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6.1 Biodegradable Microspheres

In the last quarter of century human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS) became an increasing global health, social, and economical concern. It is estimated that nearly 33 million people are infected by HIV currently across the globe, while another 25 million more have already died since the first reported case in 1981. It results in a chronic, progressive illness which assails the immune system and attacks CD4 cells, which are necessary to fight off illnesses. Eventually, the virus overwhelms the CD4 cells and depletes the count below normal levels (500-1500 cells/mm$^3$) to <200 cells/mm$^3$ of blood, resulting in opportunistic infection taking hold of weakened immune system. The association with complications is the rationale for this CD4 cell threshold to be used to define AIDS. The progression of HIV disease depends on a number of factors including genetics and mode of transmission.

The treatment of AIDS using combinations of antiretroviral drugs has highly reduced the HIV-1 related morbidity and mortality, provided that the plasma viral load can be maintained as low as possible. However, the major limitation in complete eradication of infective virus is that if resistant mutations appear the virus will escape further treatment and the localization of HIV in certain inaccessible compartments of the body such as the CNS, the lymphatic system and within the macrophages which cannot be reached with the current treatment regimens. These sites cannot be targeted by the majority of drugs in the therapeutic concentrations required and the drugs also cannot be maintained for the necessary duration at the site of HIV localization.

The ineffective drug concentrations in accordance to therapeutic response and short residence time at the required sites of action contribute significantly to both, the failure of eliminating HIV from these reservoirs and the development of multidrug resistance against the ARVs. The severe side effects associated with ARV therapy can therefore be attributed to the subsequent large doses essential for achieving a therapeutic effect, due to the inadequate drug concentrations at the site of action, and/or the poor bioavailability of several ARV drugs. Strategies currently being investigated to overcome these limitations include the examination of various dosing regimens as well as the design and development of novel drug delivery systems (NDDS) that can improve the efficacy of both existing and new ARV drugs.

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Controlled release parenteral drug delivery systems have shown the excellent exponential growth and commercial acceptability. Currently lactide-based biodegradable copolymers are being used in majority for developing novel controlled release systems due to their nontoxic nature and loss of removal needs after use. Drug loaded parenteral microspheres of biodegradable polymers have been investigated for extended release depending on their final application. These are a growing class of formulation that imparts prolonged residence of therapeutics in the body with significant therapeutic adherence and convenience benefits to patients. Sustained release parenteral formulations duplicate the benefits of intravenous infusion on a more practical basis and reduce the inherent disadvantages of conventional injectable drug administration.

Stavudine is a synthetic thymidine nucleoside analogue which is active against human Immuno deficiency virus (HIV) and have been significantly used for the treatment of HIV infected patients. In recent research investigations it has been revealed that stavudine monotherapy could stabilize CD4 counts and weight loss in heavily pretreated patients with other antiretrovirals. Moreover when stavudine is used in combination with other agents with similar toxicities, the incidence of adverse events may be higher than when it is used alone. The stated discussion has concluded and rationally justified the use of d4T for the therapeutic regimen. But the candidate drug has a very short half-life (0.8-1.5 hours) leading to rapid elimination from the body ultimately not only exhibiting poor bio-distribution and insufficient cellular uptake but also enhancing the frequency of administration to achieve therapeutic response. Modifying the drug release will certainly provide the improved therapeutic efficacy and bioavailability with reduced dosing frequency.

However the basic objective of a modified release drug delivery system is to optimize the delivery of medication to avoid the uncertain fluctuations in the in-vivo environment where drug release takes place. In order to fulfill the need of a long-term treatment with anti HIV agent, it is pertinent to develop controlled or sustained-release drug delivery systems to improve the overall therapeutic benefits. Development of tailored release system of stavudine will maintain measurable plasma concentrations for extended period and can provide the suppressed viral load to undetectable levels with the reduced viral resistance.

In current research scenario there are various means of development of long-acting parenteral formulation like liposomes, emulsions, suspensions etc, but each suffers
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from a drawback of difficulty in achieving long duration of action and tailoring of release profile of drug according to patient convenience. Among various controlled release parenteral dosage forms biodegradable polymeric microspheres play a key role in treating the untreatable. The long acting parenteral microspheres is one such system, which alleviates all such problems associated with above mentioned systems and controls the drug release over a predetermined time span usually in order of days to weeks to months.

