CHAPTER - 5

SUMMARY

Pulmonary drug delivery was selected for study due to fast onset of action, fewer gastrointestinal problems, lesser side effects and requirement of low dose of drug. The nanoparticles were selected as drug delivery system to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site specific action of the drug.

The present work was designed with an objective to formulate pharmaceutical dosage form of aerosol containing polymeric nanoparticles incorporated with drug for pulmonary application with increased bioavailability and patient compliance. The study was performed to target lungs locally to treat various lung diseases such as asthma, chronic obstructive pulmonary diseases, emphysema, cystic fibrosis and tuberculosis etc.

The melting point of terbutaline sulfate was found to be close to reported melting at 248°C. Solubility of terbutaline sulfate found out to be excellent in water and poor solubility in methanol and ethanol. The scanning of Terbutaline Sulfate in Phosphate Buffer Saline pH – 7.4 showed λ_max at 276 nm. Calibration curve of Terbutaline Sulfate prepared using 10, 20, 40, 60, 80, and 100 µg/ml concentration of Terbutaline Sulfate in Phosphate buffer saline pH-7.4 at λ_max of 276 nm was found to be straight line with regression co-efficient of r²=0.9998. The drug excipient compatibility study of terbutaline sulfate by FTIR found to be compatible with excipients (such as gelatin, PLGA, PVA and Bovine serum albumin) because FTIR peaks of Terbutaline Sulfate with excipients showed negligible change when compared with the FTIR peaks of Terbutaline Sulfate alone.

Gelatin nanoparticles were prepared by double desolvation method. PLGA nanoparticles were prepared by nanoprecipitation method. Albumin nanoparticles were prepared by desolvation method.

The particle size of gelatin nanoparticle formulations (GNps1, GNps2, GNps3 and GNps4) were found to be in range of 179.9 nm – 1545 nm. The particle size of PLGA nanoparticle formulations (PLGANps1, PLGANps2, PLGANps3, PLGANps4 and
PLGANps5) were found to be in range of 204.8 nm - 370.5 nm. The particle size of albumin nanoparticle formulations (ANps1, ANps2, ANps3, ANps4 and ANps5) were found to be in range of 81.6 nm - 148.4 nm.

The entrapment efficiency of Gelatin nanoparticle formulations were found to be in range 46.16% - 58.60%. The entrapment efficiency of PLGA nanoparticle formulations were found to be in range of 60.08% - 70.62%. The entrapment efficiency of albumin nanoparticle formulations were found to be in range of 61.74% - 73.45%.

The Zeta potential of gelatin nanoparticle formulations were found to be in range of 3.81 – 14.2. The Zeta potential of PLGA nanoparticle formulations were found to be in range of - 4.04 - 1.44. The Zeta potential of albumin nanoparticle formulations were found to be in range of (- 31.03) – (- 4.64). The Zeta potential found to be good which indicated the stability of the prepared gelatin nanoparticle formulations, PLGA nanoparticle formulations and albumin nanoparticle formulations.

The Transmission Electron Microscopy (TEM) of the selected gelatin nanoparticle formulation (GNps3), PLGA nanoparticle formulation (PLGANps4) and albumin nanoparticle formulation (ANps5) exhibited the spherical shape of the gelatin nanoparticles, PLGA nanoparticles and albumin nanoparticles, respectively.

In vitro release of all gelatin nanoparticle formulations, PLGA nanoparticle formulations and albumin nanoparticle formulations showed a biphasic pattern of drug release in which there was an initial burst phase, followed by a sustained release.

The release kinetics of gelatin nanoparticle formulations, PLGA nanoparticle formulations and albumin nanoparticle formulations were found to fit well in the Higuchi Model release kinetics due to higher regression co-efficient values ($r^2$ values) of Higuchi model as compared to the regression co-efficient values of zero order, First order and Korsmeyer Peppas model. This predicted that a water soluble drug (Terbutaline Sulfate) incorporated in the swellable matrix was mainly released by diffusional mechanism. The release exponent (n) of Korsmeyer Peppas model for gelatin nanoparticle formulations, PLGA nanoparticle formulations and albumin nanoparticle formulations were found to be
Chapter 5

Summary

in the range of 0.510 - 0.586, 0.523 - 0.631 and 0.463 - 0.542, respectively. This exhibited Non-Fickian transport of Terbutaline sulfate from nanoparticle matrix.

The gelatin nanoparticle formulation (GNps3), PLGA nanoparticle formulation (PLGANps4) and albumin nanoparticle formulation (ANps5) were aerosolized using 1,1,1,2-tetrafluoroethane (HFA 134a) as propellant into meter dose inhaler. The aerosol of gelatin nanoparticle formulation GNps3, PLGA nanoparticle formulation (PLGANps4) and albumin nanoparticle formulation (ANps5) were tested for flammability, density, moisture, aerosol valve discharge rate and spray pattern. The aerosol of gelatin nanoparticle, PLGA nanoparticle formulation (PLGANps4) and albumin nanoparticle formulation (ANps5) indicated the presence of propellant by IR analysis. The aerosolized gelatin nanoparticle formulation(GNps3), PLGA nanoparticle formulation (PLGANps4) and albumin nanoparticle formulation (ANps5) were found to be stable in meter dose inhaler when tested for stability at room temperature and at 45ºC/75% RH for 30 days as they indicated negligible change in flammability, density, moisture, aerosol valve discharge rate and spray pattern.

In vivo study using rat model by direct intratracheal administration of free terbutaline solution shown that the free terbutaline sulfate solution when administered intratracheally in the rats then blood samples of rat showed the presence of terbutaline sulfate in the plasma of rat. When gelatin nanoparticle formulation (GNps3) administered intratracheally then the blood samples of rat shown that there was insignificant amount of presence of terbutaline sulfate in the blood samples of rat at different time intervals. This indicated that there was insignificant amount of terbutaline sulfate migration from lungs of the rat to the blood of rat. This confirmed that the terbutaline sulfate remain localized in the lungs after release from the gelatin nanoparticle formulation.

When PLGA nanoparticle formulation (PLGANps4) administered intratracheally then the blood samples of rat shown that there was insignificant amount of presence of terbutaline sulfate in the blood samples of rat at different time intervals. This indicated that there was insignificant amount of terbutaline sulfate migration from lungs of the rat to the blood of rat. This confirmed that the terbutaline sulfate remain localized in the lungs after release from the PLGA nanoparticle formulation.
When albumin nanoparticle formulation (ANps5) administered intratracheally then the blood samples of rat shown that there was insignificant amount of presence of terbutaline sulfate in the blood samples of rat at different time intervals. This indicated that there was insignificant amount of terbutaline sulfate migration from lungs of the rat to the blood of rat. This confirmed that the terbutaline sulfate remain localized in the lungs after release from the albumin nanoparticle formulation.

Stability Study of gelatin nanoparticles formulations (GNps3), PLGA nanoparticles formulations (PLGANps4), albumin nanoparticles formulations (ANps5) at Refrigerated Condition (5º±3ºC), Room temperature (25º±2ºC/65%±5% RH) and Accelerated Condition (40º±2ºC/75%±5% RH) for 180 days (i.e 6 months) shown negligible change in particle size, entrapment efficiency and In-vitro drug release. This confirmed that the gelatin nanoparticle formulations (GNps3), PLGA nanoparticles formulations (PLGANps4), albumin nanoparticles formulations (ANps5) was stable when tested according to ICH guidelines.