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Exploring the Nanotechnology-Based Drug Delivery Systems for AIDS Treatment

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1. Introduction

The Acquired Immunodeficiency Syndrome (AIDS) and Human Immunodeficiency Virus (HIV) infection are a worldwide public health challenge. The emergence of antiretroviral therapy agents has significantly increased the life expectancy and the patient´s quality of life. In the 1990's, there was a great improvement in the knowledge of the disease, enlargement of therapeutic resources, a rise in life expectancy and the epidemiologic profile. Since the mid-1990's, the advancement of pharmacology studies and the arrival of protease inhibitor antiretroviral have given rise to a new era of anti-HIV agents, known as Highly Active Antiretroviral Therapy (HAART) (Geocze et al., 2010, Richman et al., 2009). The HAART's adhesion improved the clinical results, the control of the advancement of the disease and decreased the mortality rate, which resulted in an improvement of the patient's life quality. Despite the successful administration of HAART, latently infected cells can escape the viral immune response and persist for long periods of time (Alexaki et al., 2008). In addition, the HAART presents several collateral effects, such as fatigue, nausea, sickness, diarrhea and lipodystrophy. These symptoms contribute to a lack of treatment adhesion in the patient, resulting in a rise in the blood viral load and a decline in CD4+ T cells count, as well as an increased tolerance of anti-HIV drugs, treatment failure, increased opportunistic infections and in wasted investments (Geocze et al., 2010). Moreover, many antiretroviral drugs undergo extensive pre-systemic metabolism and instability in the gastrointestinal environment, resulting in inadequate and erratic oral absorption as well as low bioavailability. The half-life for most anti-HIV drugs is short, and thus, it requires frequent dosage administrations, leading to a decrease in patient compliance. Also, some antiretroviral classes present poor solubility, low absorption and limited bioavailability. Another limitation of the current HAART is the inefficiency of the regimens to eradicate HIV from various anatomical reservoirs (e.g., central nervous system (CNS) and gastrointestinal tract) and intracellular sites (e.g., macrophages, hepatocytes, dendritic cells and Langerhans cells) (Ojewole et al., 2008, Saksena & Haddad, 2003). Large concentrations are essential for eliminating HIV from these reservoirs to achieve the desired therapeutic effect, but these large doses contribute to severe side effects associated with anti-HIV therapy (Ojewole et al., 2008). Because drug development in the HIV field has slowed

(Hawkins, 2010), strategies currently being investigated to overcome these limitations include the design and development of novel drug delivery systems that can improve the efficacy of both existing and novel antiretroviral drugs (Ojewole et al., 2008). With the aim to reduce dosing frequency and to improve the compliance of the existing pharmacotherapy with patients, drug delivery system design is becoming complementary to new drug discovery (Sosnik et al., 2009). In the past decade, there has been an explosion of interest in the development of anti-HIV delivery systems (Ojewole et al., 2008). Evidence of this new interest is the emergence of several revision papers that have focused attention to the development of anti-HIV delivery systems, which have been published in the last two years (Geocze et al., 2010; Gupta & Jain, 2010; Hawkins, 2010; Neves et al., 2010; Sosnik et al., 2009, Wong et al., 2010, Khalil et al., 2011).

There is a special trend in research concerning the development of anti-HIV drug delivery systems, which apply nanotechnology to improve AIDS treatment. The basic concept behind the use of nanotechnology-based systems for antiretroviral drug delivery is the ability of these systems to compartmentalize as well as modify the properties and behavior of drugs in the biological medium. Through drug association with nanostructured systems, the properties that govern drug release are determined by the physicochemical properties of the nanosystems and not by the drug properties (Neves et al., 2010). These properties can include the protection of incorporated drugs from the metabolism, an increase of drug residence time in the human body and the possibility of targeting drugs to specific cells or organs. In addition, these properties can allow a dosage reduction, more appropriate dosage regimens, fewer adverse effects and increased patient compliance. Moreover, there is the possibility of incorporating different anti-HIV drugs in the same delivery system, which can also contribute to a simplification of drug administration schedules (Neves et al., 2010).