Although there are a variety of cells that become infected by HIV; including cells of the mononuclear phagocyte system (MPS), principally blood monocytes and macrophages. They act as reservoirs for the HIV virus and subsequently are responsible for distribution of the virus throughout the organism into various tissues. The eradication of HIV is highly unlikely as the cells of the mononuclear phagocyte system (MPS) are the specific hosts for HIV which needs to be targeted even after extended blood plasma profile of d4T to maintain viral suppression and reduced disease progression. Several studies involving ARV loaded drug carriers for targeting to the macrophages have consequently emerged in the current era which seems to be the only tool to overcome the problem of inadequate drug concentration, lower residence time at the targeted site as well as the drug resistance. Passive targeting of drugs to the MPS by biodegradable polymeric microspheres might be one of the very appropriate drug carriers for achieving therapeutic drug concentration for extended period of time with minimized chances of drug resistance and cellular toxicity.

The major advantage of targeted delivery is the ability to lower the necessary dosage, which enables a reduction in side effects. These polymeric microspheres offer decisive advantage of being recognized taken up in larger amounts by the mononuclear phagocyte system (MPS) after administration and are deposited in certain organs (liver, lymphoid tissue, lungs and brain) that are rich in macrophages exhibiting the efficient drug targeting which often is not possible with free drug. These advanced drug carriers could easily be phagocytosed by Mo/Mac facilitating the uptake of antiviral drugs in optimum concentration and enabling a considerably improved AIDS therapy.

The microsphere system may provide better therapeutic benefits as compared to plain drug as they will be treated as foreign particles by the immune system of the body which will thereby stimulate the phagocytic cells undergoing phagocytosis and inducing host defense reactions. Upon particle phagocytosis, the mononuclear phagocytic system (MPS) increases the production of cytokines and reactive oxygen intermediates (ROI),
which are involved in host defense mechanism. Thus, in addition to targeted drug delivery for the HIV infecting the macrophages, the ingestion of microparticles may result in the activation of the same for longer duration and subsequently enhance the host defense functions of the immune system, which is the ultimate goal of the therapy.

The present study also investigates the feasibility of simultaneous therapy of extended and targeted administration of the d4T loaded biodegradable polymeric microspheres for potentially effective and prolonged therapeutic regimen. The foremore treatment will maintain the drug in blood plasma for extended period of time by releasing the drug slowly through the polymeric matrix whereas targeted microspheres will disinfect the macrophages from hidden HIV and scavenge them out from their host reservoirs; which has been the route cause for development of drug resistance.

The polymeric microspheres will be phagocytised and release the maximum amount of drug at the specific targeted site. The mentioned treatment regimen has shown the potential to be the most efficacious not only in eradication of HIV but also in maintenance of viral load to undetectable levels for prolonged duration. The combination therapy will also be suitable in minimizing the resistance against d4T, which has always been the root cause of inadequate treatment and incomplete eradication of HIV. The regimen will not only cover all the aspects of the treatment including stable blood plasma concentration of stavudine, targeted HIVs hosted by macrophages and decreased possibilities of drug resistance but also enhance the therapeutic efficacy and patient compliance with improved quality of life in patients with AIDS.

The present research was aimed at the formulation of biodegradable polymer based microspheres encapsulating d4T for parenteral delivery. The study started with the preformulation studies followed by various characterization and evaluation studies. Various biodegradable polymers including Polycaprolactone (PCL), PLGA 85/15, RESOMER® 505H, RESOMER® 504H, RESOMER® 502H, PLA and PLLA were used for the formulation development of the microspheres. After several trials of o/w, w/o/w solvent evaporation technique the process was best optimized with o/o solvent evaporation method due to the higher water solubility of the drug.

The effect of various formulation variables such as polymer type and concentration, surfactant concentration and drug to polymer ratio as well as vehicle volume ratio on the characteristics of microspheres was evaluated. It was concluded that the entrapment efficiency of the microspheres were polymer concentration dependent i.e.
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on using higher polymer proportion the percentage of entrapped drug was increased; however the mean particle size of the microspheres were also enhanced with increment in polymer concentration.

