolone nanoparticles for the management of pediatric asthma. Drug Des Devel Ther 2015;9:5815-25.
6. He Q, Liu J, Liang J, Liu X, Tuo D, Li W. Chemically Surface Tunable Solubility Parameter for Controllable Drug Delivery-An Example and Perspective from Hollow PAA-Coated Magnetite Nanoparticles with R6G Model Drug. Materials (Basel) 2018;11:E247.
7. Gagliardi A, Paolino D, Iannone M, Palma E, Fresta M, Cosco D. Sodium deoxycholate-decorated zein nanoparticles for a stable colloidal drug delivery system. Int J Nanomed 2018;13:601-14.
8. Mohammadzadeh R. Nanosilver as a novel agent in keloid therapy. J Eur Acad Dermatol Venereol 2013;27:e260-1.
9. Hanifi A, Fathi MH, Mir Mohammad Sadeghi H. Effect of strontium ions substitution on gene delivery related properties of calcium phosphate nanoparticles. J Mater Sci Mater Med 2010;21:2601-9.
10. Li Z, Ye E, David, Lakshminarayanan R, Loh XJ. Recent Advances of Using Hybrid Nanocarriers in Remotely Controlled Therapeutic Delivery. Small 2016;12:4782-806.
11. Siafaka PI, Ustundag Okur N, Karavas E, Bikiaris DN. Surface Modified Multifunctional and Stimuli Responsive Nanoparticles for Drug Targeting: Current Status and Uses. Int J Mol Sci 2016;17: E1440.

12. Gdowski A, Johnson K, Shah S, Gryczynski I, Vishwanatha J, Ranjan A. Optimization and scale up of microfluidic nanolipomer production method for preclinical and potential clinical trials. J Nanobiotech 2018;16:12.
13. Tan J, Cho TJ, Tsai DH, Liu J, Pettibone JM, You R, et al. Surface Modification of Cisplatin-Complexed Gold Nanoparticles and Its Influence on Colloidal Stability, Drug Loading, and Drug Release. Langmuir 2018;34:154-63.
14. Jiao M, Zhang P, Meng J, Li Y, Liu C, Luo X, et al. Recent advancements in biocompatible inorganic nanoparticles towards biomedical applications. Biomater Sci 2018;6:726-45.
15. Dizaj SM, Vazifehasl Z, Salatin S, Adibkia K, Javadzadeh Y. Nanosizing of drugs: Effect on dissolution rate. Res Pharm Sci 2015;10:95-108.
16. Mukherjee K, Acharya K. Toxicological Effect of Metal Oxide Nanoparticles on Soil and Aquatic Habitats. Arch Environ Contam Toxicol 2018;75:175-86.
17. Mohammadzadeh R. Hypothesis: silver nanoparticles as an adjuvant for cancertherapy. Adv Pharm Bull 2012;2:133.
18. Lopez FL, Ernest TB, Tuleu C, Gul MO. Formulation approaches to pediatric oral drug delivery: benefits and limitations of current platforms. Expert Opin Drug Deliv 2015;12:1727-40.
19. Tuleu C. 'Formulating better medicines for children' – Still paving the road. Int J Pharm 2012;435:99-100.
20. Aranda JV, Stern L. Clinical aspects of developmental pharmacology and toxicology. Pharmacol Ther 1983;20:1-51.
21. Fox CB, Cao Y, Nemeth CL, Chirra HD, Chevalier RW, Xu AM, et al. Fabrication of Sealed Nanostraw Microdevices for Oral Drug Delivery. ACS Nano 2016;10:5873-81.
22. Fox CB, Chirra HD, Desai TA. Planar bioadhesive microdevices: a new technology for oral drug delivery. Curr Pharm Biotechnol 2014;15:673-83.
23. Fox CB, Kim J, Le LV, Nemeth CL, Chirra HD, Desai TA. Micro/nanofabricated Platforms for Oral Drug Delivery. J Control Release 2015;219:431-44.
24. Walsh LA, Allen JL, Desai TA. Nanotopography applications in drug delivery. Expert Opin Drug Deliv 2015;12:1823-7.
25. Balakireva AV, Kuznetsova NV, Petushkova AI, Savvateeva L, Zamyatnin AA. Trends and Prospects of Plant Proteases in Therapeutics. Curr Med Chem 2017.