Despite the improvement of the nanotechnology-based studies, many of them are still in the pre-formulation or pre-clinical phases. However, the potential of nanotechnology-based drug delivery systems to improve AIDS treatment is evident. Thus, the goal of the current chapter is to organize a systematic review about this area of study. Particular emphasis was placed on surfactant and nanoparticulated systems. The surfactant systems are formed by amphiphilic compounds and include several types of arrangements; these systems self-organize with different physicochemical properties, which can be used to design new drug delivery systems. The most popular surfactant system that incorporates antiretroviral drugs are the liposomes (Zidan et al., 2010; Clayton et al., 2009; Kaur et al., 2008); however, anti-HIV drugs were also found to be associated with microemulsions (Vyas et al., 2008), polymeric micelles (Chiappetta et al. 2010; Kaparissides et al., 2006), self-assembled drug delivery systems (Jin et al., 2010) and liquid crystals (Carvalho et al., 2010a). In addition to surfactant systems, polymeric nanoparticles have been extensively studied as nanometric carriers, and these carriers presenting different morphologies, including nanospheres or nanocapsules. In this document, these are referred to as polymeric nanoparticles (Mainardes et al., 2010; Sharma & Garg, 2010, Schäfer et al., 1992, Shah & Amiji, 2006, Destache et al., 2009, Mahajan et al., 2009) and solid lipid nanoparticles (Aji Alex et al., 2010; Kuo & Chen, 2009; Shegokara et al., 2010). The advantages and limitations of each system are discussed, thus, this work can be used as a start point for researchers focusing on nanotechnology-based drug delivery systems for the treatment of AIDS.

2. Surfactant systems

Surfactants are extensively used as excipients in drug delivery and the understanding of the physicochemical properties and behavior of these amphiphilic compounds has undergone significant development. One reason for this development is that surface chemistry is a relatively young scientific discipline, and many studies have recognized its importance for the design and controlled use of drug delivery formulations (Malmsten, 2002). The surfactant systems comprise several types of arrangements, and they self-organize with different physicochemical properties that can be used to design new drug delivery systems that are able to solubilize both water-soluble and oil-soluble compounds. Depending on the composition and molecules of the component, surfactant systems can infinitely dilute or form highly stiff matrices, both in physiological conditions. Due the capacity of surfactant systems, which can form viscous and gel-like structures with different rheological characteristics, these systems are extremely versatile and can be delineated to be applied for different routes of administration, e.g., transdermal or mucosal administration, such as vaginal, nasal, rectal and sublingual. However, almost all studies aim oral administration, where anti-HIV drugs are associated in microemulsions, polymeric micelles, self-assembled drug delivery systems, liquid crystals and liposomes. Liposomes, contrary to the other surfactant organizations, have been widely explored for orally administered anti-HIV drugs. Although the oral route is still the primary mode of delivery for antiretroviral surfactant systems, they were found to be a suitable vehicle for anti-HIV intravenous and mucosal administration (described below).

2.1 Microemulsions

Microemulsions are systems consisting of water, oil, and surfactant(s), which constitute a single optically isotropic and thermodynamically stable liquid dispersion. Such systems are useful for drug delivery due to their excellent stability, ease of preparation, optical clarity, as well as their capacity to dissolve hydrophilic and lipophilic drugs, frequently in high amounts. Microemulsions differ from emulsions and nanoemulsions because of their thermodynamic stability; these systems form spontaneously, exhibit reduced droplets sizes (typically 10–100 nm) (Malmsten, 2002), higher surface areas and free energy without the inherent creaming, flocculation, coalescence and sedimentation associated with emulsions (Gupta & Jain, 2010). Thus, microemulsions are considered to be an interesting possibility for anti-HIV drug delivery systems (Gupta & Jain, 2010). Carvalho et al. (2009) developed and characterized PPG-5-CETETH-20/oleic acid/water zidovudine-loaded microemulsions; the in vitro drug release assay showed that the drug release followed the Fickian diffusion through a disordered matrix, and the mechanism was identified by the use of Weibull mathematical model. Vyas et al. (2008), investigated the oral bioavailability of saquinavir incorporated in oil-in-water microemulsions in the study of enhanced brain disposition, a potential sanctuary site for HIV. Pharmacokinetics parameters were found to be higher in the brain, suggesting an enhanced rate and extended saquinavir absorption following oral administration of microemulsions. Thus, microemulsions may be very promising for HIV/AIDS therapy, in particular, for reducing the viral load in important anatomical reservoir sites (Vyas et al., 2008).

2.2 Polymeric micelles

Polymeric micelles are nanostructures that have been utilized for improving aqueous solubility, mucosal permeability and disease-site targeting of several drug molecules.