Prepared polymeric microspheres were characterized for different parameters. Percent yield ranged between 35-88% in various batches of microspheres. More than 90% of encapsulation efficiency was obtained by optimizing the method of microsphere preparation. Particle size distribution studies were done by Malvern mastersizer and were below 100 μ in all batches hence indicating good syringeability without any clogging. The phenomenon of enhancement in particle size distribution in microspheres of higher polymeric ratios was optimized through rationalizing the concentration of surfactant in the external phase of o/o emulsion system. It was inferred that smoother and spherical microspheres with excellent surface topography was obtained with 2% of surfactant concentration. Although the surface of microspheres of PLA and PLLA at lower drug/polymer ratios have shown a number of pits and pores with rough surface which became less prominent with increase in polymer concentration.

To study the drug distribution within the microspheres, drug polymer interaction, structural integrity and dispersion pattern of drug and the amount of residual organic solvent content, advanced characterization studies like confocal laser scanning microscopy, differential scanning calorimetry, X-ray diffraction studies and gas chromatography were used. The CLSM results have clearly revealed the uniform and thorough distribution of d4T within the microspheres. DSC studies revealed that there was no significant shift in glass transition temperature or melting point of polymers either in pure state or in microsphere form hence indicating absence of any drug polymer interactions and incompatibilities. DSC of drug loaded microspheres showed the absence of melting endotherm of the drug. All the DSC peaks were in accordance with literature reported values. The halo X-ray diffractograms and DSC results of drug loaded microspheres depicted that stavudine was completely embedded and molecularly dispersed in polymeric matrix of microspheres which helps to retard the delivery of the drug in a controlled manner for prolonged duration of time. Also, the amount of residual organic solvents like acetonitrile and dichloromethane were well within the acceptable pharmacopoeial limits indicating safe use of microspheres for parenteral administration.

Polymeric microspheres were evaluated through in-vitro, ex-vivo and in-vivo techniques. Release studies were done to study the release behavior of drug from University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh.
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Polymeric matrix of microspheres. Release profiles indicated lower burst effect of around 1-5% in case of microspheres of RESOMER® 505H, RESOMER® 504H and PLLA; whereas the microspheres of RESOMER® 502H and PLA have shown the significant burst effect in the range of 21-41%. Although even after the burst effect the microspheres of all the batches have exhibited an extended release for nearly 60 days. In case of RESOMER® 504H, only 40-50% of total amount of the encapsulated drug was released after 60 days.

Treatment of release profile data to various kinetic models have provided an insight that for a biodegradable system, the drug released from polymeric matrix is very complex, which mostly follows erosion-diffusion kinetics. Other than various governing factors the rate of erosion and hydrolysis of polymer chains majorly play a key role in development of capillary channels into the polymeric matrix to tailor-made the release in a controlled way for extended duration of time. The observations from the release kinetics studies have inferred that most of the batches of polymeric microspheres have shown a good fit to the Korsmeyer-Peppas equation which have indicated a combined effect of diffusion and erosion mechanisms for drug release; whereas the drug release mechanism was best explained through anomalous transport as the release exponent (n) of Korsmeyer-Peppas equation for most of the batches were found to be in between 0.5-1.0, except in the case of microspheres of RESOMER® 502H an PLA, whose release mechanism were best explained through quasi fickian transport, as the value of release exponent (n) for these batches were recorded as n < 0.5.

Storage stability studies were carried out for the biodegradable microspheres of polymers RESOMER® 505H, RESOMER® 504H, RESOMER® 502H, PLA and PLLA. The samples of microspheres were stored at 2-8°C and 25±2 °C for a period of 90 days. The changes with reference to increase in particle size were observed to be minor in case of 2-8°C, whereas in case of 25±2 °C, significant increment in particle size was observed over the scheduled time span of storage stability. This increase in size could be attributed to the fusion of the microparticles indicating the process of fusogenicity to be a temperature dependent phenomenon.

Scanning electron microscopy (SEM) has revealed the significant changes at 25±2 °C, with reference to number of pits and pores as well as surface topography of the microspheres. The phenomenon of aggregation was more commonly observed in case of all the polymeric microspheres at higher temperature in the second and third month of
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storage stability. However these microparticles maintained their shape and structural integrity.

