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Chapter 5

Synthetic Polymer-Based Nanoparticles: Intelligent Drug Delivery Systems

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Additional information is available at the end of the chapter

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Abstract

One of the most promising strategies to improve the bioavailability of active pharmaceutical ingredients is based on the association of the drug with colloidal carriers, for example, polymeric nanoparticles, which are stable in biological environment, protective for encapsulated substances and able to modulate physicochemical characteristics, drug release and biological behaviour. The synthetic polymers possess unique properties due to their chemical structure. Some of them are characterized with mucoadhesiveness; another can facilitate the penetration through mucous layers; or to be stimuli responsive, providing controlled drug release at the target organ, tissues or cells; and all of them are biocompatible and versatile. These are suitable vehicles of nucleic acids, oligonucleotides, DNA, peptides and proteins. This chapter aims to look at the 'hot spots' in the design of synthetic polymer nanoparticles as an intelligent drug delivery system in terms of biopharmaceutical challenges and in relation to the route of their administration: the non-invasive—oral, transdermal, transmucosal (nasal, buccal/sublingual, vaginal, rectal and ocular) and inhalation routes—and the invasive parenteral route.

Keywords: poly(ε-caprolactone), poly(lactide-co-glycolide), Eudragit, carbopol, poly(vinyl alcohol), acrylates, vinyl polymers, methacrylates, drug delivery, route of administration

1. Introduction

There is no uniform definition of drug delivery systems (DDSs). Generally, a drug delivery system consists of one or more drug compounds, the technology which carries out the drug(s) inside of the body (medical device or dosage form) and the drug-release mechanism [1]. According to the European Pharmacopoeia (Ph. Eur. 8.0; pg.777), conventional-release (or immediate-release) dosage forms are preparations showing a release of the active substance(s) which

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is not deliberately modified by a special formulation design and/or manufacturing method. These forms often suffer from some drawbacks in terms of higher dose of the active pharmaceutical ingredients (APIs), lower effectiveness, toxicity and adverse side effects. Modified-release drug delivery systems (MRDDS) have been developed to overcome the disadvantages of the conventional-release dosage forms. They could provide increased efficacy of the API and decreased toxicity/side effects, controlled and/or site-specific delivery, enhanced convenience, lower healthcare cost and better patient compliance.

Roughly, the drug substances suffer from two major problems: solubility and permeability. These two characteristics are responsible for the drug bioavailability upon oral administration and are the basis used to classify the APIs into four fundamental classes; a methodology known as the Biopharmaceutical Classification System (BCS), launched by Amidon and co-workers [2]. One of the most promising strategies to improve their bioavailability is based on the association of API with colloidal carriers, for example, polymeric nanoparticles (NPs), which are stable in biological environment, protective for encapsulated substances and able to modulate physicochemical characteristics, drug release and biological behaviour. Particular attention has to be paid to NPs made by synthetic polymers. These polymers possess unique properties due to their chemical structure, the type of the functional groups in the molecule, the degree of polymerization, the method of synthesis etc. [3–9]. For example, acrylates are pharmacologically inactive and due to their film-forming characteristics, these possess a good compatibility with mucosal membranes. Some of them are insoluble at physiological pH values and capable of swelling as opposed to the others, pH-responsive polymers, which are soluble only at pH 6–7. Those of them which are polycationic polymers are characterized by better mucoadhesive properties [10]. Furthermore, these are suitable vehicles of nucleic acids, oligonucleotides, DNA, peptides and proteins [11]. Aliphatic polyesters, such as poly(ε-caprolactone) (PCL), poly(lactic acid) (PLA) and their co-polymers, are the most exploited polymers because of their biodegradability, biocompatibility and versatility [12–14].

This chapter aims to look at the 'hot spots' in the design of synthetic polymer NPs as an intelligent drug delivery system in terms of biopharmaceutical challenges and in relation to the route of their administration: the non-invasive—oral, transdermal, transmucosal (nasal, buccal/sublingual, vaginal, rectal and ocular) and inhalation routes—and the invasive parenteral route.

2. The challenge: synthetic-based polymeric drug delivery systems and routes of administration

For the preparation of an optimal therapeutic DDS, the following knowledge is required: (i) the physiological characteristics of the organ and tissues in which the API will be absorbed, (ii) the mechanism of absorption and the degree of loss of the API in the biological layers before absorption, (iii) the influence of the properties of the active substance and the drug formulation on the process of absorption and (iv) the possibility of enhancing the bioavailability in the biological tissues and increasing the therapeutic activity of the API, by using appropriate technological approaches to create a stable, tolerable and effective drug

formulation. NPs possess an incredible potential to be the most effective DDS. These can (i) protect the drug from the hazardous environment, (ii) affect its solubility in the biological medium, (iii) improve its permeability through the biological membranes, (iv) provide a target drug delivery, (v) permit the administration of a lower dose, (vi) enhance the drug bioavailability, (vii) reduce the systemic side effects and drug toxicity and (viii) ensure a high patient compliance.

2.1. Nanoparticle drug delivery systems obtained from synthetic polymers for oral administration

Oral route of drug administration is preferred by the patients. Therefore, these dosage forms are always in the researchers' focus. It is well known that if a drug to be absorbed in the body, it should have to be in the soluble state. This is particularly true for the oral drug administration. Let us look at what kind of technological problems can create the APIs from different classes of BCS.

Class I: The drug substances which are characterized with both high solubility and high permeability fall in this class. Usually, they do not have bioavailability problems because they dissolve fast and quantitatively, and are readily taken up by intestine. A very fast increase in blood plasma levels is observed for these APIs. But sometimes, from a pharmacokinetic perspective, slower and longer lasting action would be desirable. Polymer-based nanoparticle formulations that deliberately retard drug dissolution are an option for driving the kinetics in the direction of prolonged-release systems.

Class II: Class II APIs represent the largest class of substances in today's drug delivery pipelines. These drugs easily penetrate the relevant physiological barriers but suffer from poor solubility in the aqueous body fluids. There are three main technological approaches to overcome this issue, such as the usage of surfactants, complex formation and nanotechnology. The application of the last one is being discussed later in this chapter.

Class III: These APIs are soluble in the aqueous body fluids, but suffer from low permeability. Most likely they will be excreted without exercising a physiological effect. The use of selective penetration enhancers is a mechanism that can increase the permeation of molecules through the gastrointestinal wall.

Class IV: The drugs falling in this class suffer from both low solubility and low permeability. However, in such cases, prodrugs with enhanced dissolution and permeability that will be converted into active agents under physiological conditions are certainly a possibility to consider.

In this regard, the usage of nanoparticle-based DDSs can be a very promising approach in two opposite directions: (i) To modulate drug dissolution (Class I) in order to achieve desired release kinetics and prolonged release and (ii) to improve the solubility of poorly water-soluble drugs (Class II) which represent the main group of APIs [15–17]. Synthetic-based polymer NPs may solve these problems for the oral delivering of proteins and vaccines. These are promising candidates as drug- and gene-carriers, and could be an elegant approach to cancer-targeted drug delivery.

On the other hand, another challenge of the oral delivery is a result of the obstacles presented by the gastrointestinal tract (GIT) namely, exposure to a wide range of pH environments, enzymatic degradation and poor permeability across the intestinal epithelium. Polymeric NPs could be a very promising approach to provide enhanced drug stability to overcome the mucus barrier (mucus-penetrating biopolymers) or to interact with the intestinal mucus layer (mucoadhesives) increasing the residence time and contact with the epithelium, and to ensure target drug delivery. As a result, an increased concentration of released APIs at the site of absorption could be achieved [18].

The diabetes mellitus is a socially significant disease which affects many people and will increase to 438 million worldwide by the year 2030, according to the World Health Organization (WHO) [19, 20]. Insulin therapy is the best choice for the clinical management of type I diabetes mellitus but its subcutaneous administration leads to a poor patient compliance. Oral route could be preferable but insulin cannot be well absorbed orally because of its rapid enzymatic degradation in the GIT. Polymer NPs have huge potential for the effective oral delivery of insulin. According to Alai et al. [20], polymeric NPs and micelles could provide better drug stability in the harsh GIT environment and enhanced drug transport ability. It could be ensured by biocompatible polymers with mucoadhesive and absorption-enhancing properties (e.g. Eudragit L100-55 and Eudragit S100, poly(lactide-co-glycolide) (PLGA), PCL, alginate, chitosan and dextrane).

Recently, Gutjahr et al. [21] have highlighted the potential application of biodegradable polymeric NPs-based vaccine adjuvants for lymph nodes targeting. The authors have presented the different PLGA, PLA and PCL-based nanoparticulate adjuvants as innovative systems, capable of co-delivering immunopotentiators and antigens which may (i) enhance the drug delivery, (ii) increase the persistence into lymph nodes and promote a mature immune response and (iii) direct the response to a specific antigen and allow the induction of a cytotoxic immune response. This approach could be very promising to limit the spread of diseases caused by HIV, *Chlamydia trachomatis* and *Bacillus anthracis*.

Ma et al. [22] have developed a novel delivery approach for tumour antigenic peptides in order to elicit enhanced immune responses using PLGA-NPs encapsulating tumour antigenic peptides. They have found that human dendritic cells (DCs) loaded with PLGA-NPs encapsulating a peptide cocktail induced a significantly stronger antigen-specific T lymphocytes response in comparison with those including free peptide. The PLGA-NPs loaded with a 63 times lower peptide dose showed more prominent antigen-specific T lymphocytes response *in vivo* than that emulsified in incomplete Freud's adjuvant.