Compared to the conventional surfactant based micelles, polymeric micelles are composed of block copolymers. Although the structural "core–shell" arrangement is similar to surfactant-based micelles, polymer micelles self associate at much lower concentrations. Consequently, the thermodynamic and in vivo stability of polymeric micelles is relatively high (Sharma & Garg, 2010). A study by Chiappeta et al. (2010) showed that the solubility of efavirenz, a lipophilic first-line antiretroviral drug, could be improved. Micellar systems composed of N-methylated and N-alkylated poloxamines (*X*-shaped poly(ethylene oxide)–poly(propylene oxide, PEO–PPO) diblocks connected to a central ethylenediamine group), were investigated to optimize the oral pharmacotherapy effects of efavirenz. The in vitro release was sustained for at least 24 h. The authors suggested that the polymeric micelles could be promising nanocarriers for oral or parenteral drug delivery. The aqueous solubility of the drug was increased from 0.004 mg/mL to approximately 30 mg/mL, representing the best solubilization performance in an aqueous medium of any nanocarrier described thus far (Chiappetta et al. 2010). Other characteristics of polymeric micelles present the possibility for substitution of the block copolymer micelles with specific ligands, which is a very promising strategy for a broader range of sites of activity with a considerably higher selectivity (Kaparissides et al., 2006). Micelles can be tailored by attaching hydrophilic blocks to antibodies or other ligands specific for the type of receptors present within the disease site. Lectin receptors are present on HIV reservoirs, such as T lymphocytes, dendritic cells and macrophages; therefore, this can be a promising approach for viral reservoir targeting (Sharma & Garg, 2010).

2.3 Self-assembled drug delivery systems of antiretroviral prodrugs

A novel technology involving antiretroviral prodrugs with amphiphilic properties have been developed by Jin and co-workers (Jin et al., 2008, 2009, 2010). The molecular self-assembly properties of those prodrugs in aqueous media permit the formation of nanostructures with amphiphilic characteristics, allowing them to cross biomembranes and deliver themselves in vivo without carriers (Jin et al., 2008). Recently, a series of cholesteryl derivatives of antiviral nucleoside analogues were synthesized by this group, which involved acyclovir, zidovudine and didanosine. The morphologies and the morphological transformation of cholesterylsuccinyl didanosine was investigated as a prodrug with representative self-assembly behavior in aqueous media. Results showed that the resulted nanoparticulate system had a narrow size distribution, which allowed heat sterilization and showed a site-specific distribution for the anti-HIV therapy after IV administration (Jin et al., 2008). Another example of this technology was the synthesis of the amphiphilic prodrug anti-HIV zidovudine, cholesteryl-phosphonyl zidovudine. This system degraded quickly in biological environments and showed high anti-HIV activity; in addition, the system targeted the mononuclear phagocyte system (MPS) and was followed by degradation at the targeted organs (Jin et al., 2009). Furthermore, a study was recently published on the synthesis of an amphiphilic prodrug containing dual zidovudine (Jin et al., 2010). The stable and concentrated vesicular self-assemblies were prepared through injecting the prodrug solution into water followed by adding stabilizers and removing solvents. Properties, such as their nanoscale size, stability, anti-HIV activity and macrophage targeting effects, have demonstrated that the prodrug is a promising self assembled drug delivery system. Moreover, this kind of system containing different drugs would benefit a combination therapy for AIDS treatment (Jin et al., 2010).

2.4 Liquid cristal

Liquid crystals combine the properties of both liquid and solid states. They can be made to form a range of different nanostructures, including rods, lamellae, and bicontinuously interconnected structures, with alternative polar and non-polar layers, where aqueous drug solutions can be included. (Kaparissides et al., 2006; Malmsten, 2001). The spontaneous self-assembly of some lipids used to form liquid crystalline structures can offer a potentially new class of sustained release matrices. Depending to the liquid crystalline materials, they can be highly stable to dilution, which means they can persist as a reservoir for slow drug release in excess fluids, such as the gastrointestinal tract or subcutaneous regions. Drug release rates are directly related to the nanostructure of the matrix. The particular geometry into which the lipids assemble can be manipulated through either the use of additives to modify the assembly process or through modifying conditions, such as temperature (Boyd, 2010). The structure-forming lipids can absorb a certain amount of water and then spontaneously form gel-like phases with unique internal structures into which drugs can be incorporated. Moreover, non-toxic, biodegradable and bioadhesive properties also contribute to their applications towards drug delivery (Guo et al., 2010). Liquid crystal phases have been found to be mucoadhesive, with a range of mucosal surfaces; and the mechanism of mucoadhesion probably involves the rheological properties of the system, which are similar to the in situ gelling vehicles. These liquid crystal systems can be arranged in a very strong and viscous matrix that favors the mucosal retention, impeding the immediate removal of the formulation by the mucociliary clearance (Carvalho et al., 2010b). This property was used by Carvalho et al. (2010a) to develop a mucoadhesive surfactant system for the nasal administration of zidovudine. The nasal route has been explored to avoid the extensive, first-pass metabolism and poor oral bioavailability of drugs that suffer hepatic metabolism or gastric degradation when administered by the oral route. Thus, the nasal route is an option for enhancing the therapeutic efficacy of drugs and to reduce the extent of their first-pass effect because this route is highly vascular and has a great superficial area of absorption. However, there are some mechanisms that limit the intranasal absorption, such as the mucociliary clearance, which rapidly removes the formulation from the nasal cavity. Systems composed of PPG-5-CETETH-20 as surfactant, oleic acid and water have shown to display phase transition to the lamellar phase when put in contact with the aqueous nasal-simulated mucus (SM). The phase transition was accompanied by an increase in the system's elasticity, in addition to the presentation of suitable mucoadhesive force. Thus, a viscous and mucoadhesive liquid crystalline matrix can be formed when the formulations are in contact with the SM, which may prolong the residence time of zidovudine in the nasal cavity. These findings indicate a potentially useful system for the nasal administration of zidovudine (Carvalho et al., 2010a).

