POLYMERIC NANOPARTICLE FOR THE DELIVERY OF POORLY SOLUBLE DRUGS

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By

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CONCLUSION/ Chapter - 5

During last two decades, considerable attention has been given to the development of novel drug delivery system (NDDS) for poorly soluble oral drugs. The rational for controlled drug delivery was to alter the pharmacokinetics and pharmacodynamics of drug substance in order to improve the therapeutic efficacy and safety through the use of novel drug delivery system. Drug delivery scientists are searching for an ideal nano vehicle for the delivery of poorly soluble drugs; one that would dramatically reduce drug dosage, such that, there is an improvement in the absorption and bioavailability of the drug, so that the patient can take a smaller dose, and yet have the same benefit, delivery of the drug to the right place in the living system, increase the local concentration of the drug at the desired site and eliminating side effects.

As it stands today, the scope of this emerging field seems to be limitless. However, the considerable technological and financial obstacles still need to be properly addressed by both the private sector and governments before nanotechnology's full promise can be realized. Ranking highest among the challenges is the need to develop and perfect reliable techniques to produce nanoscale particles that does not just have the desirable particle sizes, but also minimal structural defects and acceptable purity levels. This is because these attributes can drastically alter the anticipated behavior of the nanoscale particles. Nanotechnology, deals with the design, characterization, production and application of structures, devices and systems by controlling shape and size at the nanometer scale. Two principal factors cause the properties of nanomaterials to differ significantly from other materials: increased relative surface area, and quantum effects. These factors can change or enhance properties such as reactivity, strength, electrical characteristics as well as most of the biomedical properties. Nanotechnology in biomedical sciences is expected to create innovations and play a vital role, not only in drug delivery and gene therapy, but also in molecular imaging, biomarkers and biosensors. Today the application of nanotechnology in drug delivery is widely expected to change the landscape of pharmaceutical and biotechnology industries for the foreseeable future. Using nanotechnology, it may be possible to achieve the improved delivery of poorly water-soluble drugs.

Polymeric based nanoparticles have taken much attention for safe and effective delivery of proteins and antimicrobial drugs. Nanoparticles prepared, particularly in the size range from 10 nm to 200 nm, are considered optimal for ocular delivery. Nanocarriers as drug delivery systems

are designed to improve the pharmacological and therapeutic properties of conventional drugs. The incorporation of drug molecules into nanocarrier can protect a drug against degradation as well as offers possibilities of targeting and controlled release. Due to small dimensions, nanocarriers are able to cross the blood-brain-barrier (BBB) and operate on cellular level. In comparison with the traditional form of drugs, nanocarrier-drug conjugates are more effective and selective. They can reduce the toxicity and other adverse side effects in normal tissues by accumulating drugs in target sites.

In this study, few antimicrobial agents were selected like Amphotericin B, Ketoconazole, Ciprofloxacin, Vancomycin and Chloramphenicol as poorly soluble drugs. Polymeric chitosan nanoparticle formulations were prepared loaded with these drugs separately and characterized on the basis of different parameters such as formulation (concentration of polymer and polyanion TPP) and process variables (magnetic stirring time and stirring speed). Chitosan nanoparticles loaded with these poorly soluble drugs were in the size range of 10-200 nm according to SEM study and this range was suitable for the oral/ocular delivery of drugs. The chitosan nanoparticle formulation (CS1) exhibited drug entrapment efficiency above 70% in all the selected drug-loaded nanoparticle formulation (CS1). The release profile of these poorly soluble drugs from thiolated chitosan nanoparticles, chitosan nanoparticle formulation CS1 and free drug itself were studied.

Chitosan nanoparticle formulation (CS1) and thiolated chitosan nanoparticles loaded with Amphotericin B, Ketoconazole, Ciprofloxacin, Vancomycin and Chloramphenicol *in-vitro* release profile showed sustained release behavior of drugs up to 12h whereas free drug releases in biphasic pattern where initial burst release was observed in 1h for all the selected drugs. According to zeta-potential values, chitosan nanoparticles loaded with Amphotericin B, Ketoconazole, Ciprofloxacin, Vancomycin, and Chloramphenicol possess positive charge on its surface therefore responsible for increase in cellular uptake and cytotoxity and the zeta-potential value near and above +25mV in all the cases indicated the strong repulsion between the particles hence better stability due to less chances of aggregation. The ability of the ionic gelation process to form drug-loaded chitosan nanoparticles was assessed by employing FTIR to determine drug-chitosan interactions. By comparing the FTIR spectra of chitosan matrix, chitosan-TPP