Biomaterial-based nanoparticulate delivery systems that encapsulate a plasmid DNA represent a better strategy for DNA vaccine delivery compared to those delivered as naked plasmid DNA due to their degradation and inefficiency [23]. The PLA-poly(ethylene glycol) (PLA-PEG) NPs containing a high loading of plasmid DNA in a free form or co-encapsulated with either poly(vinyl alcohol) (PVA) or poly(vinyl pyrrolidone) (PVP) have been prepared by different techniques [24]. The researchers have found that plasmid DNA can be very efficiently encapsulated into PLA-PEG NPs and, depending on the processing conditions, these NPs release plasmid DNA either very rapidly or in a controlled manner. Furthermore, NPs-in-microsphere oral system (NiMOS) for gene delivery and transfection in specific regions of

the GIT has been developed and evaluated [25]. Plasmid DNA has been encapsulated in type B gelatin NPs. NiMOS have been prepared by further protecting the DNA-loaded NPs in a PCL matrix to form microspheres. The results of biodistribution studies showed that NiMOS resided in the stomach and small intestine for relatively longer duration. After 5 days of post-oral administration, the authors have observed transgene expression in the small and large intestine of rats. Based on these results, NiMOS could be considered as a potential gene delivery vehicle for therapeutic and vaccination purposes.

Environmentally responsive biomaterials are commonly used to achieve controlled drug release in the GIT [26, 27]. The pH-responsive polymers (e.g. Eudragit), mucoadhesives (e.g. carbopol), enzyme-responsive (e.g. guar gum) and pressure-sensitive polymers (e.g. PEG-ethylcellulose) are frequently incorporated into nanoparticle-loaded microdelivery devices to improve oral drug delivery [28].

Recently, a class of lipid-like materials termed 'lipidoids' (synthesized by the Michael addition of alkyl-amines to alkyl-acrylates) have been shown as potential delivery systems of siRNA to the liver and immune cells [29]. The authors established that a single 10 nM dose of siRNA-loaded lipidoid NPs depressed GAPDH mRNA expression for a week and provided powerful, dose-dependent and stable gene silencing in *Caco-2* cells. Moreover, they found no significant induction of cytotoxicity in cells or changes in intestinal barrier function. In this regard, the potential of lipidoid NPs for the treatment of intestinal disorders can be emphasized.

The investigations presented above are just a few examples that strongly suggest the enormous potential of polymeric-based NPs as DDSs for oral administration directing to improve the bioavailability of APIs.

2.2. State-of-the-art topical and transdermal drug delivery nano-carriers

Skin is the largest organ in the human body and it acts as a permeation barrier, mainly due to the *stratum corneum* which is a part of its structure. On the other hand, this large area could be used as a unique delivery pathway for APIs. They can penetrate (i) into skin strata providing topical drug delivery and (ii) through subcutaneous tissues and pass into systemic circulation providing transdermal delivery. It is well known that only APIs characterized by moderate lipophilicity and molecular weight less than 500 Da are able to permeate the *stratum corneum* and penetrate into deeper layers of the skin. Passive and active permeation enhancement methods have been widely applied to increase the skin penetration. Zhang et al. [30] have presented in depth the permeation enhancement methods as well as the major challenges for the treatment of various dermatological diseases. They have put the focus on the penetration of ultra-small NPs into skin strata, the targeted delivery of the encapsulated APIs to hair follicle stem cells, and the combination of NPs and microneedle array technologies for special applications, such as vaccine delivery. Recent literature has demonstrated that NP-based DDSs for topical application can be very successful due to the chemical and physical protection of drug used, controlled release, and cell and tissue-specific targeting [11, 31–33]. These systems combine the advantages of both the nanosized drug carriers and the topical approach, and are promising for the treatment of various skin diseases providing a high patient compliance.

A few studies have described the successful application of tyrosine-derived nanospheres (ThyroSpheres™) as DDSs of lipophilic molecules like paclitaxel and Vitamin D3 [30, 34, 35]. These polymeric nanospheres provide sustained drug release, improve the skin delivery and enhance the chemical stability of drug used. In another study, Batheja et al. [36] have investigated a gel formulation (carbopol and hydroxypropyl methylcellulose (HPMC)) containing tyrosine-derived nanospheres. The authors have found that dispersion of Nile Red-loaded nanospheres in 1% w/v HPMC gel (i) did not show any short-term cellular toxicity or tissue irritation, (ii) the deposition of Nile Red via the nanosphere gel in the upper and lower dermis has been 1.4- and 1.8-fold higher, respectively, than the amount of Nile Red deposited via an aqueous nanosphere formulation and (iii) Azone (0.2 M) incorporation into nanosphere gel formulation led to a 1.4-fold additional increase of drug deposition in porcine *stratum corneum* and epidermis. In this regard, ThyroSpheres™ dispersed in gels could provide improved topical delivery of lipophilic drugs and agents for personal hygiene.

Pharmacokinetics and anti-inflammatory effect of a novel carbopol 934 gel system containing ketoprofen-methylcellulose solid NPs have been studied by Nagai et al. [37]. The authors have established that the penetration rate (Jc) and penetration coefficient through the skin (Kp) values of the ketoprofen-NP-loaded gel have been significantly higher than those of gel containing ketoprofen micro-particles as well as apparent absorption rate constant (ka), area under the curve (AUC) and the amounts of the drug in the skin of rats have also been significantly higher than those of rats receiving the ketoprofen micro gel. These findings suggest that the topical DDS using NPs could lead to an expansion in the therapeutic use of the drug.

Methyl methacrylate copolymers (Eudragit®) have been exploited to develop transdermal patches, medicated plasters (hereinafter patches), film-forming sprays, microsponges and NPs intended to be applied on the skin. Cilurzo et al. [38] have reviewed the information regarding the application of Eudragits in the design and development of these dosage forms focusing on the impact of formulative variables on the skin drug penetration and the patch adhesive properties. The authors have reported that a strict connection between the matrix hydrophilicity and drug penetration probably exists. Moreover, micro- and nano-systems exploiting the ionizable nature of some Eudragits can offer novel opportunities to develop pH-sensitive DDSs suitable for triggering its release onto the skin.

Transcutaneous immunization is a promising vaccination strategy for the treatment of infectious diseases and cancer. Rancar et al. [39] have studied PLA and polystyrene (PS) particle-based antigen (HIV-1 p24 protein) delivery across partially disrupted skin barrier (cyanoacrylate skin surface stripping). The authors have established that the polymer particles targeted HIV-1 p24 protein to the hair follicles and it has been found in skin cells, especially in Langerhans cells and dermal DCs after diffusion of p24 protein to the epidermis and dermis. The researchers have concluded that particle-based antigen delivery across partially disrupted skin barrier is a feasible and effective approach to needle-free transcutaneous vaccination.

Microneedle skin patches represent an attractive technology for non-invasive transcutaneous delivery of vaccines. These DDSs use the accessibility and proven immune competence of the skin for enhanced immunity. They mimic several aspects of cutaneous pathogen invasion by targeting antigen to skin-resident DCs and triggering local inflammatory responses in the

skin, which are correlated with enhanced immune responses. DeMuth et al. [40] have tested whether the control over vaccine delivery kinetics can enhance the immunity through further mimicry of the kinetic profiles presented during natural acute infections. The authors have prepared microneedles which consist of a silk tip and a poly(acrylic acid) (PAA) base. The skin application of microneedle patches to deliver a vaccine with improved release kinetics led to >10-fold increases in antigen-specific T cell and humoral immune responses compared to the traditional parenteral immunization.

2.3. Synthetic-based nano- and micro-particles intended for transmucosal drug delivery

Transmucosal routes of drug delivery include transport across the nasal, rectal, vaginal, ocular and oral cavity mucous membranes, and offer distinct advantages over oral administration for systemic drug delivery. The main advantages of this route include a possible circumvention of first-pass effect and avoidance of pre-systemic elimination within the GIT.

2.3.1. Intranasal nanoparticle-based drug delivery systems

Different approaches to improve the nasal drug bioavailability have been described in the scientific literature. The strategies are limited to (i) enhancing the nasal absorption, (ii) modifying the structure of the drug and the physicochemical properties and (iii) increasing the residence time. Polymeric nano- and micro-particles can reduce the processes of drug degradation by chemical derivatization or covalent bonding and increase the residence time on the mucous membranes. These DDSs may include in addition enzyme inhibitors, promoters of absorption and/or mucoadhesive polymers in order to increase stability, membrane permeability and retention time in the nasal cavity. The intranasal route is successfully used for drug delivery of low molecular weight APIs with non-peptide structure, peptides (insulin, calcitonin and thyroid hormones), vaccines and direct delivery in the central nervous system.

Intranasal delivery seems to be a promising approach for drug delivery across the blood-brain barrier (BBB) to the brain, providing a significant advantage over currently used strategies without damaging the BBB. Alzheimer's disease is a socially significant neurological disorder that results in cognitive and behavioural impairment. It affects many people all over the world and their number increases rapidly. Fonseca-Santos et al. [41] have presented an extended review about the significant benefits that intranasal polymer nanoparticle-based DDSs could ensure in the treatment of this disorder. Polymeric NPs (quinoline-n-butyl cyanoacrylate-based NPs, rivastigmine-loaded poly(n-butyl cyanoacrylate NPs) coated with polysorbate 80 and polysorbate 80-coated solid lipid NPs have been used for both diagnostic and treatment of Alzheimer's disease.