2.5 Liposomes

Liposomes can be defined as associations of colloidal amphipathic lipids that spontaneously arrange themselves in closed structures, such as spherical shells containing aqueous cores. The unique aspect of the liposomes is that the hydrophilic drugs can be encapsulated in the aqueous layer, while the hydrophobic drugs can be incorporated into the phospholipid bilayer. They can range in size from 25 nm up to several microns, and liposomes are prepared from natural or synthetic phospholipids and cholesterol; in addition, they may include other substances, such as lipids and proteins (Sharma & Sharma, 1997). Conventional liposomes (without surface modification) are naturally taken up by cells of the

MPS, an important HIV reservoir. Additionally, the liposome surface can be modified to improve its properties. Ligands that promote active targeting of liposomes to HIV-infected cells and organs are interesting alternatives. Liposomes represent a convenient approach to improve the delivery of anti-HIV agents into infected cells, thereby improving the efficacy of drugs and reducing their adverse side effects (Desormeaux et al., 1998).

Monocytes/macrophages (M/Ms) are widely recognized as the secondary cellular target of HIV-1 and a crucial virus reservoir. HIV-1-infected M/Ms cells are widely distributed in all tissues and organs, including the CNS, and the HIV-1 replication in these cells is a crucial pathogenic event during the progression of viral infection. Also, M/Ms are resistant to the cytopathic effect of HIV-1 and produce viruses over a prolonged period, consisting of a long-term viral reservoir (Gartner et al., 1986; Garaci et al., 1999).

The primary research studies involving the application of liposomes in AIDS treatment are based in in vitro and in vivo (animals) experiments that consider the ability of liposomes to increase the intracellular delivery of antiretroviral drugs. The most popular drugs studied are zalcitabine, zidovudine, didanosine, stavudine and indinavir. One of the first studies that introduced the application of liposomes as carriers for anti-HIV drugs was realized by Szebeni and co-workers (1990). The group suggested that the capability of liposomes for targeting drugs in vivo to macrophages could potentially be exploited to improve the therapeutic index of dideoxynucleoside drugs. They also demonstrated the antiviral effects of 2',3'-dideoxycytidine-5'-triphosphate-loaded liposomes in cultured human M/Ms infected with HIV-1 and the higher drug stability in presence of liposome. Another study involving 2',3'-dideoxycytidine (zalcitabine) showed that the anionic character of the liposome seemed to be an important factor to obtain a high intracellular uptake. The lipid component can interfere in interactions between the cell and the liposome (Makabi-Panzu et al., 1998).

After the discovery of the zidovudine associated hematotoxicity (Ganser et al., 1989), the effect of liposome encapsulation on the bone marrow toxicity and antiviral activity of zidovudine in mice was determined by the Phillips group (1991, 1992). The results showed that zidovudine encapsulated in liposomes exhibited no bone marrow toxicity at doses that were cytotoxic with zidovudine solution; in addition, erythrocyte and leukocyte levels remained normal. Also, zidovudine loaded liposomes presented a better and prolonged antiretroviral response compared to the zidovudine solution. A more recent study showed that galactosylated liposomes reduced hematopoietic toxicity, enhanced cellular uptake and altered pharmacokinetics of zidovudine (Gard & Jain, 2006). Studies performed by the Jain group (2006, 2008) reported on the application of zidovudine loaded liposomes via transdermal route. The results showed that zidovudine permeation was higher from liposomal formulations, and it was able to target the drug to MPS organs more effectively than the free drug. In 2008, Kaur and co-workers demonstrated that mannosylated-liposomes were able to target zidovudine to the spleen and lymph nodes after subcutaneous administration. The mannose receptors in the spleen explain the role of mannose on the liposome surface and the highest drug localization in this organ.