Stability of d4T loaded biodegradable microspheres of various polymers in accordance to the chemical incompatibility and degradation were investigated and evaluated through DSC studies at 2-8°C as well as 25±2 °C for the storage stability schedule of three months. The DSC thermograms of d4T encapsulated microspheres of all the polymers have exhibited no significant difference in either glass transition temperature (T<sub>g</sub>) or melting point (T<sub>m</sub>) of the same. The polymeric microspheres entrapping stavudine have revealed its stability with reference to thermal as well as chemical degradation/incompatibilities for the duration of storage.

The observations attained through ex-vivo evaluation play a key role in determination of safety as well as therapeutic efficacy of the developed formulation for targeting hidden HIV form their reservoir sites. Cellular engulfment of the polymeric microspheres through macrophages has provided an understanding for not only targeting but also biodistribution of the same. The cellular internalization kinetics of the polymeric microparticles investigated through flowcytometry which has revealed the significant increment in granularity and cellular density of the macrophages engulfing the polymeric microspheres. The obtained FSC/SSC dot plots of untreated and treated macrophages have exhibited significant difference in side scattering counts (SSC) of the same. The observed phenomenon was found to be concentration dependent i.e. higher the amount of polymeric microspheres used higher will be the increase in side scattering counts, ultimately proving the tendency of cellular uptake towards higher end. The outcome of cellular uptake was also visible through optical microscopy. The engulfment studies itself generate a demand for the cytotoxicity studies or the cell viability studies in concurrent combination of hemolysis studies; as these are the criteria which need to be fulfilled before the microparticles are directed for the targeting the host reservoirs. It was observed that encapsulation of d4T into biodegradable polymeric microparticulate systems has not only decreased the cytotoxicity of the drug but also made the administration of the drug safer even at higher concentrations up to 5000 μM.

The hemolytic study of stavudine loaded microspheres has shown significant reduction in percentage hemolysis as compared to free d4T at all tested concentrations. This reduction in hemolytic toxicity might be due to encapsulation of d4T and its slow release from biodegradable polymeric microspheres providing lesser amount of free d4T.
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to cause hemolysis. Hemolysis study has inferred the suitability of stavudine loaded polymeric microspheres for administration through parenteral route.

Histopathological studies were also performed to rule out any possibility of tissue level toxicity as the biodegradable polymeric microspheres were used as parenteral depot system for sustaining the d4T for extended period of time. Administration of biodegradable polymeric microspheres parenterally will not only help to avoid the plasma level fluctuation of stavudine but also enhance the therapeutic benefits in maintaining the viral load to undetectable levels. The results of the histological showed that the polymeric microspheres were well tolerated by the surrounding subcutaneous tissue. Hence these microspheres can be used for the extended period of time for enhanced therapeutic benefits.

Pharmacokinetic evaluation of stavudine loaded microspheres of RESOMER® 505H, PLA and PLLA were carried out in female SD rats. The in vivo pharmacokinetic studies after subcutaneous injection of d4T loaded microspheres showed a sustained plasma concentration time profile of stavudine for one month as compared to free drug in which plasma levels were observed up to 4.0 hrs only. The free d4T was absorbed quickly and maximum concentration in blood plasma (C_max) was found to be 35.931 µM/ml in just 1.125 hr after injection (T_max), afterwards rapid decline in plasma concentration was observed and reached nearly to zero within 4.0 hrs which indicate the faster elimination of free drug from blood. However the microspheres of RESOMER® 505H, PLA and PLLA have revealed the extended release of drug with a peak drug concentration (C_max) of 32.341 µM/ml, 31.506 µM/ml and 28.796 µM/ml with the corresponding time to attain the same (T_max) of 8.0 hr for each polymer. Significant difference (p < 0.05) was observed in AUC_total of control group of animals (62.270 µM h/ml) and various treatment groups of d4T loaded polymeric microspheres of RESOMER® 505H, PLA and PLLA, which was found to be 3341.656 µM h/ml, 2700.218 µM h/ml and 2302.552 µM h/ml respectively.

From the stated discussions it has been investigated that targeting the drug in the form of modified release microspheres will not only destroy the HIV hosted by macrophages but also extend the therapeutic efficacy by preventing the stavudine to be eliminated from the systemic circulation due to shorter elimination half life. The microspheres through maintaining the therapeutic blood plasma concentration of d4T will reduce the viral load to undetectable levels to prevent the patients from developing resistance against the drug, which will be proved as milestone of the therapy. These
polymeric microspheres have not only enhanced effectiveness of the treatment but also provided an edge in accordance to safety profile of d4T at higher concentrations for better patient compliance.

