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1. INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is an unvoiced killer and everyday 15,000 Human immunodeficiency virus (HIV) infections are supplemented. HIV infection and AIDS, universally referred to as HIV/AIDS, comprise one of the most solemn infectious disease challenges to public health globally, and has had an attenuating effect in certain parts of the world. There are at present, 33.4 million people living with HIV/AIDS worldwide [1, 2]. The fatality of HIV infection has been transformed to a manageable chronic infectious disease by interventions such as AIDS counseling, educational tools and antiretroviral drug therapy etc. Despite the availability of these measures, the above statistics signify that much remains to be accomplished as the number of newly reported HIV infections still remains inaptly high [3, 4].

In milieu to above scenario, the approach of present research is focused to provide a novel solution to this global pandemic. Antiretroviral (ARV) therapy refers treating HIV viral infections with drugs that do not kill the virus; however they slow down the growth of HIV virus [5]. The reduction in CD4 cells count from normal levels (500-1500 cells/mm$^3$) to <200 cells/mm$^3$ renders the HIV patient susceptible to the unique opportunistic infections (OIs) and tumors and thus provide the rationale for using CD4 cell threshold to define AIDS [6].

Of late, highly active antiretroviral therapy (HAART) has been the most frequently used treatment for HIV; including the combination therapy regimen. Albeit, the failure of treatment due to the development of resistance mutations to both; the specific drug in question and cross-resistance to other available treatment options is playing a pivotal role with regard to its efficacy as well [7, 8]. However, a randomized trial for “Salvage therapy” of stavudine (d4T) has shown that in heavily pre-treated patients, the antiviral efficacy may be associated with the recycling of antiretroviral agents that have been utilized previously [9, 10]. In consonance with the above statement, a recently completed phase II trial revealed that stavudine treatment resulted in delayed progression of clinical disease in patients who had previously been treated with other antiretrovirals. Salvage therapy with stavudine can diminish viral loads to undetectable levels whereas stavudine monotherapy can stabilize CD4 counts and weight loss in heavily pre-treated individuals [11]. Benefits were evident in all CD4+ cell strata and clinical stages of HIV disease as stavudine is well tolerated and has been proved to delay AIDS progression. Nonetheless, the extended blood plasma profile of stavudine, the...
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Eradication of HIV a highly arduous task since the cells of the mononuclear phagocyte system (MPS) which are the specific hosts for HIV needs to be targeted in order to maintain viral suppression and reduced disease progression [12, 13]. The competence of developing new drug molecules has immensely expanded by the introduction of high-throughput screening, combinatorial libraries and automated synthesis methods. Nevertheless, it has been widely recognized that a large portion of the potential value of drugs has been squandered due to inadequate delivery strategies [14, 15]. The release behavior of drug from conventional drug delivery systems is largely dependent upon the biological environment, thereby making it difficult to be predicted and controlled.

Successful drug therapy may be achieved in three ways: delivering the drug efficiently to the target site; modifying the drug for increased therapeutic efficacy; or developing a novel drug of inherently higher efficiency [16]. Of these three methods, the development of an efficient novel means of drug delivery is the most cost-effective one. Since developing a new drug molecule costs an average of 250-300 million dollars and 12-15 years of hardcore research which is unreasonable for most of the pharmaceutical firms [17]. These facts have abstracted the focus of most pharmaceutical concern over quickly developing the economic and innovative drug delivery technologies to which can consign the drug moiety to the desired targeted site so as to achieve its specific therapeutic efficacy [18, 19].

The design and development of various novel drug delivery technologies has moved the existing drug molecules in to a new era where not only the market value and demand but also the patent lives of the existing molecules have enhanced dramatically [20, 21]. Apart from serving a means to extend the patent life, the innovative drug delivery technologies should also enable difficult-to-deliver compounds; offer improved efficacy, safety, and patient compliance to already existing drug molecules [22-25].

1.1 Controlled Drug Delivery Systems

The fundamental objective for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and physiological parameter inherent in selected route of administration. It is desirable that the duration of drug action become more a designed property of a rate controlled dosage form and less or not at all, a property of the drug molecules intrinsic kinetic properties. Thus optimal
design of controlled release systems requires a comprehensive understanding of pharmacokinetics and pharmacodynamics of drug [26-29].