The Désormeaux group (1994) was one of the first to study liposomal formulations for didanosine. They found that the liposomes modified the drug tissue distribution and plasma pharmacokinetics, resulting in a marked improvement of drug biodistribution, especially into the MPS. Furthermore, they reported that didanosine was efficiently targeted to lymph nodes and macrophage-rich tissue when it was loaded in liposomes. The group showed that the liposomes were able to increase the plasma half-life of the drug, and also

the sterically stabilized liposomes remain concentrated in the spleen (Harvie et al., 1995, 1996). In a recent study, a prodrug of didanosine in a liposomal formulation displayed antiviral activity and showed a promising enhancement of the drug activity against HIV-1 in in vitro infected cell cultures (Lalanne et al., 2007).

The effect of the liposome composition and cholesterol on the cellular uptake of stavudine by human M/Ms was verified by Katragadda and co-workers (2000). The cells were up-taken more expressively by the negatively charged liposomes (containing phosphatidylserine and dicetyl phosphate) compared to either the neutral or positive liposomes. The authors suggested that the difference in stavudine liposome uptake in the presence of charge might be due in part to the extent of the interaction between the charged bilayer and the cells. Other studies involving stavudine and liposomes were studied by Garg et al. (2006, 2007). Primarily, they observed that the elimination half-life and mean residence time of stavudine were increased when they were encapsulated in the mannosylated and galactosylated liposomes. Stavudine-loaded mannosylated liposomes presented in vitro antiretroviral activity. In addition, the two liposomal formulations resulted in reduced hematological toxicity and enhanced the hepatic cellular uptake of the stavudine. Furthermore, the group demonstrated that the antiretroviral activity of stavudine in galactosylated liposomes is dose-dependent, in a study with infected cell culture (Garg et al., 2008).

Immunoliposomes (liposomes with antibody attached) have also been used to deliver antiretroviral drugs to HIV targets. The Betageri group (1993a, 1993b) attached a mouse antibody in liposomes containing stavudine-triphosphate or zalcitabine-triphosphate and observed a significant increase in uptake by human macrophages compared to the free drug and unmodified liposomes. Gagné and co-workers (2002) showed that immunoliposomes were very efficient in delivering high concentrations of indinavir to lymphoid tissues (126 times higher than the free drug) for at least 15 days, post a single subcutaneous injection in mice. The HLA-DR determinant of major histocompatibility complex class II is highly expressed on macrophages and activated CD4+ T cells. Also, the authors showed that the immunoliposomal indinavir was as efficient as the free drug to inhibit HIV-1 replication in cultured cells. A recent study (Clayton et al., 2009) demonstrated specific targeting and delivery of a novel protease inhibitor encapsulated in PEGylated immunoliposomes (coated with a F105 Fab' fragment). The immunoliposome was shown to enable selective delivery of the drug to HIV-1-infected cells and also demonstrated that the effect of the targeted drug on viral replication was greater than the effect of a comparable concentration of the free drug or non-targeted drug. Therefore, the potential of liposomes and various ligands for the active targeting of antiretroviral drugs loaded on liposomes has on development. These studies have shown potential benefits of liposomes for improving antiretroviral drug therapy.

3. Polymeric nanoparticles

Nanoparticles are solid, colloidal particles consisting of macromolecular substances varying in size from 10 to 1,000 nm. The drug can be dissolved, entrapped, adsorbed, attached or encapsulated into a nanoparticle. Depending on the method of preparation, nanospheres or nanocapsules can be developed with different properties; in addition, different release characteristics for the encapsulated therapeutic agent can also be developed. For nearly three decades, polymeric nanoparticles have been extensively studied due to their unique

and valuable physicochemical and biological properties. Nanoparticles can improve drug actuation by the following characteristics: protecting it from degradation (higher physical stability during storage and in biological fluids), enhancing its transport and distribution (possibility through drug targeting by modification of surface charge with inserted ligands, such as antibodies, surfactants, and polymers) and prolonging its release (ability to sustain the drug release over a period of days to weeks). Therefore, nanoparticles may improve the plasma half-life of the entrapped drug (Allémann et al., 1993; Oppenheim, 1981). The drug pharmacokinetics parameters are altered when the drug is loaded in nanoparticles, and the particle surface composition plays an important role in drug bioavailability, which can be greater or lower than the drug solution/powder ratio, depending on the polymer used (Ubrich et al., 2005). Some characteristics of nanoparticles, such as particle size and surface charge, can be modulated by modifying some process parameters of formulation; they can be used in various applications. The research involving the applications of polymeric nanoparticles in AIDS treatment is primarily directed to increasing the intracellular and brain delivery of antiretroviral drugs. Thus, it is clear that M/Ms represent an important target for antiretroviral drugs and for carriers loaded with these drugs. The nanoparticles represent an attractive alternative in AIDS treatment because they consist of a carrier system intended for targeting M/Ms. When administered intravenously, conventional nanoparticles are rapidly cleared from the bloodstream by the MPS, represented by M/Ms. The particle uptake by cells is affected by the particle's physicochemical properties, such as particle size, surface charge, hydrophobicity and presence of a coating (varying in density/conformation) (Stolnik et al., 2005; Owens & Peppas, 2006).

