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Poly (lactide-co-glycolide) microspheres of levonorgestrel for parenteral contraception

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Novel drug delivery technologies have now gradually evolved to allow the formulation of new dosage forms. Over the years, the implantable devices and microparticulate systems have undoubtedly improved the performance of the drugs. Generally referred to as a "miniaturised system", this second generation particulate carrier system holds promise for the delivery of new chemical moieties. The primary objective was to design a levonorgestrel containing microsphere system intended for long-term contraception in an endeavour to improve quality care in family planning. Biodegradable polymers have been the first line of choice for delivery of drugs by the parenteral route (Burger et al 1985; Arshady 1991). Levonorgestrel loaded parenteral-grade microspheres were formulated by an interrupted o/w emulsification- solvent evaporation technique (Benita et al 1984). While poly(lactide-co-glycolide) was employed as the encapsulating agent, methyl cellulose and polyvinyl alcohol were used as the emulsifiers. The method optimisation involved drug-polymer ratio (1:5, 2:5, 3:5, 4:5 and 1:1), emulsifier concentration, ratio of dispersed to continuous phase, speed of agitation, mode of solvent removal and evaporation time period.

The microparticles were characterized for process yields, particle size, sphericity, moisture content (karl fischer), drug encapsulation efficiency and syringeability-injectability studies. Sedimentation-resuspendability study was carried out to select a suitable suspending vehicle for the formulation. In-vitro release kinetics of the drug loaded batches was performed using a shaker water-bath maintained at 37 ± 0.5°C. To examine the surface texture of the microparticles, surface topographical studies viz. scanning electron microscopy was done. Solid state stability studies were conducted by subjecting pure and microparticulate system to various doses of gamma radiation (0.5, 1, 1.5, 2 and 2.5 M.Rad.). The batches exposed to gamma radiation were tested for sterility as per the standard pharmacopoeial method.

Pyrogen testing was performed on the final product. Residual solvent in the final product was determined by head space gas chromatography. Drug-excipient compatibility studies comprised of differential scanning calorimetry, infra-red spectroscopy and x-ray diffractometry. High performance liquid chromatography and high performance thin layer chromatography methods were employed for the estimation of levonorgestrel.

Formulation variables as well as process parameters played a vital role in the drug loading. An optimised polymer to drug ratio gave improved drug payloads of 84-86% without free drug crystallisation. The method gives a good process yield of more than 85%. The microparticles displayed excellent sphericity (99-100%) and had desirable flow properties with good aspiration qualities. At low speeds of agitation, clumping and aggregation behaviour was observed. The drug is stable to gamma radiation at all the experimental doses studied. The residual methylene chloride content was observed to be well below the acceptable pharmacopoeial limit. The differential scanning calorimetry thermograms and infra red spectra do not reveal any degradation of the drug and suggests good drug-polymer compatibility. Scanning electron photomicrographs unveils a smooth surface texture of the microspheres without any folding or invagination; free from structural defects. The drug release follows zero-order kinetics for a period of one month.

The two-step solvent evaporation microencapsulation procedure eliminates the formation of free drug crystals in the aqueous phase or on the microparticle surface.

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