nanoparticles and drug loaded chitosan nanoparticles; it was observed that drugs were present in the nanoparticles without possessing any kind of chemical linkage or interactions with the chitosan matrix and the integrity of the drugs was maintained. XRD and FTIR studies were performed to investigate the physical state of the drug in the nanoparticles and possible interaction between drug-polymer, since these aspects may influence the release characteristics of the drug. The XRD spectra of pure chitosan, chitosan nanoparticles, pure drugs and drug loaded chitosan nanoparticles indicated that all the other drugs such as Amphotericin B, Ketoconazole, Ciprofloxacin, Vancomycin and Chloramphenicol were present in amorphous state which was considered as suitable state to enhance the solubility as well as bioavailability whereas all the free drugs showed polycrystalline (many sharp peaks) behavior which was disappeared after getting entrapped in chitosan nanoparticles. The antimicrobial study of the entire drugs loaded chitosan nanoparticle exhibited similar activity as that of free drugs therefore it could be concluded that activity of drug was not hampered after getting entrapped in the chitosan matrix. Kinetic modeling of all the drug loaded chitosan nanoparticles was also studied. Studies on kinetic modeling on drug release showed that these models have been mainly established to describe the relationship between drug dissolution and geometry on drug release patterns mathematically. Applying cumulative release profile data of all the drug loaded chitosan nanoparticle formulation CS1 on different mathematical equations of models such as Zero-order, First-order, Higuchi, Korsmeyer-peppas and Hixon model , it was concluded that Amphotericin B and Chloramphenicol loaded chitosan nanoparticle formulations were following Zero-order kinetics (constant release of drug with respect to time) and other drugs such as Ketoconazole, Ciprofloxacin, Vancomycin loaded chitosan nanoparticle formulation CS1 were best fitted with First-order kinetics (with increase in drug concentration, the rate of reaction also increased). All the free drugs were obeying First-order release kinetics. Hence it can be concluded that the newly designed oral sustained drug delivery systems of polymeric chitosan nanoparticles loaded with Amphotericin B, Ketoconazole, Ciprofloxacin, Vancomycin and Chloramphenicol may be considered to be ideal and effective in the management of microbial infections with enhanced dissolution/bioavailability.

CONCLUDING REMARKS

Around 40% of marketed drugs and nearly 90% of drugs in research and development pipeline are poorly soluble. Numerous drugs associated with poor solubility and low bioavailability which results in suboptimal drug delivery. Amphotericin B, Ketoconazole, Ciprofloxacin, Vancomycin & Chloramphenicol were few poorly bioavailable oral drugs. Therefore chitosan and thiolated chitosan nanoformulations loaded with these poorly soluble oral drugs were prepared through optimized ionotropic gelation method where cross-linking agent used was TPP only to increase the bioavailability of these above mentioned antimicrobials. All the drug loaded chitosan nanoparticles were characterized on the basis of different parameters such FTIR plot, Zeta-potential, XRD plots, drug entrapment efficiency, practical yield and antimicrobial activity. It was seen that as compared to other formulations CS1 was found to have greater stability and higher entrapment efficiency. With the results of FTIR and XRD, it was concluded that the drug was present inside matrix of chitosan without any kind of chemical linkages and in amorphous form respectively. The kinetic modeling was also done for drug loaded CS1 formulations and observed that all the drugs like Ketoconazole, Ciprofloxacin, Vancomycin loaded CS1 formulation were following First-order release kinetics but Amphotericin B and Chloramphenicol loaded CS1 formulations were best fitted with Zero-order kinetics. Free drugs (Amphotericin B, Ketoconazole, Ciprofloxacin, Vancomycin & Chloramphenicol) release profile were found to be best fitted with First-order kinetic model. In the case of Zero-order release kinetics drug release does not depends upon the concentration but with First-order kinetics the release rate of drug completely depends upon the concentration or amount of drug. Over the last decade, polymeric nanoparticles considered as a novel approach to improve the solubility of poorly soluble drugs since the technique was simple and effective which can quickly launch product to the market. Additionally, drug loaded polymeric chitosan nanoparticles found to be a universal approach generally applied to all poorly soluble oral drugs for the reason that all drugs can be disintegrated into nanometer-sized particles.