Schäfer and co-workers (1992) were pioneers in studies involving antiretroviral drugs and macrophage targeting using nanoparticles. The authors found that the physicochemical properties, including the composition, surface characteristics and size, of poly(alkylcyanoacrylate) (PACA), poly(metylmethacrylate) (PMMA) and human serum albumin (HSA) nanoparticles containing zidovudine influenced the rate of uptake by macrophages, particularly when these cells were infected by HIV (up to 60% more than for uninfected macrophages). Also, the group demonstrated the effectiveness of poly(hexylcyanoacrylate) (PHCA) and HSA nanoparticles containing zidovudine and didanosine in preventing HIV infection in M/Ms cultures in vitro (Bender et al., 1994). Furthermore, the group prepared PHCA nanoparticles as carriers for saquinavir or zalcitabine and demonstrated that the both nanoparticles formulations led to a dose-dependent reduction of HIV-1 antigen production in vitro in primary human M/Ms cultures (Bender et al., 1996). In a similar study, saquinavir carried in poly(ethyleneoxide)-modified poly(epsilon-caprolactone) (PEO-PCL) nanoparticles was significantly internalized by the THP-1 human M/Ms cell line at a 10-fold higher rate than an aqueous solution of saquinavir (Shah & Amiji, 2006). In another study, Hillaireau et al. (2006) demonstrated that nanocapsules composed of PIBCA and poly(ethyleneimine) increased the intracellular uptake of azidothymidine-triphosphate 10- to 30-fold higher that the free drug, in a mouse macrophages culture. Destache and co-workers (2009) developed poly(lactic-co-glycolic) acid (PLGA) nanoparticles containing ritonavir, lopinavir and efavirenz and the results of the in vitro release of the drugs from the nanoparticles in human peripheral blood mononuclear cells showed an intracellular peak of each drug over a 28-day period, while the free drugs were eliminated in 2 days. The authors also demonstrated that nanoparticles were not significantly cytotoxic over macrophages. These results are important because they demonstrate that the three drugs can be incorporated into a single nanoparticle for drug

delivery and because the use of a single antiretroviral in the treatment of HIV-1 only resulted in the development of resistant strains and treatment failures. In another study, the same group showed that these nanoparticles were able to maintain the plasmatic drug concentrations for a prolonged period, after intraperitoneal administration in mice. Also, the drug concentration in the brain was significantly higher with drug-loaded nanoparticles than with the free drug. Additionally, the antiretroviral drug-loaded nanoparticles were able to interact with the M/Ms infected with HIV-1 and inhibit virus replication up to 1000-fold for 10 days compared to the free drugs (Destache et al., 2010). Poly(lactic) acid (PLA) and PLA-polyethylene glycol (PLA-PEG) blended nanoparticles containing zidovudine were developed, and their uptake by polymorphonuclear leucocytes from rats was studied in vitro. The results showed that the PLA nanoparticles were more efficiently phagocytosed than PLA-PEG blends and were able to activate a larger number of cells than the blended PLA-PEG nanoparticles (Mainardes et al., 2009). Furthermore, the group evaluated the pharmacokinetic profile of these nanoparticles in rats after a single intranasal administration. Blended PLA-PEG nanoparticles exhibited a sustained release of the drug over 24 h, while PLA nanoparticles were sustained up to 10 h. The half-life of zidovudine also varied among the formulations. The slow elimination rate (Ke) resulted in significantly prolonged $t_{1/2}$ values for zidovudine from the PLA and blended PLA-PEG nanoparticles compared to the zidovudine solution. Because of the slow release of zidovudine from the nanoparticles, its metabolic breakdown was also slower, increasing the mean half-life. The significant increase ($p< 0.05$) in the value of the area under curve (AUC) for the zidovudine-loaded PLA-PEG nanoparticles, compared to the PLA nanoparticles and zidovudine aqueous solution, distinctly indicated the improved intranasal bioavailability of the blended system (Mainardes et al., 2010). Thus, the results of this study corroborated those of the first study, indicating that the physicochemical characteristics of nanoparticles intended for controlled drug release is very important because these characteristics can govern the application of the formulation and can be used to predict its behavior in the biological medium. The size and surface charge are also important parameters in a nanostructured system because these characteristics interfere directly in biological processes, such as the transport across biological membranes and the recognition by M/Ms and biodistribution.

