CHAPTER I

INTRODUCTION

Poly (methyl methacrylate) (PMMA) has been invented more than half a century ago. The excellent biocompatibility of PMMA has been detected very early, so that many medical tools, which come into direct contact with blood, are made from PMMA. Due to the good dermal and mucosal tolerance, PMMA has opened up possibilities for usages in sprays and in ointment bases for protecting wounds in pharmaceutical purposes. The chemical structure of PMMA is composed of a continuous chain of carbon atoms as a backbone, which is additionally stabilized by methyl groups. The ester groups in its structure are very resistant to hydrolysis, since PMMA is non-biodegradable (Lehmann, 1997). For this reason, PMMA has not extensively been used in implantable controlled-release drug delivery system. The controlling action of drug release for a week or for a month has not been investigated.

It is well-recognized that inflammation around implant is a process of normal host defense mechanisms brought about by the results of surgical implantation, as well as, the presence of the implant material (Stinson, 1960; Menei et al., 1993; Uhrich et al., 1996; Ibim et al., 1998). In polymeric implant the inflammatory reaction depends on the extent of injury, size, shape and degradation rates of polymers, as well as the chemical, physical and mechanical properties of the implant materials (Little and Parkhouse, 1962; Homsy, 1970; Wood, Kaminski, and Oglesby, 1970; Turner, Laurence, and Autian, 1973; Ibim et al., 1998). Ibim et al. (1998) found that a zone of cellularity was observed in tissues adjacent to the implant when polymeric matrix began to erode and degradable products started to diffuse. The increase of cellular filtration in these tissues could be associated with faster polymer degradation rate because the tissues were probably exposed to higher concentrations of degradation products with faster degradation times. Due to non-biodegradable property, degradation products of PMMA cannot occur. Therefore, the possibility of inflammation taking place in the tissues around implant using PMMA as a release controlling agent may be trivial.

Eudragit® RS (ERS) and Eudragit® RL (ERL) are composed of ethyl acrylate (EA): methyl methacrylate (MMA): trimethylammonioethyl methacrylate chloride (TAMCl) at the ratio of 1:2:0.1 and 1:2:0.2, respectively. These two polymers are weakly cationic polymers, which are in methacrylate ester copolymer group, and are insoluble in pure water, dilute acids, buffer solutions, or digestive fluids over the entire physiological pH range. Thus implant using ERS or ERL as release controlling agents should be unalterable throughout the release study. Due to their good binding properties, ERS and ERL dry powders can be used in the formulation of matrix tablet in which drug is embedded in a spongy matrix of polymer. In such dosage form, direct compression is generally available technique (Lehmann, 1997). Therefore, matrix implant with 2.0 mm in diameter using ERS or ERL as release controlling agents can be produced by direct compression. This type of implant can be inserted into subcutaneous tissue by implantable applicator. The size of injury as a consequence of implantation is tiny.

The limitation of direct compression in production of implant with 2.0 mm in diameter is inability of using high compression force through punch and die in order to achieve favorable hardness. To prevent matrix disintegration in the dissolution medium of matrix tablet produced by direct compression with a low compression force, treatment with solvent vapor technique was invented by Carelli et al. (2000). The solvent vapor provides the welding of polymer particles resulting in the increase of hardness and the decrease of drug release. This technique was applied in development of matrix implant which released drug with slow release rate in this study.