Although the results presented by Zhuang et al. [42] suggest that intranasal delivery of an anti-inflammatory agent, such as curcumin, and the anti-Stat3 agent, JSI-124, provides a promising non-invasive approach for the treatment of brain inflammatory-related diseases, such as malignant gliomas, biosafety considerations have been challenging. Recently, the researchers have developed a grapefruit-derived nanovector hybrid with polyethylenimine (pGNV) for effective intranasal delivery of miRNA to the brain [43]. The authors have found

that the hybrid not only enhanced the capacity to carry RNA but also eliminated the toxicity of the polyethylenimine. Enhanced targeting has been further achieved by coating pGNVs with the tumour targeting moiety, folic acid.

The use of polymeric carriers for drug delivery to the brain via the nose-to-brain route holds great promise, on the basis of pre-clinical research and clinical data. On the other hand, a strict toxicity assessment of NPs regarding to the morphology and functions of nasal mucosa, the target drug delivery and the biopharmaceutical characteristics and pharmacokinetics of NPs is needed before these find a clinical utility [44]. The regulatory agencies recommend the implementation of 'Quality by Design' (QbD) and the process optimization for the product development to produce a safe and effective intranasal DDS. The characteristics of the NPs, such as particle size, size distribution, particle shape, surface chemistry and structure are crucial for nanoparticle uptake by the nasal mucosa and will determine the therapeutic effect and possible toxicity.

The PLGA has been widely explored for preparation of polymeric NPs and is well reported for its mucoadhesive properties, improved drug stability and enhanced entrapment efficiencies. Lorazepam-loaded PLGA-NPs have been formulated using a nanoprecipitation approach [45]. This DDS showed controlled lorazepam release and potential outcome which have been optimized using 4-factor, 2-level Box-Behnken design.

Furthermore, stimuli responsive polymers have been widely exploited as nasal DDSs. These smart polymers possess liquid state at room temperature and in response to the nasal temperature, pH and ions present in mucous, can undergo *in situ* gelation in the nasal cavity. These are able not only to enhance the drug retention in the nasal cavity but also to provide controlled release, ease of administration, enhanced drug permeation and protection of the drug from mucosal enzymes. Some of the aspects of the stimuli responsive polymers and their gelling mechanisms have already been discussed [46]. Thermoresponsive polymers (e.g. poloxamer 407) and combination thereof with mucoadhesive carbomers, chitosan and cellulose derivatives are widely used to improve the drug bioavailability. For example, to improve the intranasal absorption of plasmid DNA, Park et al. [47] have designed delivery systems composed of *in situ* gelling poloxamers and mucoadhesive polycarbophil or polyethylene oxide (PEO) polymers. The authors have found that at 3 h post-dose, the nasal tissue levels of plasmid DNA given in poloxamer/polycarbophil and poloxamer/PEO 0.8% have been 10- and 40-fold higher relative to saline. These findings have indicated the safety and effective utilization of *in situ* gelling and mucoadhesive polymers for intranasal plasmid DNA delivery.

In another study, Nakamura et al. [48] have formulated mucoadhesive pH-sensitive budesonide micro-particles of poly(methacrylic acid) and PEG for nasal delivery. Following nasal administration of the budenoside-loaded polymeric micro-particles, the peak plasma concentration has been reached in about 45 min, and the concentration in plasma remained constant for a minimum of 8 h compared to intravenous drug administration where the plasma concentration peaked immediately and decreased rapidly over the next 4 h. Thus, intranasally administered budesonide-polymer DDS possesses enhanced durability of the drug concentration in plasma. Furthermore, polyvinyl acetal dimethyl aminoacetate pH-sensitive gel has provided controlled release of chlorpheniramine maleate and tetrahydrozoline hydrochloride incorporated [49].

All the experimental results presented above disclose the huge potential of the intranasal route for drug administration especially using polymeric-based nano- and micro-particle DDSs. The considerations according to their biosafety, the quantity of API administered nasally that will be transported directly from nose to the target tissues and the mechanism of this transport should be estimated.

2.3.2. Rectal and vaginal route of drug delivery

Towards the development of vaginal DDSs, the most often used polymers are PCL, PLA, PLGA, poly(methyl methacrylate), PS etc. They may incorporate low molecular weight APIs as well as nucleic acids for the prevention of viral infections, responsible for genital herpes, AIDS and cervical carcinoma. Usually, these polymers possess good mucoadhesiveness and thereby increasing the residence time, they provide a higher bioavailability. The efforts are aimed at creating muco-penetrating NPs for vaginal and rectal administration [50]. For example, different surface-engineered PCL NPs have been designed to modulate the permeability and retention of dapivirine (microbicide against HIV/AIDS) in vaginal and rectal mucosa [51]. The results presented demonstrated that PEO-modified PCL NPs are very suitable carriers for vaginal and rectal delivery of microbicides due to their ability to modify drug permeability and retention in mucosal tissues.

An even greater challenge is the use of so-called 'gene silencing' in the treatment of vaginal infections and carcinomas. Woodrow et al. [50, 52] have provided significant evidence that siRNA complexes could be successfully delivered by PLGA-NPs, providing sustained gene silencing in the female reproductive tract. Later, Steinbach et al. [50, 53] have showed that siRNA delivery via PLGA-NPs could provide protection against vaginal infection. Furthermore, these results are further evidence that siRNA-loaded PLGA-NPs may provide vaginal protection from sexually transmitted infections with improved safety compared to conventional siRNA delivery vehicles.

Nanofibres have various applications, one of which is drug delivery, especially in local chemotherapy. Recently, drug-loaded ultrafine fibres have been used in local chemotherapy of cervical cancers. Biodegradable PLA fibre mats loaded with paclitaxel showed strong inhibition of xenograft U14 cervical cancer [54]. In another study, *in vivo* trials of cisplatin-loaded PEO/PLA composite electrospun nanofibres demonstrated enhanced anti-tumour efficacy with better systemic safety than the intravenous injection group [55]. This indicates the benefits of localized delivery over systemic delivery. Ordikhani et al. [56] have summarized some of the recent research in systemic and localized DDSs and compared the advantages and disadvantages of these methods in the treatment of cervical cancer.

Yoo et al. [57] have reported the development of pH-responsive NPs prepared from Eudragit® S-100 that are characterized by low encapsulation efficiency for hydrophilic compounds (26%) compared to hydrophobic compounds (71%). Burst release occurred at pH 7.4 in the range expected when semen contacts vaginal mucus because this formulation has been made of pH-sensitive polymer. The pH-sensitive NPs would be a promising carrier for the vaginal-specific delivery of various therapeutic drugs including microbicides and peptides or proteins.

For inflammatory bowel disease treatment, local delivery of molecules loaded in NPs to the inflamed colon could be a promising strategy. Mucoadhesive and pH-sensitive ovalbumin (OVA)-loaded NPs as well as NPs for sustained drug delivery have been obtained from trimethylchitosan (TMC), Eudragit® S100 and a polymer mixture (PLGA, PEG-PLGA and PEG-PCL), respectively, for a target colon delivery to the inflamed tissues [58]. Mannose or a specific peptide has been grafted on the PEGylated NPs to ensure the target drug delivery. The TMC NPs had the highest apparent permeability for OVA in the untreated model. However, in the inflamed model, there was no difference between TMC, PLGA-based and Eudragit® NPs. Mannose-grafted PLGA-NPs showed the highest accumulation of OVA in inflamed colon. Based on these results, active targeting of macrophages and DCs may be a promising approach for targeting the colon in inflammatory bowel disease.

2.3.3. Recent advances in ophthalmic nanoparticulate drug delivery carriers

Prospects for the application of polymeric micro- and nano-carriers as DDSs in ophthalmic preparations are related to an improved solubility of less soluble drugs, a controlled release, a targeted transport and an enhanced chemical stability in order to increase efficiency and reduce side effects, overcoming physiological barriers and delivery of APIs to the posterior segment of the eye, wherein the penetration is usually hampered [59–67]. An important feature of ophthalmic DDSs is the ability of retention in the ocular tissues. In this regard, the characteristics of polymers like mucoadhesivness and option for modelling of their surface properties are crucial. Synthetic-based polymer NPs obtained by polyacrylates, polymethylmetacrylates, polyalkylcyanoacrylates and polyvinyl acetates (PVAc), PCL, PLA, PLGA etc. meet these basic features and their properties as DDSs can be modified [59–66]. Giannavola et al. [67] have found that both, uncoated and PEG-coated acyclovir-loaded PLA NPs, characterized with sustained drug release have been well tolerated, but PEG-coated NPs have shown greater efficacy compared to uncoated NPs. A great number of studies, related to the preparation of nanoparticulate DDSs that provide a good retention and sustained drug release, can be found in the scientific literature. There are examples like indomethacin-loaded PVAc/carbopol NPs, indomethacin-loaded PVAc/chitosan NPs, pilocarpine-loaded chitosan/carbopol NPs, rapamycin-loaded chitosan/PLA NPs, gatifloxacin/prednisolone-loaded NPs of Eudragit RS100 and RL100 coated with hyaluronic acid, sparfloxacin- and levofloxacin-loaded PLGA-NPs, etc. [61, 62, 68–72]. Generally, the authors have concluded that the use of this kind of polymers leads to increased pre-corneal residence time and improve the drug penetration across the cornea. As previously mentioned, these nanoparticulate DDSs provide enhanced drug stability, increased residence time, better bioavailability in ophthalmic tissues, controlled release and good biotolerability.

In the past few years, a variety of novel stimuli responsive ophthalmic DDSs have been reported. The combination of NPs and *in situ* gel has been developed [73, 74]. It is known as 'nanoparticle laden *in situ* gel'. In an extensive review, Kumar et al. have described every aspect of this novel formulation [75]. The polymeric nanoparticle-loaded *in situ* gel provides a sustained and prolonged release. Biodegradable and water-soluble polymers make them more acceptable and excellent DDSs. These *in situ* activated gel-forming systems seem to be

favoured as they can be administered in a drop form and produce considerably less blurred vision. Owing to its control of drug release, the dosage form is more acceptable by the patients and thus increases the patient compliance [75].