Another important factor that must be taken into account in the design strategies used to improve AIDS treatment is the brain delivery system of antiretroviral drugs. Because of the restricted entry of anti-HIV drugs, the brain is thought to form a viral sanctuary, and the treatment and control of HIV within this reservoir must be primordial. Nanoparticles can enhance the brain-drug delivery by three major pathways, which include the following: i) increasing the local drug gradient at the Blood Brain Barrier (BBB) by passive targeting, ii) allowing drug-trafficking by non-specific or receptor-mediated endocytosis and iii) blocking drug efflux transporters at the BBB (Wong et al., 2010). Consequently, the use of nanocarriers should help to achieve higher concentrations of encapsulated drugs and also allow their prolonged residence in the CNS.

One of the most used polymers for the development of nanoparticles intended for brain delivery is poly-(butylcyanoacrylate) (PBCA) (Koziara et al., 2006). Studies have shown that the surface modification of PBCA nanoparticles using other polymers or surfactant agents, such as polysorbate 80, could increase the transport of particles through the BBB. Polysorbate 80 has been found to increase the translocation of nanoparticles by increasing the particle interaction with the low density lipoprotein (LDL) receptor-mediated endocytic pathway in brain endothelial cells and by inhibition the efflux function of P-gp (Goppert & Muller, 2005).

Kuo and Chen (2006) showed that methylmethacrylate-sulfopropylmethacrylate (MMSPM) nanoparticles were able to significantly increase the BBB permeability of zidovudine and lamivudine by 100%, using blood-brain-microvascular endothelial cells model. In the same study, PBCA nanoparticles increased the BBB permeability of zidovudine 8- to 20-fold and lamivudine 10- to 18-fold. The authors also demonstrated that the drug permeability increased with the decrease in particle size of the two polymeric carriers. Furthermore, these authors observed an increase in the BBB permeability (in vitro) of stavudine-, delaviridine- and saquinavir-loaded PBCA and MMSPM nanoparticles coated with polysorbate 80 and solid lipid nanoparticles; in addition, a higher drug permeability was obtained with smaller particles (Kuo & Fu, 2007).

The transferrin receptors present in the luminal membrane of brain endothelial cells have been used as preferential targets for enhanced antiretroviral drug delivery to the CNS by means of nanoparticulate systems (Kreuter, 2001). PEGylated albumin nanoparticles encapsulating zidovudine were prepared, and its surface was modified by anchoring transferrin as a ligand for brain targeting. A significant enhancement of brain localization of zidovudine was observed when it was delivered by transferrin-anchored PEGylated albumin nanoparticles compared to unmodified nanoparticles (Mishra et al., 2006).

Recently, the properties of cell-penetrating peptides have been explored to further enhance the cellular permeability of drug carrier systems. In this approach, certain proteins or peptides can be tethered to the hydrophilic drug of interest, and together, the construct possesses the ability to translocate across the plasma membrane and to deliver the payload intracellularly (Jeang et al., 1999). The Tat peptide, the most frequently used cell-penetrating peptide, is derived from the transcriptional activator protein encoded by HIV-1 (Torchilin, 2008). Thus, nanoparticles containing Tat are promising systems for transport across the BBB and entry into the brain. Therefore, Rao and co-workers (2008) hypothesized that anti-HIV drugs loaded in nanoparticles could bypass the efflux action of P-gp and that Tat conjugation would enhance their transport across the BBB, thereby enhancing the CNS bioavailability of anti-HIV drugs. In their study, ritonavir-loaded PLA nanoparticles conjugated with the Tat peptide were developed, and it was demonstrated to enhance and sustained brain delivery of the system without influencing the integrity of the BBB; these data suggested that the transport occurred through transcytosis across the endothelium of the brain vasculature. At two weeks post administration, the brain ritonavir level after administration of the conjugated nanoparticles was 800-fold higher than that with the drug delivered in solution. It was concluded that Tat-conjugated nanoparticles enhanced the ritonavir CNS bioavailability and maintained therapeutic drug levels in the brain for an effectively sustained period for reducing the viral load in the CNS, which acts as a reservoir for the replicating HIV-1 virus.