26. Chinnadurai GS, Krishnan S, Perumal P. Studies on detection and analysis of proteases in leaf extract of medicinally important plants. Phytomed 2018;40:176-88.
27. Mahler GJ, Esch MB, Tako E, Southard TL, Archer SD, Glahn RP, et al. Oral exposure to polystyrene nanoparticles affects iron absorption. Nat Nanotechnol 2012;7:264-71.
28. Babu VR, Patel P, Mundargi RC, Rangaswamy V, Aminabhavi TM. Developments in polymeric devices for oral insulin delivery. Expert Opin Drug Deliv 2008;5:403-15.
29. Dos Santos Ramos MA, Da Silva PB, Sposito L, De Toledo LG, Bonifacio BV, Rodero CF, et al. Nanotechnology-based drug delivery systems for control of microbial biofilms: a review. Int J Nanomed2018;13:1179-213.
30. Alexis F, Pridgen EM, Langer R, Farokhzad OC. Nanoparticle technologies for cancer therapy. Handb Exp Pharmacol 2010;197:55-86.
31. Smart AL, Gaisford S, Basit AW. Oral peptide and protein delivery: intestinal obstacles and commercial prospects. Expert Opin Drug Deliv 2014;11:1323-35.
32. Salata O. Applications of nanoparticles in biology and medicine. J Nanobiotechnol 2004;2:3.
33. Jiao M, Zhang P, Meng J, Li Y, Liu C, Luo X, et al. Recent advancements in biocompatible inorganic nanoparticles towards biomedical applications. Biomater Sci 2018;6:726-45.
34. Zafar N, Fessi H, Elaissari A. Cyclodextrin containing biodegradable particles: from preparation to drug delivery applications. Int J Pharm 2014;461:351-66.
35. Sodagar A, Akhavan A, Hashemi E, Arab S, Pourhajibagher M, Sodagar K, et al. Evaluation of the antibacterial activity of a conventional orthodontic composite containing silver/hydroxyapatite nanoparticles. Prog Orthod 2016;17:40.
36. Moreira DM, Oei J, Rawls HR, Wagner J, Chu L, Li Y, et al. A novel antimicrobial orthodontic band cement with in situ-generated silver nanoparticles. Angle Orthod 2015;85:175-83.
37. Cole LE, Ross RD, Tilley JM, Vargo-Gogola T, Roeder RK. Gold nanoparticles as contrast agents in x-ray imaging and computed tomography. Nanomed 2015;10:321-41.
38. Chieruzzi M, Pagano S, Moretti S, Pinna R, Milia E, Torre L, et al. Nanomaterials for Tissue Engineering In Dentistry. Nanomaterials 2016;6:134.
39. Liu H, Xu Y, Wen S, Chen Q, Zheng L, Shen M, et al. Targeted tumor computed tomography imaging using low-generation dendrimer-stabilized gold nanoparticles. Chemistry 2013;19:6409-16.
40. Cho EC, Glaus C, Chen J, Welch MJ, Xia Y. Inorganic nanoparticle-based contrast agents for molecular imaging. Trends Mol Med 2010;16:561-73.
41. Panáček A, Kvítek L, Smékalová M, Večeřová R, Kolář M, Röderová M, et al. Bacterial resistance to silver nanoparticles and how to overcome it. Nat Nanotech 2018;13:65-71.
42. Jurasin DD, Curlin M, Capjak I, Crnkovic T, Lovric M, Babic M, et al. Surface coating affects behavior of metallic nanoparticles in a biological environment. Beilstein J Nanotechnol 2016;7:246-62.
43. Yakoh A, Pinyorospathum C, Siangproh W, Chailapakul O. Biomedical Probes Based on Inorganic Nanoparticles for Electrochemical and Optical Spectroscopy Applications. Sensors 2015;15:21427-77.
44. Prasad NK, Rathinasamy K, Panda D, Bahadur D. Mechanism of cell death induced by magnetic hyperthermia with nanoparticles of [gamma]-MnxFe2-xO3 synthesized by a single step process. J Mater Chem 2007;17:5042-51.
45. Park J-H, von Maltzahn G, Xu MJ, Fogal V, Kotamraju VR, Ruoslahti E, et al. Cooperative nanomaterial system to sensitize, target, and treat tumors. Proc Natl Acad Sci U S A 2010;107:981-6.