The bioavailability of ophthalmic drugs can be improved by soft contact lenses-based ophthalmic DDSs. For example, the cross-linked NPs based on PCL, 2-hydroxyethyl methacrylate (HEMA) and poly-ethylene glycol diacrylate (PEG-DA) have been prepared by surfactant-free mini emulsion polymerization. The lens material has been prepared through photopolymerization of HEMA and N-vinylpyrrolidone (NVP) using PEG-DA as cross-linker. NPs and hydrogel showed high viability, indicating the absence of cytotoxicity and stimulatory effect. The drug-release studies revealed that the hydrogel embedded with NPs released the loteprednol etabonate for a period of 12 days [76].

Many polymeric systems have been used to fabricate ocular inserts to improve ocular bioavailability and drug retention. The inserts have shown some advantages like reduced dosing frequency and increased corneal residence time. For example, a cross-linked and Eudragit RL-100-coated ocular insert of gatifloxacin provides better *in vitro* drug release and sustained up to 11 h [77]. Recently, Thakur et al. [78] have prepared bioerodable insert of azithromycin in order to prolong the release time and improve the ocular availability in ophthalmic infections. The model comprising of 1.5% HPMC and 3% Eudragit RL100 has been found to be optimized formulation on the basis of uniformity of thickness and weight, surface pH, folding endurance, percentage moisture loss, percentage moisture absorption, drug content, *in vitro* release, AUC for *in vitro* and *in vivo* release which have been higher than pure drug and shelf life. Furthermore, better ocular tolerability has been found.

GrayBug's controlled release technologies are based on proprietary biodegradable drug-loaded PLGA-NPs, micro-particles and injectable implants providing extended release of small to large molecules for intraocular applications to treat neovascular diseases, such as age-related macular degeneration (AMD), diabetic retinopathy and glaucoma [79].

The Particle Replication in Non-wetting Templates (PRINT) technology offers a unique ability to reproducibly fabricate particles of virtually any size, shape, chemistry, surface functionality, modulus and porosity. Additionally, PRINT has been shown previously to be broadly compatible with a wide range of biodegradable polymers (e.g. PLGA) and molecular entities including small molecules, nucleic acids, enzymes and therapeutic monoclonal antibodies [80]. The unique flexibility of PRINT has been used to develop biodegradable nano- and micro-particle suspensions and biodegradable implants for extended drug delivery into the eye. Such products are ENV515 intra-cameral extended-release prostaglandin analogues and ENV705 extended-release anti-VEGF formulation for AMD therapy. In the ENV705 implant, a trehalose/bevacizumab mixture is dispersed within a polyglycolic acid matrix allowing drug release of effective concentrations over 3–6 months [81].

The use of NPs in ophthalmic formulations can solve most of the problems of drug delivery, mainly related with low bioavailability in the target eye tissues. Mucoadhesive, mucus-penetrating NPs or nanoparticle-loaded *in situ* gelling systems may significantly increase the pre-corneal residence time and ocular penetration, thus improving the drug bioavailability.

The undeniable advantages that these systems provide, as a sustained drug release, a reduced administration frequency and a higher patient compliance, give us grounds to believe that in the next few years, some of them will find their place on the ophthalmic market [82].

2.3.4. Buccal/sublingual route of drug administration

The buccal cavity has a very limited surface area (around 50 cm^2) but the easy access to the site makes it a preferred location for delivering APIs. Buccal route of drug administration is used for the treatment of local diseases of the oral cavity as well as for achievement of systemic effect by avoiding hepatic first-pass metabolism. The sublingual mucosa is relatively more permeable than the buccal mucosa due to the presence of a large number of smooth muscle and immobile mucosa. Therefore, sublingual formulations are designed to release the APIs quickly. The buccal cavity is more suitable for mucoadhesive DDSs and the API could be released in a controlled manner. Bioadhesive micro- and NPs offer more advantages compared to conventional buccal tablets due to their high surface area which allows them to make contact with a larger mucosal surface. The polymers used to prepare these systems must meet the following requirements, such as rapid attachment to the mucosal surface, maintaining a strong interaction which prevents any displacement and the bioadhesion performance should not be impacted by surrounding environmental pH. The various mucoadhesive polymers used for the development of buccal DDSs include cyanoacrylates, PAA, sodium carboxymethylcellulose, hyaluronic acid, hydroxypropyl cellulose, polycarbophil, chitosan and gellan [83].

For example, nanofibre-based mucoadhesive films were invented for oromucosal administration of drug- and vaccines-loaded nano-carriers [84]. The mucoadhesive film consists of (i) an electrospun nanofibrous reservoir layer where the NPs can be reversibly adsorbed or they can be deposited in the pores between the nanofibres, (ii) a mucoadhesive film layer and (iii) a protective backing layer. After mucosal application, nanofibrous reservoir layers are intended to provide prolonged release of NPs into the submucosal tissue. To prove this concept, trans-/intra-mucosal and lymph-node delivery of PLGA-PEG NPs has been demonstrated in a porcine model. This system can mainly be used for sublingual immunization and the development of 'printed vaccine technology'.

Carvedilol nanosuspension has been loaded into mucoadhesive buccal films containing three similar layers: mucoadhesive layer, nanosuspension-containing layer and backing membrane [85]. Carvedilol-loaded nanosuspension has been prepared by a precipitation-ultrasonication method with PVA. Nanosuspension incorporated drug-gel layer was optimized to contain 3% HPMC and 50 mg carbopol 934P. The authors have suggested that the increased relative bioavailability of the obtained formulations was due to the increased surface area of carvedilol and by-passing the hepatic metabolism.

Sapre and Parikh have formulated polymeric NPs-based mucoadhesive system intended for oral mucosal delivery of fluoxetine hydrochloride [86]. In this study, the drug has been encapsulated into poly(methyl vinyl ether/maleic anhydride) (Gantrez MS-955) mucoadhesive NPs. This buccal mucoadhesive system comprising a fluoxetin-loaded NPs layer and an ethyl cellulose layer has been characterized by by-pass first-pass effect, with relatively rapid onset, higher absorption and sustained release effect to increase bioavailability compared to oral absorption.

In another study, Al-Dhubiab has designed and evaluated zolpidem-loaded PLGA nanospheres-impregnated buccal films to prolong the duration of its action [87]. Zolpidem nanospheres have been loaded into mucoadhesive films composed of different concentrations of HPMC K100, Eudragit® RL100 and carbopol 974P. The prepared films showed adequate mucoadhesive strength and excellent physicomechanical strength. The results of the *in vitro* drug-release tests have depicted the potential of the films to provide extended drug release, while *ex vivo* studies have justified the potential of the nanospheres to permeate across the buccal membranes at a controlled rate. Furthermore, *in vivo* the studies have reinforced findings from the *in vitro* and *ex vivo* studies, demonstrating prolonged release and enhanced bioavailability of zolpidem.

Mucoadhesive drug delivery will play an even more important role in delivering of a large number of molecules: new drug molecules due to drug discovery and well-known APIs, which suffer from low solubility, poor bioavailability or chemical instability.

2.4. Nanoparticle-mediated pulmonary drug delivery

The pulmonary route, as a non-invasive method of drug administration for both local and systemic delivery of APIs, is preferable for APIs acting on pulmonary diseases and disorders. Additionally, this route offers many advantages, such as high surface area with rapid absorption due to high vascularization and circumvention of the first-pass effect [88]. The challenges for the pulmonary drug delivery are related with three main clearance mechanisms namely (i) pulmonary clearance, (ii) enzymatic degradation and (iii) rapid systemic absorption. As a result, the inhaled drugs exhibit low bioavailability in the lungs. It is well known that the particulate-based DDSs could solve the problem with drug bioavailability providing (i) drug protection from enzymatic degradation, (ii) evade pulmonary clearance, (iii) target drug delivery to the desired site at the lungs, (iv) controlled drug release, (v) reduce dose frequency, (vi) maximize the therapeutic efficiency and (vii) minimize side effects [89].

For therapeutic purposes, the most commonly used synthetic polymers include PLA, PLGA and PCL. These polymers have numerous advantages mentioned above. Furthermore, several factors, such as aerodynamic diameters, shape and surface properties of these polymer carriers can be tailored and optimized to obtain a particulate-based DDS with high therapeutic efficiency. In an extensive review, El-Sherbiny et al. [89] have presented the factors influencing pulmonary drug deposition and bioavailability as well as the significance of particulate-based pulmonary drug delivery.

For example, rifampicin-loaded PLGA microspheres with adequate aerodynamic properties for lung delivery as aerosols have been recently formulated and studied *in vitro* [90]. The solvent evaporation method with premix membrane homogenization has been applied, with class-3 ethyl acetate as organic solvent, to produce narrowly size-distributed rifampicin-loaded PLGA microspheres for sustained lung delivery as aerosol.

Recently, the development and *in vitro* characterization of PLGA microspheres loaded with totarol (an antibacterial natural drug) for the treatment of long-term bacterial infections has been presented [91]. Moreover, pitavastatin-loaded PLGA-NPs have been designed for the

treatment of pulmonary artery hypertension [92]. The authors observed delivery of NPs into alveolar macrophages and small pulmonary arteries for up to 14 days after a single intratracheal administration. The PLGA nanoparticulate-mediated drug delivery has been more effective than systemic administration of pitavastatin, attenuating the development of pulmonary artery hypertension. In addition, treatment with pitavastatin-NPs 3 weeks after monocrotaline injection induced regression of pulmonary artery hypertension and improved survival rate.