The mentioned treatment regimen will have the potential to be the efficacious not only in terms of eradication of HIV but also in maintenance of viral load to undetectable levels for prolonged duration. The simultaneous extended and targeted therapy will certainly be suitable in minimizing the drug resistance against d4T, which has always been identified as the key factor for incomplete eradication of HIV leading to inefficient therapy.

All the stated studies and results have led to the following conclusions:

✓ Stavudine could be effectively encapsulated within biodegradable polymeric microspheres using suitable technique.

✓ Optimized formulation of microspheres using various biodegradable polymers could be successfully made using o/o solvent evaporation technique.

✓ The prepared polymeric microspheres were well characterized in terms of percent yield, percent encapsulation efficiency, Fourier transform infrared spectroscopy and particle size distribution.

✓ Scanning electron microscopy has revealed the detailed description of shape, size and surface topography.

✓ The optimized microspheres have shown no incompatibilities or chemical degradation not only during formation but also throughout the time of stability studies.

✓ An acceptable amount of residual solvent content was obtained within the biodegradable microparticles of all the polymers indicating the safe use for parenteral administration.

✓ The halo pattern of the X-ray diffractograms of drug loaded microspheres of various used biodegradable polymers suggested that stavudine was completely embedded and molecularly dispersed within the microsphere matrix.

✓ Advanced characterization technique of CLSM has revealed the throughout and uniform distribution of rhodamine/coumarine labeled stavudine entrapped inside the microsphere shells of different polymers.
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✓ The in-vitro release profile of stavudine from the polymeric microspheres of RESOMER® 502H and PLA have shown an initial burst release followed by slower release pattern; whereas the microparticles of RESOMER® 505H, RESOMER® 504H and PLLA have maintained a tailored release for extended period of time without an initial release.

✓ The storage stability studies of the biodegradable microspheres have shown the intactness and integrity without any chemical/thermal degradation or incompatibilities throughout the time frame; inferring the stable microsphere system.

✓ The ex-vivo evaluation including cellular uptake studies through flowcytometry have exhibited the potential of polymeric microspheres to be used as targeted carriers to seavenge the hidden HIV inside the host reservoirs.

✓ The developed polymeric particles encapsulating d4T exhibited nearly 100 % cell viability during cytotoxicity studies in comparison to pure d4T.

✓ Histological studies have revealed the in-vivo biocompatibility and hemolysis studies have certified the liability of formulation to be used parenterally exhibiting no significant hemolytic toxicity.

✓ The in-vivo pharmacokinetics have shown the extended drug release from microsphere matrix up to a month exhibiting the stable d4T concentration in blood, avoiding fluctuation of the same which will decrease the probabilities of development of resistance against the treatment.

✓ The study successfully demonstrated the feasibility of prolonged delivery of stavudine using various biodegradable polymeric microspheres to overcome the challenges faced during the therapy including patient compliance, reduced possibilities of drug resistance and reduced dosing frequency leading to minimized side effects with enhanced therapeutic efficacy, which was the ultimate goal of the therapy.

✓ Presenting the drug in the form of parenteral depot formulation and targeted systems will provide an edge in the treatment of HIV disease in case of neonatal infections from HIV positive mother, unconscious patients unable to take oral medications and 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.
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- Combination of targeted and subcutaneous administration of d4T will not only provide the stable and extended release of drug but also eradicate the hidden HIV hosted by the macrophages.
- The concomitant regimen will potentially enhance the therapeutic efficacy with patient compliance, renewing new hopes for better management and improved quality of life of AIDS patients.

Further studies providing the consolidated data in accordance to cost effectiveness, clinical applicability and efficacy may provide a platform for Industrial applicability as well as scale up processes.

6.2 Unit/Multiparticulate systems

Among the various sections of the drug delivery, the field of oral controlled release drug delivery system is constantly evolving and developing. It is most preferred and patient compliant way of drug administration. In the current research environment controlled release systems are unavoidable tools for the exploitation of the concept of therapeutic treatment with enhanced drug efficacy, patient compliance and minimal side effects. Owing to the cost effectiveness, ease of manufacturing, uniform release profiles with a high resistance to drug dumping as compared to coated systems, matrix systems have gained even more importance in the field of controlled drug delivery.

