Development and Characterization of Multiparticulate Drug Delivery System for Immunosuppressant and Antimigraine Drug

Introduction

Multiparticulate systems have been used for localized drug delivery to reduce side effects as well as to improve the therapeutic response at the local site. The nanoparticles were first developed about 35 years ago. They were initially developed as carriers for vaccines and cancer chemotherapy agents. In delivery of any microparticles and nanoparticle inside the body pharmacokinetics and pharmacodynamics play a very important role. Pharmacokinetics deals with drug delivery inside the human body. When the drugs enter in the body intravenously it goes through absorption, distribution, metabolism and elimination. The results depend mainly on the physiochemical properties of the drug (Molecular weight, shape, charge, and aqueous solubility) and therefore on its chemical nature. At present, 95% of all new potential therapeutics has poor pharmacokinetics and biopharmaceutical properties (Brayden D. J., 2003, D.P. Rao, et. al. (2010).

Several disease related drugs/bioactive molecules are successfully encapsulated to improve bioavailability, bioactivity and control delivery (Budhian A., 2005, Gomez-Gaete C. 2007, Cheng Q. 2008). Microparticulate medicines and nanomedicines of the dreadful diseases like cancer (Mu L., 2003), AIDS (Coester C., 2000), Diabetes (Damge C., 2007), Malaria (Patravale V.B., 2007), Prion disease (Calvo P., 2001) and Tuberculosis Ahmad Z., 2006) are in different trial phase for the testing and some of them are commercialized (Kim S.Y., 2001, Lee K.S.). Nanomedicine formulation depends on the choice of suitable polymeric system having maximum encapsulation (higher encapsulation efficiency), improvement of bioavailability and retention time. (Vlerken L.E.v., 2007). These drug microparticulate and nanoparticulate formulation systems are superior to traditional medicine with respect to control release, targeted delivery and therapeutic impact. These targeting capabilities of nanomedicines are influenced by particle size, surface charge, surface modification, and hydrophobicity. Among these, the size and size distributions of microparticles and nanoparticles are important to determine their interaction with the cell membrane and their penetration across the physiological drug barriers. The size of microparticles and nanoparticles for crossing different biological barriers is dependent on the tissue, target site and circulation (Brannon-Peppas L., 2004). For the cellular internalization of the microparticles and nanoparticles, surface charge is important in determining whether the both
systems would cluster in blood flow or would adhere to, or interact with oppositely charged cells membrane (Feng S.S., 2004). Cationic surface charge is desirable as it promotes interaction of the nanoparticles with the cells and hence increases the rate and extent of internalization (Kim S.Y., 2001). For targeted delivery, persistence of microparticles and nanoparticles are required in systemic circulation of the body. But conventional multiparticulate system with hydrophobic surface are rapidly opsonized and massively cleared by the fixed macrophages of the mononuclear phagocytic system (MPS) organs. For increasing circulation time and persistence in the blood, surface of conventional multiparticulate systems are modified with different molecules. Coating of hydrophilic polymers can create a cloud of chains at the particle surface which will repel plasma proteins (Brigger I., 2002). Finally, the performance of multiparticulate system in vivo is influenced by morphological characteristics, surface chemistry, and molecular weight. Surface modified multiparticulate system have anti-adhesive properties by virtue of the extended configuration on the particle surface which acts as steric barrier reducing the extent of clearance by circulating macrophages of the liver and promoting the possibility of undergoing enhanced permeation process. Release mechanism can be modulated by the molecular weight of the polymer used. Higher the molecular weight of polymer slower will be the in vitro release of drugs (Soppimath K.S., 2001). Careful design of these delivery systems with respect to target and route of administration may solve some of the problems faced by new classes of active molecules.

Biodegradable multiparticulate systems are frequently used to improve the therapeutic value of various water soluble/insoluble medicinal drugs and bioactive molecules by improving bioavailability, solubility and retention time (Amiji M.M., 2005). These multiparticulate system –drug formulations reduces the patient expenses, and risks of toxicity (Glen A., 2005). In multiparticulate system encapsulation of medicinal drugs (such as microparticles and nanomedicines) increases drug efficacy, specificity, tolerability and therapeutic index of corresponding drugs (Safra T., 2000, Schroeder U., 1998, Raghuvanshi R.S., 2002, Kreutera J., 1997, Fassas A., 2003, Jean-Christophe L., 1996). These nanomedicines have many advantages in the protection of premature degradation and interaction with the biological environment, enhancement of absorption into a selected tissue, bioavailability, retention time and improvement of intracellular penetration (Alexis F., 2008).
Applications and advantages of multiparticulate system as drug carriers

Polymeric microparticles and nanoparticles made from natural and synthetic polymers have received the majority of attention due to their stability and ease of surface modification (Vauthier, C. 2003, Kreuter, J. 1994b). They can be tailor-made to achieve both controlled drug release and disease-specific localization by tuning the polymer characteristics and surface chemistry (Murray J.C. 2001, Labhasetwar V. 2003, Sahoo S.K. 2003b). It has been established that nanocarriers can become concentrated preferentially to tumors, inflammatory sites, and at antigen sampling sites by virtue of the enhanced permeability and retention (EPR) effect of the vasculature. Once accumulated at the target site, hydrophobic biodegradable polymeric microparticles and nanoparticles can act as a local drug depot depending on the make-up of the carrier, providing a source for a continuous supply of encapsulated therapeutic compound(s) at the disease site, e.g., solid tumors. These systems in general can be used to provide targeted (cellular or tissue) delivery of drugs, improve bioavailability, sustain release of drugs or solubilize drugs for systemic delivery. This process can be adapted to protect therapeutic agents against enzymatic degradation (i.e., nucleases and proteases) (Amidon G.L., (1997). Thus, the advantages of using microparticles and nanoparticles for drug delivery are a result of two main basic properties: small size and use of biodegradable materials. Microparticles and nanoparticles, because of their small size, can extravasate through the endothelium in inflammatory sites, epithelium (e.g., intestinal tract and liver), tumors, or penetrate microcapillaries. In general, the nanosize of these particles allows for efficient uptake by a variety of cell types and selective drug accumulation at target sites (Labhasetwar V. 2003, Yang C., 2002). Many studies have demonstrated that nanoparticles have a number of advantages over microparticles (N1 µm) as a drug delivery system. Nanoparticles have another advantage over larger microparticles because they are better suited for intravenous delivery. The smallest capillaries in the body are 5–6 µm in diameter. The size of particles being distributed into the bloodstream must be significantly smaller than 5 µm, without forming aggregates, to ensure that the particles do not cause an embolism. The use of biodegradable materials for nanoparticle preparation allows for sustained drug release within the target site over a period of days or even weeks. Biodegradable microparticles and nanoparticles formulated from PLGA and PLA have been developed for sustained drug delivery and are especially effective for drugs with an intracellular target...
(Labhasetwar V., 2002, Sahoo S.K. 2003b). Rapid escape of hydrophobic PCL-coated nanoparticles from endo-lysosomes to the cytoplasm has been demonstrated [Labhasetwar, V., 2002, Illum L., 2001). Greater and sustained antiproliferative activity was observed in vascular smooth muscle cells that were treated with dexamethasone-loaded nanoparticles and then compared to cells given drug in solution (James W. L. Jr. 2009).