The NPs possess sizes that allow them to be easily inhaled and to reach the deep lung. On the other hand, according to the same reason, these could be exhaled. The ideal particle sizes for the pulmonary alveoli administration are between 2 and 5 μm. The Trojan micro-particles contain drug-loaded NPs. These systems offer a compromise between the range of NPs with their main advantages and the benefits which provide micro-particles. Anton et al. [93] have presented the physical principles and experimental procedure involved in the fabrication of these unique systems and their impact on drug delivery and release kinetics. The authors have paid particular attention to the biopharmaceutical application of the Trojan micro-particles. For example, an efficient Trojan delivery of tetrandrine by PVP-block-PCL NPs has shown enhanced apoptotic induction of lung cancer cells and inhibition of its migration and invasion [94].

Furthermore, Simultaneously Manufactured Nano-In-Micro (SIMANIM) particles for the pulmonary delivery of antibodies have been prepared by the spray-drying of a double-emulsion containing human IgG (as a model antibody), lactose, PLGA and dipalmitoylphosphatidylcholine [95]. The continuous release of the model antibody has been observed for 35 days in pH 2.5 release media and released antibody has been shown to be stable and active. 'SIMANIM' particles could be beneficial for the delivery of antibodies targeted against inhaled pathogens or other extracellular antigens, as well as having potential applications in the delivery of a wide range of other APIs.

Nanoparticulate-mediated pulmonary drug delivery provides many advantages compared to the conventional-release dosage forms. Although the synthetic polymer carriers used for pulmonary drug delivery are usually biocompatible and biodegradable, a strict and precise assessment of the potential toxicity and side effects is necessary to be done due to the high surface area and vascularization of the lung.

2.5. Advances in novel parenteral drug delivery systems

The parenteral route of administration is the most effective route for the delivery of the APIs with narrow therapeutic index and poor bioavailability. Major progress has been done in the field of formulation technologies using innovative polymer-based DDSs so as to provide a targeted and sustained release of drug in predictable manner and to overcome the problems associated with conventional parenteral DDSs.

For example, one of the most intriguing strategies to overcome the limitation of classical cytotoxic drugs is their formulation into nanopharmaceutical platforms, that is, nano-carriers, such as liposomes, polymeric NPs and more recently into nanocontainers based on host-guest

interactions. Furthermore, biodegradable and injectable *in situ* forming DDSs represent an attractive alternative to microspheres and implants as parenteral depot systems.

Recently, Bao et al. have evaluated daunorubicin (DNR)-loaded PLGA-poly-l-lysine (PLL)-PEG-transferrin (Tf) NPs as a DDS providing sustained release at the specific site and reduced toxicity in normal tissues [96]. The authors have observed a higher drug intra-cellular concentration in *K562* cells, an enhanced anti-cancer activity and a regulation of the expression of some proteins. In another study, to increase the encapsulation of DNR and multi-drug resistance reversal agent tetrandrine (Tet) in the DDS of NPs, Liu et al. [97] have synthesized a functional copolymer PLGA-PLL-PEG, and then it was loaded with DNR and Tet simultaneously (DNR/Tet-PLGA-PLL-PEG-NPs). These NPs have been further modified with transferrin (Tf) due to its specific binding to Tf receptors, which is highly expressed on the surface of tumour cells. The results showed that the accumulated release of DNR and Tet could be sustained over 1 week. Furthermore, the authors have found that the new DNR-loaded NPs have been more effective than DNR alone, inhibiting the cell proliferation of *K562* and *ADR* lines in a dose-dependent manner. The experimental results presented show that PLGA-PLL-PEG-Tf formulation could be very promising DDS having excellent features for target delivery.

7-Ethyl-10-hydroxy camptothecin (SN38) is a potent topoisomerase inhibitor and a metabolite of irinotecan with poor solubility which hampered its clinical development. To overcome this problem, methoxy PEG-2000 (mPEG2K)-SN38 and mPEG2K-PLA1.5K-SN38 conjugates have been prepared and then dispersed into an aqueous medium to form micelles [98]. The authors have found that SN38-loaded micelles with PLA induced a significant tumour inhibition after 30 days compared to those without PLA.

Furthermore, recent report has presented the formulation and evaluation of a core-shell type star polymer with a branched hydrophobic PS core and covalently attached poly(tert-butyl acrylate) arms, as a DDS for cisplatin [99]. The stars were loaded with cisplatin via ligand exchange reaction achieving remarkable high drug payload of 45% (w/w). The release profile of the platinum (II) complexes indicated sustained manner of drug release with no initial burst effect. *In vitro* cell viability study, using different human tumour cell lines, proved that the conjugates exhibited lower cytotoxicity compared to the free agent. Further, the design strategy has been based on functionalization of the polyacrylate arms by a PEGylated cisplatin analogue, allowing for detachment of the coating following hydrolysis in biological environment [100].

It has been noted before that nanoparticulate-based DDSs possess distinct advantages for brain drug delivery. Penetratin (a cell-penetrating peptide with relatively low content of basic amino acids) has been functionalized to PEG-PLA NPs to achieve desirable pharmacokinetic and biodistribution profiles for brain drug delivery [101]. *In vivo* pharmacokinetic and biodistribution studies showed that penetratin-functionalized PEG-PLGA-NPs exhibited a significantly enhanced brain uptake and reduced accumulation in the non-target tissues compared with low-molecular-weight protamine (a cell-penetrating peptide with high arginine content)-functionalized NPs. The application of these penetratin-functionalized NPs can be a promising strategy for brain-targeting drug delivery as well as a basis for the optimization of brain DDSs via surface charge modulation.

Recently, Shamma et al. [102] have investigated injectable *in situ* forming scaffolds loaded with risedronate (bone resorption inhibitor) and with lornoxicam (anti-inflammatory drug) for non-surgical treatment of periapical lesions. They have tested two insoluble copolymers, such as PLGA (ester-terminal) and PLGA-A (acid-terminal). Additionally, sucrose acetate isobutyrate (SAIB) has also been added as a high viscosity water-insoluble carrier as well as porogenic agents like hydrolysed collagen. The scaffolds prepared using 30% (w/v) PLGA or combined PLGA: SAIB (1:1, w/w) with total polymer concentration of 30% (w/v) possessed the most sustained drug-release profile and their application improved the inflammation and enhanced the formation of new bony regions. These results confirm the success of the prepared scaffolds as an innovative approach in the treatment of bone defects.

Nagarajan et al. [103] have synthesized two star-shaped PLA polymers with dipyridamole molecular core as a coating material for making coronary stents. The authors have used L-lactide and DL-lactide for their preparation. The difference in the features of both coating biomaterials was explained with the crystallinity of the polymers synthesized as well as with the fact that the L-form is normally available in humans. The experimental results showed that the new star-shaped PLA polymers with dipyridamol core were bio- and hemo-compatible, and possessed enhanced angiogenic properties. This is another proof for the great importance of the synthetic-based polymer carriers and their application in the pharmaceutical practice.

3. Conclusion and future prospects

The main application of NPs as DDSs and the challenges, regarding to this, lies on the efficient administration of these carriers. Along with all the benefits that these DDSs provide, the choice of route of administration is essential to their performance. The difficulties are related to their absorption at the proper organs, tissues and cells.

Unconditionally, the use of NPs as DDSs may solve most of the problems of drug delivery, mainly related with low bioavailability in the target tissues. Mucoadhesive, mucus-penetrating NPs or 'nano-in-micro-particle' DDSs may significantly increase the retention time on the mucous surface by enhancing the drug absorption and thereby improving drug bioavailability. Nanotechnologies are able to overcome the physiological barriers of the different tissues regarding the route of administration. Polymeric carriers have a stabilizing role on the drug included. They protect it from the unfavourable impact of the environment or the biological fluids. The synthetic-based polymer nano-carriers can assure a controlled release in the target tissue and minimize the side effects. The advantages that these could provide unconditionally improve the drug bioavailability, reduce the administration frequency and dose and enhance the patient compliance. Still not well assessed, the problem with the eventual toxicity and adverse effects of these drug carriers must draw our attention. Although polymeric particles may be biodegradable, their degradation rate must be analysed and toxicity profiles must be assessed in various *in vitro*, *ex vivo* and *in vivo* models. The development and application of strict safety rules are needed to create an effective and safe drug formulation.

In the future, the main emphasis of investigations will be put on the achievement of a non-invasive drug administration, aiming targeted and controlled release of API with a minimal

effective dose. The comprehensive exploration of the problems, associated with the route of drug administration within its complexity, the tissues under normal and pathological conditions, and the multi-compartment pharmacokinetics, will significantly accelerate the further progress in this field.