Controlled drug delivery systems (CDDS) serve two functions it involves targeted delivery of the drug to specific tissues or organs as well as delivers the drug in a constant and therapeutic rate for a extended period of time. Thus CDDS are used to enhance the therapeutic response by expressing the more consistent drug levels in blood plasma than conventional dosage forms [30]. They release the drug at predetermined and controlled rate for a definite period of time with enhanced potential of therapeutic efficacy and reduction in dosing frequency so as the adverse reactions. They result in drug levels within the therapeutic window avoiding higher systemic toxic levels; providing patient compliance and overall effective therapeutic regimens [31-35].

To utilize the numerous benefits as well as added advantages of unit/multiparticulate dosage forms, like cost effectiveness, ease of manufacturing, packaging and great industrial potential with enhanced therapeutic benefits, hydrophilic matrix tablets and pellets were also formulated employing carbopol and polyethylene oxide (PEO) as controlled release matrix formers, whereas ethyl cellulose (EC) was used as functional coating polymer over the beadlets formed through extrusion-spheronization technique The formulated systems were evaluated for various physical parameters and in-vitro release profiles.

1.2 Controlled Release Biodegradable Systems

Currently lactide-based biodegradable copolymers are being used in majority for developing novel controlled release systems [36]. Such drug delivery systems have had an impact on nearly every branch of medicine including cardiology, immunology, oncology, ophthalmology and endocrinology. In the United States alone, annual sales of advanced drug delivery systems have exceeded $10 billion and are still rising rapidly [37]. The world market of advanced drug delivery systems is currently valued at $50 billion a year, occupying 12.5% of world total pharmaceutical sales [38]. Hydrolysis of the polymeric chains of biodegradable polymers eventually leads to their conversion into smaller and biologically acceptable compounds. For example, polylactides (PLA), polyglycolides (PGA) and their copolymers (PLGA) hydrolyze into lactic acid and glycolic acid, which further break down into carbon dioxide and water under physiological conditions.
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The bulk hydrolysis leads to degradation, wherein, the polymer degrades in a uniform manner throughout the matrix. The polymer matrices most remarkably, comprising of polyanhydrides and poly (ortho esters) (POEs), undergo degradation only at the surface resulting in a release rate that is proportional to the surface area of the drug delivery system. It was reported that the microspheres made from PLGA degraded through bulk hydrolysis in water or body fluids, yielding smaller and irregular forms over time. In contrast, POE showed significant surface erosion after 9-16 weeks of implantation while the core of the matrices remained intact [39].

**1.3 Development of Controlled Release Parenterals**

The past few years have witnessed the substantial upsurge in development of newer injectable drug delivery system. This interest can be ascribed to the merits this delivery system possess, which embrace ease of application, localized delivery for a site specific action, prolonged delivery periods, decreased body drug dosage with concurrent reduction in probable detrimental side effect frequent to most forms of systemic delivery and enhanced patient compliance and comfort [40]. In general parenteral products include all systems administered outside of the GI tract. However, parenteral routes are more commonly restricted to injectable administration such as intravenous, intramuscular, subcutaneous, intraperitoneal, intrathecal, and intraventricular injections [41-43].

Invariably, parenteral drug administration, and in particular, intravenous infusion, leads to easy and absolute absorption of drug in systemic circulation, eliciting a prompt drug response whereas a fairly rapid onset of action followed by rapid decline in the blood-drug level leading to a relatively shorter duration of therapeutic response [44, 45]. But for attaining the efficacy of the therapeutic regimen it is desirable to maintain the blood plasma level of the drug in therapeutic window until the complete therapy. Thus, the injectable depot formulation by virtue of controlling the drug release over a predetermined time seems to provide the solution for the problems associated with different modes of parenteral drug administration [46, 47].

These systems, *in vivo* are capable of delivering a sustained dose ranging from a few days to weeks and to months with decreased drug dose, reduced side effects and better drug utilization. Generally, for life-threatening diseases or those in which the quality of life is drastically impaired, injectable controlled-release administration may be the most appropriate tool [48]. Currently, proteins and peptides are most administered...
substances via the parenteral route due to their short half-lives. Products based on PLGA and a small peptide, luteinizing hormone and releasing hormone (LHRH) are successfully running in the market. The microspheres containing recombinant human growth hormone have also been developed and marketed successfully \[49, 50\]. The demand for prolonged release parenteral drug delivery systems has grown exponentially with an annual rise of 9.5%, in spite of severe competition from the alternative modalities. Invariably, parenteral depot systems achieve constant, “infusion-like” plasma level time profiles and thus minimize side effects. Furthermore, the potential benefits include avoidance of saw tooth kinetics and reduced frequency as well as dose and thus consequential enhanced patient compliance \[51\].

