ABSTRACT

Research work concerns with synthesis, characterization of biodegradable polymers and its evaluation in particulate drug delivery systems. The work is presented in three chapters and a brief outline of each is given below.

Chapter I: Synthesis and characterization of biodegradable polymers

Poly P-hydroxy acid's synthesized previously are highly crystalline and water insoluble. So, their application regions are limited. On the other hand, the polydepsipeptides, alternating copolymers of α-amino acids and α-hydroxy acids, are also known to be biodegradable polymers [1,2]. These polymers are expected to serve as useful drug delivery system (DDS) because they strongly interact with biocells to demonstrate high metabolism [3]. The copolymerization technique permits the synthesis of an unlimited range of polymers. It is widely used to obtain a better balance of properties for the commercial applications of polymeric materials. The objective of this work was to design and evaluate new poly[Llactic acid-(glycolic acid-leucine)] copolymers (PLDL) for the development of particulate drug delivery systems.

The PLDLs were synthesized by ring opening polymerization. Various parameters in polymerization reaction were studied to achieve a polymer of suitable mechanical strength such as effect of monomer feed ratio, initiator concentration, polymerization time and polymerization temperature. The optimized copolymer was characterized by FTIR, NMR spectroscopy, molecular weight determination by GPC, glass transition temperature by DSC, and crystallinty by XRD studies. The weight average molecular weight of the polymers was in range of 3500-7500 Da. The glass transition temperature of the optimized copolymer (Tg) was 36.27^0C and melt temperature (Tm) was 159.62^0C. XRD studies showed that the optimized copolymer was semicrystalline. *In-vitro* PLDL particle degradation in pH 7.0 buffer and in presence of enzyme was studied by molecular weight loss by gel permeation chromatography, the polymer showed higher degradation in presence of enzyme. Evaluation of *in-vivo* biological reactivity tests for PLDL in albino mice as per USP26 NF 21 revealed that polymer was nontoxic and can be used for further investigation.

Chapter II: Development and evaluation of diclofenac sodium polymeric nanosuspension system

Most ocular diseases are treated with a topical application of drug solutions administered as eye-drops; however, they often require frequent instillation of highly concentrated solutions, due to the rapid pre-corneal loss from the eye. A significant effort towards new DDS for ophthalmic administration has then been seen over the last few decades; herein hydrogels, micro- and nanoparticles, liposomes and collagen shields have been investigated. Among them, nanoparticle technologies are at present catalyzing increasing efforts in many pharmaceutical areas and have shown to give efficient ocular DDS [4]. The objective of this work was development and evaluation of diclofenac sodium (DS) polymeric nanosuspension (NS) systems encapsulating optimized PLDL and commercial poly(lactide-co-glycolide) (PLGA) polymers for achieving higher corneal residence time.

NS were prepared by a emulsion and solvent evaporation technique. Various formulation and processing parameters like ultrasonication time, polymer concentration in organic phase, stabilizer concentration in aqueous phase, stirring rate and drug-to-polymer ratio were optimized to achieve nanosize polymeric nanoparticles with higher encapsulation efficiency. The optimized NS were characterized on the basis of physicochemical properties and drug release features. The nanoparticle system showed interesting size distribution suitable for ophthalmic application. *In vitro* dissolution tests showed a controlled release profile of DS from the nanoparticles. Stability for NS was studied at 5^0C or at 25^0C/60% RH, the preparations were found to be stable at selected storage conditions up to 6 months. To verify the absence of irritancy toward the ocular structures, blank NS were applied to rabbit eye and a modified Draize test was performed. Polymer nanoparticles appeared to be avoiding of any irritant effect on cornea, iris and conjunctiva up to 24 hrs after application, thus appearing to be a suitable inert carrier for ophthalmic drug delivery.

Chapter III: Development and evaluation of valdecoxib polymeric microparticle system

Rheumatoid Arthritis (RA) is a chronic systemic autoimmune disease characterized by progressive damage of the joint [5]. Inflammation that predominates the joints often exhibits a

tendency of remission in 90% of the patients. Rheumatologists have identified three forms of RA. In the first case the patient has mild, self-limiting disease that generally resolves within a period of one year. The second case involves patient in which there is mild progression of disease that responds to conventional treatments with near normal clinical examination. The third category is the one in which arthritis is more aggressive and difficult to control with drug treatment. There is radiological deterioration accompanied with functional decline. Thus, RA has significant long-term morbidity and is associated with early mortality. NSAIDs are most widely used in clinical practice world over because of their four-fold actions comprising analgesic, antipyretic, anti-inflammatory and antithrombotic effect. The therapeutic regimen often involves the daily administration of these agents. The objective of this work was to formulate Valdecoxib (a drug from the NSAID class) loaded polymeric microparticulate (MP) injectable system for the long-term delivery of the active agent using biodegradable polymer PLDL for avoiding the problems associated with daily dosing and to improve patient compliance.

Valdecoxib (VC) loaded PLDL MP's were prepared by o/w emulsion and solvent evaporation technique. Various process parameters involved in microparticle formulation were studied. The microparticles were characterized for process yield, particle size, moisture content and drug encapsulation efficiency. Drug-excipients interactions were examined by FTIR, XRD and DSC. Solid state stability to gamma radiation was conducted by subjecting the pure drug and the microparticulate system to various gamma radiation doses. FTIR and DSC revealed no interaction between VC, PLDL and excipients. VC and the developed MP were stable at 2.5 Mrad dose of gamma radiation. *In-vitro* release of the drug loaded MP's were investigated by the static method at a $37^0 \pm 0.5^0$C, the studies revealed that all MP formulations followed near zero order sustained release. Stability studied for VC loaded MPs showed that the preparations were stable at 5^0C and 25^0C/60%RH up to one year. Relative bioavailability for synthetic drug and VC-PLDL MPs was studied in New Zealand white rabbits. A single intramuscular dose of VC-loaded PLDL MPs resulted in sustained therapeutic drug levels in the plasma for 49 days. The bioavailability was increased several-fold as compared with unencapsulated drug. Therefore, injectable PLDL microparticles hold promise for increasing drug bioavailability and reducing dosing frequency for better management of rheumatoid arthritis.

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