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References

[1] Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P, Bannerjee SK. Mint: Drug delivery systems: An updated review. International Journal of Pharmaceutical Investigation. 2012;**2**:2-11. DOI: 10.4103/2230-973X.96920

[2] Amidon GL, Lennernas H, Shah VP, Crison JR. Mint: A theoretical basis for a biopharmaceutic drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharmaceutical Research. 1995;**12**:413-420

[3] Rao JP, Geckeler KE. Mint: Polymer nanoparticles: Preparation techniques and size-control parameters. Progress in Polymer Science. 2011;**36**(7):887-913. DOI: http://dx.doi.org/10.1016/j.progpolymsci.2011.01.001

[4] Arun A, Reddy BSR. Mint: Polymeric drug for antimicrobial activity studies: Synthesis and characterization. Journal of Bioactive and Compatible Polymers. 2003;**18**:219-228

[5] Baskar G, Chandrasekar K, Reddy BSR. Mint: Associated structures of aqueous solution of comblike polymers from 2-acrylamido-2-methyl-1-propanesulfonic acid, dodecylmethacrylate and poly(ethyleneglycol) acrylate macromonomer. Polymer. 2004;**45**:6507-6517

[6] Gaspar LJM, Baskar G, Reddy BSR, Ranganathan R, Peric M. Mint: Effect of N-Glycinyl Maleamic Acid on microstructural characteristics and solubilization properties of SDS micellar assemblies. Langmuir. 2004;**20**:9029-9035

[7] Rani SU, Pandian K, Reddy BSR. Mint: Syntheses and characterization of silver nanoparticles in the acrylate copolymers. Journal of Experimental Nanoscience. 2009;**4**:285-299

[8] Madhavan K, Reddy BSR. Mint: Smaller molecules doing bigger things: A challenge to nanotechnology in separation science. Science Reporter. 2007;**44**(7):17. Available from: www.niscair.res.in/sciencecommunication/popularization%20of%20science/SciRep/scirep2k7/Scirep_sept07.asp [Accessed: 4 February 2017]

[9] Vijay R, Angayarkanny S, Reddy BSR, Mandal AB, Baskar G. Mint: Adsorption and emulsification properties of amphiphilic poly(styrene-co-octadecyl maleamic acid salt) with comb-like architecture. Journal of Colloid and Interface Science. 2010;**346**:143-152

[10] Marschütz MK, Bernkop-Schnürch A. Mint: Thiolated polymers: Self-crosslinking properties of thiolated 450 kDa poly(acrylic acid) and their influence on mucoadhesion. European Journal of Pharmaceutical Sciences. 2002;**15**(4):387-394

[11] Srividhya M, Preethi S, Gnanamani A, Reddy BSR. Mint: Sustained release of protein from poly (ethylene glycol) incorporated amphiphilic comb like polymers. International Journal of Pharmaceutics. 2006;**326**(1-2):119-127

[12] Nagarajan S, Reddy BSR. Mint: Bio-absorbable polymers in implantation-An overview. Journal of Scientific & Industrial Research. 2009;**68**(12):993-1009

[13] Nagarajan S, Reddy BSR. Mint: Preparation of PLA-PDMS-HMDI based polyurethane membranes for drug permeation studies. Journal of Polymeric Materials. 2011;**28**:543-549

[14] Nagarajan S, Reddy BSR, Tsibouklis J. Mint: Fluorescence-detectable, star-shaped polylactic acid construction for implantation. European Polymer Journal. 2012;**48**:1357-1360

[15] Bakrudeen B, Tsibouklis J, Reddy BSR. Mint: Facile fabrication of mesoporous ZnO nanospheres for the controlled delivery of captopril. Journal of Nanoparticle Research. 2013;**15**(3):1505-1509

[16] Lakshmi MS, Sriranjani M, Bakrudeen HB, Kannan AS, Mandal AB, Reddy BSR. Mint: Carvedilol/montmorillonite drug nanoparticles: Processing, characterization and dissolution studies. Applied Clay Science. 2010;**48**:589-593

[17] Madurai SL, Joseph SW, Mandal AB, Tsibouklis J, Reddy BS. Mint: Intestine-Specific, oral delivery of Captopril/Montmorillonite: Formulation and release kinetics. Nanoscale Research Letters. 2011;**6**(1):15. DOI: 10.1007/s11671-010-9749-0

[18] Pridgen EM, Alexis F, Farokhzad OC. Mint: Polymeric nanoparticle drug delivery technologies for oral delivery applications. Expert Opinion on Drug Delivery. 2015;**12**(9):1459–1473. DOI: 10.1517/17425247.2015.1018175

[19] Card JW, Magnuson BA. Mint: A review of the efficacy and safety of nanoparticle-based oral insulin delivery systems. American Journal of Physiology – Gastrointestinal and Liver Physiology. 2011;**301**:G956-G967

[20] Alai MS, Lin WJ, Pingale SS. Mint: Application of polymeric nanoparticles and micelles in insulin oral delivery. Journal of Food and Drug Analysis. 2015;**23**(3):351-358

[21] Gutjahr A, Phelip C, Coolen A-L, Monge C, Boisgard A-S, Paul S, Verrier B. Mint: Biodegradable polymeric Nanoparticles-Based vaccine adjuvants for lymph nodes targeting. Vaccines. 2016;**4**(4):34. DOI: 10.3390/vaccines4040034

[22] Ma W, Chen M, Kaushal S, McElroy M, Zhang Y, Ozkan C, Bouvet M, Kruse C, Grotjahn D, Ichim T, Minev B. Mint: PLGA nanoparticle-mediated delivery of tumorantigenic

peptides elicits effective immune responses. International Journal of Nanomedicine. 2012;**7**:1475-1487. DOI: 10.2147/IJN.S29506

[23] Farris E, Brown DM, Ramer-Tait AE, Pannier AK. Mint: Micro- and nanoparticulates for DNA vaccine delivery. Experimental Biology and Medicine (Maywood). 2016;**241**(9):919-929. DOI: 10.1177/1535370216643771

[24] Perez C, Sanchez A, Putnam D, Ting D, Langer R, Alonso MJ. Mint: Poly(lactic acid)-poly(ethylene glycol) nanoparticles as new carriers for the delivery of plasmid DNA. Journal of Controlled Release. 2001;**75**(1-2):211-224

[25] Bhavsar MD, Amiji MM. Mint: Gastrointestinal distribution and *in vivo* gene transfection studies with nanoparticles-in-microsphere oral system (NiMOS). Journal of Controlled Release. 2007;**119**(3):339-348

[26] Arun A, Reddy BSR. Mint: *In vitro* drug release studies from the polymeric hydrogels based on HEA and HPMA using 4-{(E)-[(3Z)-3-(4-(acryloyloxy)benzylidene)-2-hexylidene]methyl}phenyl acrylate as a crosslinker. Biomaterials. 2005;**26**:1185-1193

[27] Arun A, Reddy BSR. Mint: *In Vitro* drug release studies of 2-hydroxyethyl acrylate or 2-hydroxypropyl methacrylate_4-{(1E,4E)-5-[4-(acryloyloxy)phenyl]-3-oxopenta-1,4- dienyl}phenyl acrylate copolymer beads. Journal of Biomedical Materials Research Part B: Applied Biomaterials. 2005;**73**(2):291-300

[28] Phua K, Leong KW. Mint: Microscale oral delivery devices incorporating nanoparticles. Nanomedicine (London, England). 2010;**5**(2):161-163. DOI: 10.2217/nnm.09.113

[29] Ball RL, Knapp CM, Whitehead KA. Mint: Lipidoid nanoparticles for siRNA delivery to the intestinal epithelium: *In vitro* investigations in a Caco-2 model. PLoS One. 2015;**10**(7):e0133154. DOI: 10.1371/journal.pone.0133154

[30] Zhang Z, Tsai P-C, Ramezanli T, Michniak-Kohn BB. Mint: Polymeric nanoparticles-based topical delivery systems for the treatment of dermatological diseases. WIREs Nanomedicine and Nanobiotechnology. 2013;**5**:205-218. DOI: 10.1002/wnan.1211

[31] Reddy CU, Arun A, Amalraj A, Reddy BSR. Mint: Polymeric drugs based on sulphanilamide: Synthesis, antimicrobial studies and drug release studies. Journal of Pharmaceutical Sciences. 2007;**59**:1207-1213

[32] Bakrudeen HB, Sudarvizhi C, Reddy BSR. Mint: Starch nanocrystals based hydrogels: Construction, characterization and transdermal application. Materials Science and Engineering C: Materials for Biological Applications. 2016;**68**:880-889

[33] Nagarajan S, Reddy BSR, Tsibouklis J. Mint: *In vitro* effect on cancer cells: Synthesis and preparation of polyurethane membranes for controlled delivery of curcumin. Journal of Biomedical Materials Research Part A. 2011;**99A**:410-417

[34] Kilfoyle BE, Sheihet L, Zhang Z, Laohoo M, Kohn J, Michniak-Kohn BB. Mint: Development of paclitaxel-TyroSpheres for topical skin treatment. Journal of Controlled Release. 2012;**163**(1):18-24. DOI: 10.1016/j.jconrel.2012.06.021

[35] Ramezanli T, KilfoyleBE, Zhang Z, Michniak-Kohn BB. Mint: Polymeric nanospheres for topical delivery of vitamin D3. International Journal of Pharmaceutics. 2017;**516**(1-2): 196-203. DOI: 10.1016/j.ijpharm.2016.10.072

[36] Batheja P, Sheihet L, Kohn J, Singer AJ, Michniak-Kohn B. Mint: Topical drug delivery by a polymeric nanosphere gel: Formulation optimization and *in vitro* and *in vivo* skin distribution studies. Journal of Controlled Release. 2011;**149**(2):159-167. DOI: 10.1016/j.jconrel.2010.10.005

[37] Nagai N, Iwamae A, Tanimoto S, Yoshioka C, Ito Y. Mint: Pharmacokinetics and antiinflammatory effect of a novel gel system containing ketoprofen solid nanoparticles. Biological and Pharmaceutical Bulletin. 2015;**38**(12):1918-1924. DOI: 10.1248/bpb.b15-00567

[38] Cilurzo F, Selmin F, Gennari CG, Montanari L, Minghetti P. Mint: Application of methyl methacrylate copolymers to the development of transdermal or loco-regional drug delivery systems. Expert Opinion on Drug Delivery. 2014;**11**(7):1033-1045. DOI: 10.1517/17425247.2014.912630