Present research investigates the formulation of modified release dosage forms including unit as well as multiparticulate drug delivery systems. Matrix tablet is the most conventional, simplest and cost-effective method of fabricating a modified release dosage form. Development and evaluation of a typical matrix formulation consisting drug with one or more polymers, excipients such as fillers, a glidant and a lubricant was investigated. In comparison to unit dosage forms pelletized systems offer benefits of homogeneous distribution and better absorption throughout the GIT, increased residence time with lesser susceptibility to dose dumping. The processing of development of controlled release beadlets was started from development of pellets through extrusion-spheronization technique, followed by functional coating of suitable polymer using suitable process variables for controlling the release of stavudine for prolonged duration of time.
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Not only to utilize the numerous therapeutic benefits as but also for added advantages of unit/multiparticulate dosage forms, like cost effectiveness, ease of manufacturing with potential industrial, the hydrophilic matrix tablets and pellets were also formulated. Various grades of carbopol and polyethylene oxide (PEO) were employed 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.

Different polymers viz. Carbopol 971P, Carbopol 71G NF and Poly-ethylene oxide (PEO) were utilized to formulate matrix tablets for sustained delivery of stavudine. Initially tablet batches were prepared using two different fillers MCC (ST1) and DCP (ST2). Tablets of MCC (ST1) released 92.32 ± 4.29% of drug within one hour of dissolution study whereas the tablets containing DCP tablets (ST2) have released only 40.42 ± 1.18% of drug after the completion of dissolution study of one hour. Thus MCC was used as the filler in all the other batches for development of matrix tablets.

Polymer carbopol 971P was used with varying proportions from 20% to 60% as matrix former for controlled delivery of stavudine. Retardation in release was clearly evident in carbopol based matrix tablets as compared to pure MCC tablets. Batch CP 3 with the highest polymer concentration released 56.89 ± 3.40% drug at 6.0 hours whereas 78.00 ± 2.53% of drug in a controlled manner after 12.0 hours. Comparing the release patterns of all the batches, CP 3 was found to be the most suitable composition to control the release of stavudine for extended period of time.

Carbopol 71G NF was also utilized as hydrophilic matrix system in a concentration range of 20% to 60%. The retardation in release of d4T was observed on increment of polymer into the matrix system which might be due to the formation of gelatinous layer upon hydration of the surface of the tablet. Batch CG 3 with the maximum polymeric concentration significantly reduced the drug release up to 38.20 ± 4.99% after four hours of dissolution. However it has released 58.40 ± 3.46% as well as 72.74 ± 2.06% of stavudine from the polymeric matrix in a controlled manner after 8.0 and 12.0 hours of dissolution respectively.

Polyethylene oxide (PEO) was used as another hydrophilic matrix former for sustained delivery of stavudine over a period of 24 hours. Batches PEO 5, PEO 10 and PEO 20 have utilized the polymeric content of 5%, 10% and 20% (w/w) respectively.
Batch PEO 20 have not only retarded the drug release to 22.56 ± 2.68% after one hour but also prominently controlled the release to 43.45 ± 2.47% after four hours of the dissolution study, however 88.77 ± 3.62% of drug was released after twelve hours of the dissolution. Matrix tablets of batch PEO 20 have sustained the drug release with greater efficiency and exhibited good controlled release characteristics.

Comparing the drug release profile of batches CP 3, CG 3 and PEO 20, it was evident that although carbopol 971P and carbopol 71G NF have controlled the drug release till extended duration of time but the proportion of the polymeric content has reached upto 60%, whereas batch PEO 20 provided the controlled release of stavudine for similar duration of time by the use of 20% polymer proportion, however the matrix of the batch PEO 20 got completely dissolved during the dissolution studies.

Multiparticulate systems were formulated for stavudine owing to their high degree of flexibility in the design and development of oral dosage forms, homogeneous distribution throughout the gastrointestinal tract, 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. In the present study the pellets of stavudine were prepared using drug and MCC with water as granulating fluid through extrusion-spheronization technique by controlling the extruder speed, spheronization speed and time spend for spheronization as these process variables responsible for the variability in size, shape and various other properties. The prepared pellets were coated to different coating levels by GLATT particle coater using fluidized bed coating technology to control the drug release for extended period of time.