Drug-loaded parenteral microspheres of biodegradable and non-biodegradable polymers have been extensively investigated prolonged residence of therapeutics in the body. These are gaining importance since these impart significant therapeutic adherence and convenience benefits to patients \[52, 53\]. Non-biodegradable polymers are not preferred due to shortcomings of toxicity and difficulty in removal after use which leads the evolution of biodegradable polymers. The advent of biodegradable polymers for sustained release parenteral drug delivery began in early 1970s. The US Food and Drug Administration (FDA) has approved these polymers for human use as surgical sutures, implantable devices, and drug delivery systems \[54\]. The application of parenteral microspheres formulated using biodegradable polymers such as polylactide (PLA) and poly (lactide-co-glycolide) (PLGA) to deliver small molecules, proteins, and macromolecules using multiple routes of administration have been studied and successfully used for the treatment of a variety of disease states. The microspheres as drug delivery devices offer a myriad of advantages such as continuous and controlled drug release, enhanced stability of protein therapeutics, reduced dosage, reduced frequency of administration consequential increased patient compliance, decrease in systemic side effects and reduced possibility of dose dumping \[55, 56\].

Stavudine is available in a dose of 60-80 mg/day. Present investigation aims at formulation of stavudine loaded biodegradable polymeric microspheres as a depot system for parenteral delivery which will facilitate patient compliance by reducing the dosing frequency and providing the maximum therapeutic benefits but also avoid the plasma level fluctuations of the drug. Prolonged release of stavudine will effectively help in the
reduction of viral load. Thereby delaying the AIDS progression and also alleviates the symptoms of HIV infection [50-54].

Microspheres were prepared from various biodegradable polymers including Polycaprolactone (PCL), PLGA 85:15, various grades of PLGA 50:50 (RESOMER® 505 H, 504H and 502 H), PLA and PLLA by various techniques with different drug/polymer ratios (1:2, 1:4, 1:8, 1:10, 1:20, 1:50 and 1:100) and optimum solution/vehicle ratios [40-44]. The effects of various formulation variables like polymer type and concentration, surfactant concentration and drug to polymer ratio on the characteristics of microspheres were evaluated [46, 57]. The polymeric particles encapsulating d4T were also evaluated for specific ex vivo parameters including cell viability studies, hemolysis studies, cellular internalization studies and histological biocompatibility studies. [14, 15, 58, 59].

The parenteral depot formulation of drug will provide an edge in the treatment of HIV disease especially in neonatal infections from HIV positive mother, unconscious patients incapable to take oral medications [50-53]. Moreover, the patients with damaged hepatic or gastric systems due to complications associated with HIV infections which are the major indications associated with the disease will be benefitted by the parenteral depot therapy. The present research also investigates the feasibility of simultaneous therapy including parenteral and targeted administration of the d4T loaded biodegradable polymeric microspheres for potentially effective and prolonged therapeutic regimen. The concomitant therapy will not only provide the stable and extended release of drug but also eradicate the hidden HIV hosted by macrophages [60, 61]. The mentioned regime will potentially enhance the therapeutic efficacy with patient compliance; renewing new hopes for complete cure and improved quality of life in patient with AIDS.

1.4 Controlled Release Unit/Multiparticulate Systems

Controlled release matrix tablets are designed to attain continual drug delivery at predictable and reproducible kinetics over an extended period of time in the circulation [26, 27]. The potential advantages of this concept include minimisation of drug related side effects due to controlled therapeutic blood levels instead of fluctuating blood levels, improved patient compliance due to reduced frequency of dosing and the reduction of the total dose of drug administered [28-30]. In matrix based systems, the dissolved or dispersed drug is distributed uniformly in an inert polymeric matrix. The matrix systems

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offer significant advantages like ease of manufacturing, cost effectiveness and more reproducibility compared to coated systems [31, 33].

Multiparticulate systems offer high degree of flexibility in the design and development of oral dosage forms, ability to deliver the incompatible agents simultaneously, homogeneous distribution throughout the GIT, augmented absorption of the drug, minimal local irritation, reduced risk of dose dumping, attainment of stable drug plasma levels and reduced inter and intra patient variability [34, 35].