[39] Rancan F, Amselgruber S, Hadam S, Munier S, Pavot V, Verrier B, Hackbarth S, Combadiere B, Blume-Peytavi U, Vogt A. Mint: Particle-based transcutaneous administration of HIV-1 p24 protein to human skin explants and targeting of epidermal antigen presenting cells. Journal of Controlled Release. 2014;**176**:115-122. DOI: 10.1016/j.jconrel.2013.12.022

[40] DeMuth PC, Min Y, Irvine DJ, Hammond PT. Mint: Implantable silk composite microneedles for programmable vaccine release kinetics and enhanced immunogenicity in transcutaneous immunization. Advanced Healthcare Materials. 2014;**3**(1):47-58. DOI: 10.1002/adhm.201300139

[41] Fonseca-Santos B, Gremião MPD, Chorilli M. Mint: Nanotechnology-based drug delivery systems for the treatment of Alzheimer's disease. International Journal of Nanomedicine. 2015;**10**:4981-5003. DOI: 10.2147/IJN.S87148

[42] Zhuang X, Xiang X, Grizzle W, Sun D, Zhang S, Axtell RC, Ju S, Mu J, Zhang L, Steinman L, Miller D, Zhang H-G. Mint: Treatment of brain inflammatory diseases by delivering exosome encapsulated Anti-inflammatory drugs from the nasal region to the brain. Molecular Therapy. 2011;**19**(10):1769-1779

[43] Zhuang X, Teng Y, Samykutty A, Mu J, Deng Z, Zhang L, Cao P, Rong Y, Yan J, Miller D, Zhang H-G. Mint: Grapefruit-derived nanovectors delivering therapeutic miR17 through an intranasal route inhibit brain tumor progression. Molecular Therapy. 2016;**24**(1):96-105

[44] Ong WY, Shalini SM, Costantino L. Mint: Nose-to-brain drug delivery by nanoparticlesin the treatment of neurological disorders. Current Medicinal Chemistry. 2014;**21**(37):4247-4256

[45] Sharma D, Maheshwari D, Philip G, Rana R, Bhatia S, Singh M, Gabrani R, Sharma SK, Ali J, Sharma RK, Dang S. Mint: Formulation and optimization of polymeric

nanoparticles for intranasal delivery of lorazepam using Box-Behnken design: *In vitro* and *in vivo* evaluation. BioMed Research International. 2014. Article ID 156010. DOI: 10.1155/2014/156010

[46] Chonkar A, Nayak U, Udupa N. Mint: Smart polymers in nasal drug delivery. Indian Journal of Pharmaceutical Sciences. 2015;**77**(4):367-375

[47] Park JS, Oh YK, Yoon H, Kim JM, Kim CK. Mint: *In situ* gelling and mucoadhesive polymer vehicles for controlled intranasal delivery of plasmid DNA. Journal of Biomedical Materials Research. 2002;**59**(1):144-151

[48] Nakamura K, Maitani Y, Lowman AM, Takayama K, Peppas NA, Nagai T. Mint: Uptake and release of budesonide from mucoadhesive, pH-sensitive copolymers and their application to nasal delivery. Journal of Controlled Release. 1999;**61**:329-335

[49] Aikawa K, Matsumoto K, Uda H, Tanaka S, Shimamura H, Aramaki Y. Mint: Hydrogel formation of the pH response polymer polyvinylacetaldiethylamino acetate (AEA). International Journal of Pharmaceutics. 1998;**167**:97-104

[50] Ensign LM, Cone R, Hanes J. Mint: Nanoparticle-based drug delivery to the vagina: A review. Journal of Controlled Release. 2014;**0**:500-514. DOI: 10.1016/j.jconrel.2014.04.033

[51] das Neves J, Araújo F, Andrade F, Michiels J, Ariën KK, Vanham G, Amiji M, Bahia MF, Sarmento B. Mint: *In vitro* and *Ex vivo* evaluation of polymeric nanoparticles for vaginal and rectal delivery of the Anti-HIV drug dapivirine. Molecular Pharmaceutics. 2013;**10**(7):2793-2807. DOI: 10.1021/mp4002365

[52] Woodrow KA, Cu Y, Booth CJ, Saucier-Sawyer JK, Wood MJ, Saltzman WM. Mint: Intravaginal gene silencing using biodegradable polymer nanoparticles densely loaded with small-interfering RNA. Nature Materials. 2009;**8**:526-533

[53] Steinbach JM, Weller CE, Booth CJ, Saltzman WM. Mint: Polymer nanoparticles encapsulating siRNA for treatment of HSV-2 genital infection. Journal of Controlled Release. 2012;**162**:102-110

[54] Li SF, Liu DX, Zheng YH, Yue Y, Huang YB, Jing XB. Mint: Inhibitory effects of paclitaxel-loaded PLA nanofibers against mice cervical cancers. Acta Metallurgica Sinica. 2012;**0**(9):1029-1034. DOI: 10.3724/SP.J.1105.2012.12066

[55] Zong S, Wang X, Yang Y, Wu W, Li H, Ma Y, Lin W, Sun T, Huang Y, Xie Z, Yue Y, Liu S, Jing X. Mint: The use of cisplatin-loaded mucoadhesive nanofibers for local chemotherapy of cervical cancers in mice. European Journal of Pharmaceutics and Biopharmaceutics. 2015;**93**:127-135. DOI: 10.1016/j.ejpb.2015.03.029

[56] Ordikhani F, Arslan ME, Marcelo R, Sahin I, Grigsby P, Schwarz JK, Azab AK. Mint: Drug delivery approaches for the treatment of cervical cancer. Pharmaceutics. 2016;**8**(3):23. DOI: 10.3390/pharmaceutics8030023

[57] Yoo JW, Giri N, Lee CH. Mint: pH-sensitive Eudragit nanoparticles for mucosal drug delivery. International Journal of Pharmaceutics. 2011;**403**:262-267

[58] Coco R, Plapied L, Pourcelle V, Jérôme C, Brayden DJ, Schneider YJ, Préat V. Mint: Drug delivery to inflamed colon by nanoparticles: Comparison of different strategies. International Journal of Pharmaceutics. 2013;**440**(1):3-12. DOI: 10.1016/j.ijpharm.2012.07.017

[59] Andonova V, Georgiev G, Toncheva V, Kassarova M. Mint: Preparation and study of Poly(vinyl acetate) and Poly(styrene) nanosized latex with Indometacin. Pharmazie. 2012;**67**(7):601-604

[60] Andonova VY, Georgiev GS, Georgieva VT, Petrova NL, Kassarova M. Mint: Indomethacin nanoparticles for applications in liquid ocular formulations. Folia Medica. 2013;**55**(1): 76-82

[61] Andonova V, Georgiev G, Toncheva V, Petrova N, Karashanova D, Penkov D, Kassarova M. Mint: Indomethacin loading and *in vitro* release properties from vinyl acetate homo- and co-polymer nanoparticles, coated with polyzwitterion and carbopol® shells. International Journal of Pharmaceutics. 2014;**6**(1):691-699

[62] Andonova V, Georgiev G, Toncheva V, Karashanova D, Katsarov P, Kassarova M. Mint: Carbopol® and chitosan coated nanoparticles with in-situ loaded indomethacin. American Journal of PharmTech Research. 2014;**4**(1):664-678

[63] Andonova V, Draganov M, Feodorova Y, Georgiev G, Kassarova M. Mint: Biological activity of Indomethacin-Loaded nanoparticles. World Journal of Pharmaceutical Research. 2014;**4**(1):85-101

[64] Andonova V, Zagorchev P, Katsarov P, Kassarova M. Mint: Eye drops with nanoparticles as drug delivery systems. International Journal of Pharmaceutical Sciences and Research. 2015;**7**(2):431-435

[65] Andonova V, Georgiev G, Dimitrova S, Katsarova M, Kassarova M. Mint: Characterization, *in vitro* evaluation and stability studies of Indomethacin-Loaded polyzwitterionic copolymer nanoparticles. International Journal of Drug Delivery Technology. 2015;**5**(3):89-97

[66] Almeida H, Amaral MH, Lobão P, Silva AC, Loboa JM. Mint: Applications of polymeric and lipid nanoparticles in ophthalmic pharmaceutical formulations: Present and future considerations. Journal of Pharmaceutical Sciences. 2014;**17**(3):278-293

[67] Giannavola C, Bucolo C, Maltese A, Paolino D, Vandelli MA, Puglisi G, Lee VH, Fresta M. Mint: Influence of preparation conditions on acyclovir loaded poly-d,l-lactic acid nanospheres and effect of PEG coating on ocular drug bioavailability. Pharmaceutical Research. 2003;**20**(4):584-590

[68] Kao HJ, Lin HR, Lo YL, Yu SP. Mint: Characterization of pilocarpine-loaded chitosan/carbopol nanoparticles. Journal of Pharmacy and Pharmacology. 2006;**58**(2):179-186

[69] Yuan XB, Yuan YB, Jiang W, Liu J, Tian EJ, Shun HM, Huang DH, Yuan XY, Li H, Sheng J. Mint: Preparation of rapamycin-loaded chitosan/PLA nanoparticles for immunosuppression in corneal transplantation. International Journal of Pharmaceutics. 2008;**349**(1-2):241-248

[70] Ibrahim HK, El-Leithy IS, Makky AA. Mint: Mucoadhesive nanoparticles as carrier systems for prolonged ocular delivery of gatifloxacin/prednisolone bitherapy. Molecular Pharmaceutics. 2010;**7**(2):576-585

[71] Gupta H, Aqil M, Khar RK, Ali A, Bhatnagar A, Mittal G. Mint: Sparfloxacin-loaded PLGA nanoparticles for sustained ocular drug delivery. Nanomedicine: Nanotechnology, Biology and Medicine. 2010;**6**(2):324-333