46. Singh R, Lillard JW. Nanoparticle-based targeted drug delivery. Exp Mol Pathol 2009;86:215-23.
47. Ribeiro AM, Amaral C, Veiga F, Figueiras A. Chapter 8 - Polymeric micelles as a versatile tool in oral chemotherapy. In Design and Development of New Nanocarriers, Ed. Grumezescu AM. William Andrew Publishing;2018. 293-329.
48. Cho H, Kwon GS. Polymeric Micelles for Neoadjuvant Cancer Therapy and Tumor-Primed Optical Imaging. ACS Nano 2011;5:8721-9.
49. Li J, Wang X, Zhang T, Wang C, Huang Z, Luo X, et al. A review on phospholipids and their main applications in drug delivery systems. AJPS 2015;10:81-98.
50. Bozzuto G, Molinari A. Liposomes as nanomedical devices. Int J Nanomed 2015;10:975-99.
51. Deshpande PP, Biswas S, Torchilin VP. Current trends in the use of liposomes for tumor targeting. Nanomed2013;8:1509-28.
52. Sawant RR, Torchilin VP. Challenges in Development of Targeted Liposomal Therapeutics. AAPS J 2012;14:303-15.
53. Guterres SS, Alves MP, Pohlmann AR. Polymeric Nanoparticles, Nanospheres and Nanocapsules, for Cutaneous Applications. Drug Target Insights 2007;2:147-57.
54. Champion JA, Walker A, Mitragotri S. Role of Particle Size in Phagocytosis of Polymeric Microspheres. Pharm Res 2008;25:1815-21.
55. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res 1995;12:413-20.
56. Chalasani KB, Russell-Jones GJ, Yandrapu SK, Diwan PV, Jain SK. A novel vitamin B12-nanosphere conjugate carrier system for peroral delivery of insulin. J Control Release 2007;117:421-9.
57. Petkar KC, Chavhan SS, Agatonovik-Kustrin S, Sawant KK. Nanostructured materials in drug and gene delivery: a review of the state of the art. Crit Rev Ther Drug Carrier Syst 2011;28:101-64.
58. Kumar B, Jalodia K, Kumar P, Gautam HK. Recent advances in nanoparticle-mediated drug delivery. J Drug Deliv Sci Technol 2017;41:260-8.
59. Diaz MR, Vivas-Mejia PE. Nanoparticles as Drug Delivery Systems in Cancer Medicine: Emphasis on RNAi-Containing Nanoliposomes. Pharmaceuticals 2013;6:1361-80.

60. Kolte A, Patil S, Lesimple P, Hanrahan JW, Misra A. PEGylated composite nanoparticles of PLGA and polyethylenimine for safe and efficient delivery of pDNA to lungs. Int J Pharm 2017;524:382-96.
61. Lu JM, Liang Z, Wang X, Gu J, Yao Q, Chen C. New polymer of lactic-co-glycolic acid-modified polyethylenimine for nucleic acid delivery. Nanomed2016;11:1971-91.
62. Zhang J, Tang H, Liu Z, Chen B. Effects of major parameters of nanoparticles on their physical and chemical properties and recent application of nanodrug delivery system in targeted chemotherapy. Int J Nanomedicine 2017;12:8483-93.
63. Elsaesser A, Howard CV. Toxicology of nanoparticles. Adv Drug Deliv Rev 2012;64:129-37.
64. Reddy AV, Jaafar J, Umar K, Majid ZA, Aris AB, Talib J, et al. Identification, control strategies, and analytical approaches for the determination of potential genotoxic impurities in pharmaceuticals: a comprehensive review. J Sep Sci 2015;38:764-79.
65. Dow LK, Hansen MM, Pack BW, Page TJ, Baertschi SW. The assessment of impurities for genotoxic potential and subsequent control in drug substance and drug product. J Pharm Sci 2013;102:1404-18.
66. Peppas NA. Historical perspective on advanced drug delivery: how engineering design and mathematical modeling helped the field mature. Adv Drug Deliv Rev 2013;65:5-9.
67. Kumarathasan P, Breznan D, Das D, Salam MA, Siddiqui Y, MacKinnon-Roy C, et al. Cytotoxicity of carbon nanotube variants: a comparative in vitro exposure study with A549 epithelial and J774 macrophage cells. Nanotoxicology 2015;9:148-61.
68. Salatin S, Yari Khosroushahi A. Overviews on the cellular uptake mechanism of polysaccharide colloidal nanoparticles. JCMM 2017;21:1668-86.