Batch SPP which was uncoated MCC pellets have shown the least mean particle size of 722.35 μm, whereas the batches SP 10, SP 20, SP 30 and SP 40; having the 10, 20, 30 and 40% of polymer coat have exhibited the mean particle size of 773.9 μm, 957.65 μm, 1100.52 μm and 1274.46 μm respectively which has been rationally increased on increasing the coating levels.

The shape analysis of pellets was done by optical microscopy and image analysis. Various shape factors viz. elongation, rectang and roundness were calculated by measuring the diameter of pellets in different directions. For all the batches of pellets the elongation factor ranged from 1.085 ± 0.019 to 1.143 ± 0.075 and in case of roundness values ranged from 0.891 ± 0.047 to 0.928 ± 0.015 which suggests that overall the pellets
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The bulk and tapped densities of various batches of stavudine pellets along with their Carr’s indices and Hausner’s ratios were calculated. The bulk densities of the batches SPP, SP 10, SP 20, SP 30 and SP 40 were found to be 0.732 ± 0.006 g/cm³, 0.739 ± 0.006 g/cm³, 0.765 ± 0.007 g/cm³, 0.777 ± 0.007 g/cm³ and 0.824 ± 0.008 g/cm³. It was observed that on increasing the coating levels the bulk density of the pellets increased. Similar kind of interpretations was observed with tapped densities of the various pellet batches.

The Hausner ratio for various batches lies between 1.025 and 1.071. Similarly, the Carr’s index for most of the batches was more than 5. According to the Hausner’s ratio and Carr’s index, all the batches have excellent flow properties. The value of angle of repose was varied between 13.781 ± 1.095 to 21.420 ± 0.629 for the different batches of stavudine pellets. All the reported values were below 30° indicating excellent flow of the pellets. The values of flow rate ranged from 1.353 ± 0.021 to 2.810 ± 0.036, indicating the excellent flow of pellets. No significant effect of various coating levels was observed on flow rates of various batches of pellets.

The dissolution studies were carried out to evaluate the effect of functional coating of ethyl cellulose on retardation of drug release. The uncoated pellets of MCC (SPP) have exhibited 82.56 ± 3.15% of drug release in initial one hour and more than 90% drug was released within six hours of the dissolution study. Various batches of pellets were coated with ethyl cellulose using isopropyl alcohol and water (9:1) as solvent over the fluidized bed coater. The batch SP 10 (10% w/w coat weight) resulted in retarded release in initial one hour with 65.12 ± 1.63% drug release, although 80.99 ± 2.38% d4T was released within four hours of the dissolution study. Hence this coating level was not sufficient to retard the drug release from the pellets. Gradual increment in coating levels in batches SP 20 (20% w/w) and SP 30 (30% w/w) have exhibited the controlled behaviour of drug release from the matrix pellets; even then 70.40 ± 3.36% and 60.18 ± 2.54% of drug was released after four hours of the dissolution study from the respective batches of coated pellets.

It was observed that 30% w/w of coating over the plain pellets retarded the drug release in initial hours but not to a significant extent. To retard the drug release in order to get the drug release for an extended period, the coating level was further enhanced up to
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40% w/w (SP 40). Batch SP 40 was not only able to control the drug release in initial one hour to 11.09 ± 2.68% but also retarded the drug release to 39.08 ± 3.41% after four hours of the in-vitro dissolution testing. However 54.39 ± 3.01% drug was released within six hours of the dissolution study. More than seventy percent (76.67 ± 4.23%) of the drug was released after eight hours of the study, whereas 99.05 ± 2.57% of the drug was released after 24 hours of dissolution from the coated matrix pellets of SP 40. The release profiles depicted that release of d4T decreased with increase in coating thickness.

Hydrophilic matrix tablets as well as pellets were successfully formulated for extended release of the drug which will provide the numerous benefits and advantages of unit/multiparticulate dosage forms, like cost effectiveness, ease of manufacturing, patient acceptability, packaging and great industrial potential with enhanced therapeutic benefits.