[72] Gupta H, Aqil M, Khar RK, Ali A, Bhatnagar A, Mittal G. Mint: Biodegradable levofloxacin nanoparticles for sustained ocular drug delivery. Journal of Drug Targeting. 2011;**19**(6):409-417

[73] Gupta H, Aqil M, Khar RK, Ali A, Bhatnagar A, Mittal G. Mint: Nanoparticles laden in situ gel for sustained ocular drug delivery. Journal of Pharmacy and Bioallied Sciences. 2013;**5**(2):162-165

[74] Gupta H, Aqil M, Khar RK, Ali A, Bhatnagar A, Mittal G. Mint: Nanoparticles laden in situ gel of levofloxacin for enhanced ocular retention. Drug Delivery. 2013;**20**(7):306-309

[75] Kumar D, Jain N, Gulati N, Nagaich U. Mint: Nanoparticles laden in situ gelling system for ocular drug targeting. Journal of Advanced Pharmaceutical Technology & Research. 2013;**4**(1):9-17

[76] Nasr FH, Khoee S, Dehghan MM, Chaleshtory SS, Shaffie S. Mint: Preparation end evaluation of contact lenses embedded with polycaprolactone-based nanoparticles for ocular drug delivery. Biomacromolecules. 2016;**17**(2):485-495

[77] Khurana G, Arora S, Pawar PK. Mint: Ocular insert for sustained delivery of gatifloxacinsesquihydrate: Preparation and evaluations. International Journal of Pharmaceutical Investigation. 2012;**2**(2):70-77. DOI: 10.4103/2230-973X.100040

[78] Thakur R, Swami G, Rahman M. Mint: Development and optimization of controlled release bioerodable anti infective ophthalmic insert. Current Drug Delivery. 2014;**11**(1):2-10

[79] O'Rourke M, Hanes J. Company profile: GrayBug, LLC. OnDrug Delivery 2014;**48**:8-9. Available from: www.ondrugdelivery.com/publications/48/Issue_48_Lo_Res.pdf [Accessed: 3 July 2017]

[80] Navratil T, Maynor B, Yerxa B. Improving outcomes in ophthalmology via sustained drug delivery. OnDrug Delivery. 2014;**48**:10-13. Available from: www.ondrugdelivery.com/publications/48/Issue_48_Lo_Res.pdf [Accessed: 3 July 2017]

[81] Rupenthal ID. Ocular drug delivery technologies: Exiting times ahead. OnDrug Delivery. 2015;**54**:7-11. Available from: http://www.ondrugdelivery.com/publications/54/Issue_54_Lo_Res.pdf [Accessed: 3 July 2017]

[82] Andonova V. Mint: A new direction in ophthalmic development: Nanoparticle drug delivery systems. Current Pharmaceutical Design. 2016;**22**(41):6313-6329

[83] Boddupalli BM, Mohammed ZN, Nath RA, Banji D. Mint: Mucoadhesive drug delivery system: An overview. Journal of Advanced Pharmaceutical Technology & Research. 2010;**1**:381-387

[84] Mašek J, Lubasová D, Lukáč R, Turánek-Knotigová P, Kulich P, Plocková J, Mašková E, Procházka L, Koudelka Š, Sasithorn N, Gombos J, Bartheldyová E, Hubatka F, Raška M, Miller AD, Turánek J. Mint: Multi-layered nanofibrous mucoadhesive films for buccal and sublingual administration of drug-delivery and vaccination nanoparticles – important step towards effective mucosal vaccines. Journal of Controlled Release. 2016;**249**:183-195

[85] Rana P, Murthy RSR. Mint: Formulation and evaluation of mucoadhesive buccal films impregnated with carvedilol nanosuspension: A potential approach for delivery of drugs having high first-pass metabolism. Drug Delivery. 2013;**20**(5):224-235

[86] Sapre AS, Parikh RK. Mint: Design of a buccal mucoadhesive, nanoparticles based delivery system of fluoxetine. Journal of Pharmaceutical Science and Bioscientific Research. 2012;**2**(3):148-161

[87] Al-Dhubiab BE. Mint: *In vitro* and *in vivo* evaluation of nano-based films for buccal delivery of zolpidem. Brazilian Oral Research. 2016;**30**(1):e126. DOI: 10.1590/1807-3107BOR-2016.vol30.0126

[88] Paranjpe M, Christel C. Müller-Goymann. Mint: Nanoparticle-Mediated pulmonary drug delivery: A review. International Journal of Molecular Sciences. 2014;**15**:5852-5873. DOI: 10.3390/ijms15045852

[89] El-Sherbiny IM, El-Baz NM, Yacoub MH. Mint: Inhaled nano- and microparticles for drug delivery. Global Cardiology Science & Practice. 2015;**2015**:2. DOI: 10.5339/gcsp.2015.2

[90] Doan TV, Couet W, Olivier JC. Mint: Formulation and *in vitro* characterization of inhalable rifampicin-loaded PLGA microspheres for sustained lung delivery. International Journal of Pharmaceutics. 2011;**414**(1-2):112-117. DOI: 10.1016/j.ijpharm.2011.05.007

[91] Reinbold J, Hierlemann T, Hinkel H, Müller I, Maier ME, Weindl T, Schlensak C, Wendel HP, Krajewski S. Mint: Development and *in vitro* characterization of poly(lactide-co-glycolide) microspheres loaded with an antibacterial natural drug for the treatment of long-term bacterial infections. Drug Design, Development and Therapy. 2016;**10**:2823-2832

[92] Chen L, Nakano K, Kimura S, Matoba T, Iwata E, Miyagawa M, Tsujimoto H, Nagaoka K, Kishimoto J, Sunagawa K, Egashira K. Mint: Nanoparticle-mediated delivery of pitavastatin into lungs ameliorates the development and induces regression of monocrotaline-induced pulmonary artery hypertension. Hypertension. 2011;**57**(2):343-350. DOI: 10.1161/HYPERTENSIONAHA.110.157032

[93] Anton N, Jakhmola A, Vandamme TF. Mint: Trojan microparticles for drug delivery. Pharmaceutics. 2012;**4**(1):1-25. DOI: 10.3390/pharmaceutics4010001

[94] Xu H, Hou Z, Zhang H, Kong H, Li X, Wang H, Xie W. Mint: An efficient Trojan delivery of tetrandrine by poly(N-vinylpyrrolidone)-block-poly(ε-caprolactone) (PVP-b-PCL) nanoparticles shows enhanced apoptotic induction of lung cancer cells and inhibition of its migration and invasion. International Journal of Nanomedicine. 2014;**9**:231-242. DOI: 10.2147/IJN.S55541

[95] Kaye RS, Purewal TS, Alpar HO. Mint: Simultaneously manufactured nano-in-micro (SIMANIM) particles for dry-powder modified-release delivery of antibodies. Journal of Pharmaceutical Sciences. 2009;**98**(11):4055-4068. DOI: 10.1002/jps.21673

[96] Bao W, Liu R, Wang Y, Wang F, Xia G, Zhang H, Li X, Yin H, Chen B. Mint: PLGA-PLL-PEG-Tf-based targeted nanoparticles drug delivery system enhance antitumor efficacy via intrinsic apoptosis pathway. International Journal of Nanomedicine. 2015;**10**:557-566. DOI: 10.2147/IJN.S75090

[97] Liu R, Wang Y, Li X, Bao W, Xia G, Chen W, Cheng J, Xu Y, Guo L, Chen B. Mint: Synthesis and characterization of tumor-targeted copolymer nanocarrier modified by transferrin. Drug Design, Development and Therapy. 2015;**9**:2705-2719. DOI: 10.2147/DDDT.S80948

[98] Xie J, Zhang X, Teng M, Yu B, Yang S, Lee RJ, Teng L. Mint: Synthesis, characterization, and evaluation of mPEG-SN38 and mPEG-PLA-SN38 micelles for cancer therapy. International Journal of Nanomedicine. 2016;**11**:1677-1686. DOI: 10.2147/IJN.S103110

[99] Kowalczuk A, Stoyanova E, Mitova V, Shestakova P, Momekov G, Momekova D, Koseva N. Mint: Star-shaped nano-conjugates of cisplatin with high drug payload. International Journal of Pharmaceutics. 2011;**404**(1-2):220-230

[100] Stoyanova E, Mitova V, Shestakova P, Kowalczuk A, Momekov G, Momekova D, Marcinkowski A, Koseva N. Mint: Reversibly PEGylated nanocarrier for cisplatin delivery. Journal of Inorganic Biochemistry. 2013;**120**:54-62

[101] Xia H, Gao X, Gu G, Liu Z, Hu Q, Tu Y, Song Q, Yao L, Pang Z, Jiang X, Chen J, Chen H. Mint: Penetratin-functionalized PEG-PLA nanoparticles for brain drug delivery. International Journal of Pharmaceutics. 2012;**436**(1-2):840-850. DOI: 10.1016/j.ijpharm.2012.07.029

[102] Shamma RN, Elkasabgy NA, Mahmoud AA, Gawdat SI, Kataia MM, Abdel Hamid MA. Mint: Design of novel injectable in-situ forming scaffolds for non-surgical treatment of periapical lesions: *In-vitro* and *in-vivo* evaluation. International Journal of Pharmaceutics. 2017;**521**(1-2):306-317

[103] Nagarajan S, Kiran MS, Tsibouklis J, Reddy BSR. Mint: Multifunctional star-shaped polylactic acid implant for potential use in angioplasty. Journal of Materials Chemistry B. 2014;**2**:6549-6559

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