4. Solid Lipid Nanoparticles (SLN)

In the last decade of the last century, SLN have gained considerable interest as novel particulate drug delivery systems. SLN are solid, particulate carriers that are nano-sized and composed of biodegradable/biocompatible lipids, suitable for the incorporation of lipophilic and hydrophilic drugs in the lipid matrix in high concentrations. SLNs can be prepared from fatty acids and the stabilization of dispersions with emulsifiers and co-emulsifiers, such as polysorbates, poloxamers, fatty acid co-esters, lecithin and bile salts (Gupta & Jain, 2010). Although few reports about the anti-HIV drug SLN have been published, some studies have

proved the suitability of this system to dissolve lipophilic anti-HIV drugs and sustain the drug release; in addition, these studies have shown the feasibility of scaling up SLN production. Cationic SLN were found to be beneficial to the entrapment efficiency of saquinavir. SLN were fabricated via a microemulsion method and stabilized by polysorbate 80; in addition, the lipid phase contained cationic stearylamine, dioctadecyldimethyl ammonium bromide, non-ionic Compritol 888 ATO and cacao butter. The in vitro drug release assay suggested that the carriers could sustain drug delivery without an apparent initial burst (Kuo & Chen, 2009). Aji Alex et al. (2010) investigated the use of SLNs to target intestinal lymphatic vessels. Lopinavir, a poor orally available anti-HIV, was successfully encapsulated in glyceryl behenate-based SLNs produced via a hot homogenization process followed by ultrasonication. In vitro release studies showed that SLNs presented a low release profile; the intestinal lymphatic transport study showed an increase in the cumulative percentage dose of lopinavir secreted into the lymph. These results significantly enhanced the percentage of lopinavir bioavailability. SLNs have been obtained using large-scale production methods, and the study of Shegokara et al. 2010 showed promising results, in which the scaling up of the stavudine production for intravenous injection was possible. The SLNs were produced by the high-pressure homogenization of the stavudine lipid melt, dispersed in a hot surfactant solution (pre-emulsion). For the investigated formulation, the homogenization system seemed to be rather robust, producing very similar SLN sizes.

5. Challenges involving clinical trials of antiretroviral drug delivery systems

Despite the current increase of published original studies on nanotechnology-based antiretroviral drug delivery systems with promising strategies and pre-clinical results, these studies generally have not extended to the clinical studies and, consequently, patients have not received the benefits. Clinical trials are the best way to confirm the efficacy of new medicines; however, this type of study also utilizes placebos, which present serious ethical challenges. The placebo-group has been disapproved in cases of AIDS research because the patient that does not receive the effective regimen can suffer serious consequences in the absence of AIDS therapy. Studies using placebos have been considered unethical in the case where an efficient treatment is known (Scheffer, 2000). Since the Declaration of Helsinki (World Medical Association, 2008), a document with guidelines of ethical principles for the medical community about human experimentation, researchers worldwide must protect the life, health, privacy, and dignity of the human subject, although those principles may contradict many economic and political interests. Thus, a discussion about human experimentation and the investigation of new in vitro models in cells and animals are also extremely important to circumvent the problems with clinical trials of new antiretroviral drug delivery systems.

6. Conclusion

The development of systems for drug delivery will not only benefit the therapy of AIDS and other viral diseases but also accelerate the development of systems for bacterial diseases, fungi and mycobacteria. For this, new challenges for the future of drug delivery systems are the feasibility of scaling-up processes to bring to the market quickly innovative therapeutic and the possibility of obtaining multifunctional systems that will be able to fulfill the different biological and therapeutic requirements.

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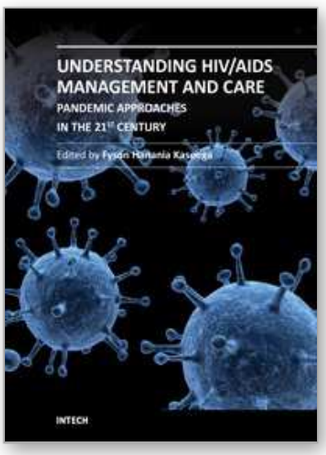

Understanding HIV/AIDS Management and Care - Pandemic Approaches in the 21st Century

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Like any other book on the subject of HIV/AIDS, this book is not a substitute or exhausting the subject in question. It aims at complementing what is already in circulation and adds value to clarification of certain concepts to create more room for reasoning and being part of the solution to this global pandemic. It is further expected to complement a wide range of studies done on this subject, and provide a platform for the more updated information on this subject. It is the hope of the authors that the book will provide the readers with more knowledge and skills to do more to reduce HIV transmission and improve the quality of life of those that are infected or affected by HIV/AIDS.

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