Drug released from matrix system follows the square root of time kinetics, which is known elsewhere. The release rate of drug from this system is inversely proportional to the square root of time (Higuchi, 1961; Higuchi and Hiestand, 1963; Higuchi, Rowe, and Hiestand, 1963; Higuchi, 1963; Chien, 1982; Chien, Cabana, and Mares, 1982; González-Rodriguez et al., 1997; Costa and Lobo, 2001; Siepmann and Peppas, 2001), so that drug release rate of the initial phase is higher than that of the last phase. The ineffectiveness or unwanted toxic effects may happen from this type of drug release. This is a disadvantage of this dosage form. The primary goal of drug released from controlled drug delivery system is the zero-order or near zero-order release. Geomatrix® technology was designed to achieve a zero-order release rate of matrix tablet with soluble drugs (Conte, Maggi, and Colombo, 1993; Conte and Maggi, 1996; Conte and Maggi, 2000; Maggi, Bruni, and Conte, 2000; Abdul and Poddar, 2004). It is a multi-layer tablet with a matrix core containing the active ingredient and one or more barrier layers directly applied to the core during the tableting process. The barriers are able to delay the interaction of the core with the dissolution medium by reducing the surface available for drug release and by controlling the solvent penetration rate. Therefore, initial drug release can be reduced and drug release can be extended with quite constant rates. The release rate can be easily modulated by varying the formulations of the different barrier layers (Conte and Maggi, 2000). Implants, 2 mm in diameter, in this study have been designed based on Geomatrix® technology in order to achieve constant release rates for drugs with a narrow therapeutic index.

17β-estradiol (E_2) and norethindrone (NET) have widely been recognized in hormone replacement therapy. Continuous administration of E_2 combined with NET is generally used in controlling early menopausal symptoms. This combination administration can reduce the risk of endometrial hyperplasia (Anderson, Knoben, and Troutman, 2002). Implant dosage form is appropriate for continuous drug administration because it can decrease frequency of drug administration and enhance patient compliance. Furthermore, both E_2 and NET are low molecular weight drugs. The diffusion coefficients of these two drugs are high enough to promote drug diffusion through non-biodegradable polymer matrix such as ERS and ERL matrices (Hutchinson and Furr, 1990). Thus, E_2 and NET are employed as model drugs in development of implant using ERS or ERL as release controlling agents in this research.

In controlled-release drug delivery system, the goals of development are not only the zero-order release but also consistent release of drug from the devices.

The uniformity of drug dispersed or dissolved in polymeric matrix is an important factor to decrease variation of drug release. Miscibility of drug and polymer indicates the possibility to achieve the uniformity of drug in the polymer matrix (Greenhalgh et al., 1999). Thermal Analysis has been adopted to determine the miscibility of polymer blends. A single glass transition temperature (T_g) point is the most conventionally used as a criterion for the miscibility of a polymer blend. On the contrary, an immiscible polymer blend exhibits more than one T_g. In case of blends in which one or two components are semi-crystalline, melting point depression provides important information about its miscibility and its associated polymer-polymer interaction parameter (Kuo and Chang, 2001; Kuo, Huang, and Chang, 2001; Maldonado-Santoyo et al., 2004). Over the years, various equations have been offered to predict the variation of T_g of random copolymers or miscible blends as a function of composition, which can be well interpreted in terms of specific interaction within a polymer blend (Schneider, 1988). However, this technique has not widely been applied in determination of the miscibility of drug and polymer. To apply this method in drug-polymer system, solid state of drug dispersed or dissolved in polymer matrix is an important factor for selection of appropriate criteria in the determination. A single T_g point is suitable for blends composed of amorphous drug dissolved in polymer matrix. In any way, the depression of melting point is proper for blends composed of crystalline drug dispersed in polymeric matrix. If drug-polymer blends exhibit behavior as same as polymer blends, equations, which are ordinarily used in polymer blends, can be utilized in this system.

The present study was worked for these approaches;

(i) to apply ERS or ERL as release controlling agents in implantable controlled-release drug delivery system. This work indicated the possibility of utilizing these polymers in controlled-release dosage form requiring long-term action.

(ii) to apply Geomatrix® technology in development of subcutaneous implant. It is a challenge to fabricate a constant rate of drug released from subcutaneous implant, which is basically controlled by matrix diffusion. Thus, the effect of Geomatrix® components on drug-release profiles was investigated.

(iii) to examine solid state of drug embedded in polymeric matrix. It is a confronter to characterize solid state of drug, i.e. amorphous form or crystalline form, blended with amorphous material in binary mixture.

(iv) finally to apply the principle of determination and prediction of the miscibility of polymer blends to drug-polymer blends by thermal analysis. It is a question that the determination of the miscibility of blend components and equations originally used to predict the behavior of polymer blends are suitable for drug-polymer blends.