DEVELOPMENT AND EVALUATION OF A MATRIX CONTROLLED RELEASE IMPLANT SYSTEM FOR TESTOSTERONE

By

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Thesis submitted in fulfillment of the requirements of Master of Sciences

BY THE NAME OF ALLAH,
ALL-MERCIFUL, MOST BENEFICENT

TO THOSE WHO HAVE PROVIDED THE COUNTERPOINT: MY PARENTS, MUSTAFA HAMAD AND FATIMA HAMAD, AND TO ALL MY BROTHERS AND SISTERS

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ABSTRAK

Sistem implan yang dibuat daripada hidroksipropril metilselulosa (HPMC K100) dan kanji dengan nisbah 9:1 adalah licin serta mempunyai bentuk yang seragam dan kekerasan yang mencukupi. Kanji ditambah pada kepekatan yang rendah untuk memudahkan ekstrusi sistem implan. Sistem implan tersebut juga mempamerkan pelepasan testosteron secara terkawal, di mana pelepasan yang boleh dijangka ini boleh diubahsuai dengan mengubah nisbah drug kepada polimer.

Kesan HPMC dengan gred kelikatan yang berlainan dan penambahan agen aktif permukaan anionik ke atas profil pelepasan drug juga dinilai. HPMC dengan gred kelikatan yang tinggi dan penambahan natrium lauril sulfat (SLS) berkeupayaan untuk merencat pelepasan testosteron daripada sistem implan.

Dua formulasi sistem implan yang berlainan juga dinilai di dalam satu kajian in vivo dengan menggunakan 12 ekor tikus Sprague Dawley (SD) jantan. Kedua-dua sistem implan tersebut mengandungi 10 mg testosteron dengan nisbah drug kepada polimer 8:2 dan 4:6. Sepanjang jangkamasa kajian, pelepasan drug yang perlahan dan terkawal boleh diperhatikan. Sistem implan dengan nisbah drug kepada polimer 8:2 mempunyai kadar pelepasan drug lebih kurang dua kali lebih cepat daripada sistem implan dengan nisbah 4:6. Ini menunjukkan bahawa pelepasan drug mempunyai korelasi yang baik dengan kandungan polimer di dalam sistem implan dan keputusan ujian pelarutan in vitro. Tambahan pula, paras testosteron di dalam plasma sepanjang 24 jam boleh dikatakan seragam.

ABSTRACT

Implant systems fabricated using hydroxypropyl methylcellulose (HPMC K100) and starch at a ratio of 9: 1 were smooth and uniform in shape with adequate hardness. Starch was added in low concentrations to facilitate the extrusion of the implant system. The implant systems also displayed a controlled release of testosterone, which could be varied in a predictable manner by varying the drug to polymer ratio.

The effect of different viscosity grades of HPMC and the addition of anionic surfactant on the release profile of the implant systems were also evaluated. Higher viscosity grades of HPMC and the addition of sodium lauryl sulphate (SLS) were capable of further retarding the release of testosterone from the implant system.

Two formulations of the implant systems were further evaluated in an in-vivo study using twelve Sprague Dawley (SD) male rats. Both formulations contained 10 mg of testosterone with drug to polymer ratios of 8: 2 and 4: 6. A slow and sustained release of testosterone was observed after the implantation and during the entire study period. The rate of testosterone release from implant system with 8: 2 drug to polymer ratio was approximately two times higher than that with 4: 6 drug to polymer ratio; thus indicating that the release was highly correlated with the polymer content in the formulation as well as the in-vitro dissolution results. Moreover, plasma testosterone levels throughout the 24 hours were reasonably constant throughout the day period.

CHAPTER ONE

INTRODUCTION

1.1 CONTROLLED RELEASE DOSAGE FORMS

1.1.1 GENERAL PRINCIPLES

Conventional drug delivery systems are primary pharmaceutical products that are designed to provide a prompt release of drug, thus, giving a maximum rate and extent of absorption. However, multiple daily dosing is required and wide fluctuations in plasma levels are often observed with these products, thus making it undesirable with drugs for chronic diseases such as asthma and male hypogonadism as well as drugs with narrow therapeutic indices. In such instances, sustained release dosage forms or controlled release dosage forms appeared to be a more attractive mean for delivering drugs into the systemic circulation (Zaffaroni, 1980).

Sustained release dosage forms are drug delivery systems designed to retard the release of drug such that its appearance in the systemic circulation is delayed or prolonged and hence, the drug concentrations are maintained in the blood over an extended period of time.

Controlled release dosage forms, on the other hand, are formulated to release drug at a precise rate profile that is kinetically predictable and reproducible from one unit to another (Chien, 1992). The drug is ideally released at a zero-order rate to obtain a constant plasma concentration over prolonged periods of time (Hussain *et al.*, 1984).

Many attempts have been made to obtain a suitable controlled drug release system, which is capable of maintaining a sustained drug level in plasma or target tissue. One of the earliest orally extended release dosage forms was Spansule® capsule, which was introduced in 1945 by Smith, Kline and French Laboratories (SK&F). It was designed to release the therapeutic agent at rates independent of the gastrointestinal environment. In 1950, Saunder et al suggested that the extended release of ionizable drug could be obtained by binding it with an ion exchange resin. Swintosky in 1959 introduced the first liquid preparation of extended release dosage form for oral administration, while Ostholm and Sandell also patented a tablet containing plastic matrix (Javaid, 1996). One of the earliest attempts toward producing a controlled release dosage form was done by the German dermatologist, Unna in 1884, he found that the release of the drug from the tablets took place in the intestine and would not dissolve in gastric acid fluid (Helfand and Cowen, 1982; Mumtaz, 1993).

1.1.2 METHODS TO ACHIEVE CONTROLLED RELEASE OF DRUGS

There are a variety of methods to control the release of drug from a dosage form. The determining factors in selecting a particular technique include cost, the potency and the properties of the drug, the requirement for biodegradability of the polymers and most importantly, the release rate desired.

In general, controlled release of drug can be obtained through chemical and pharmaceutical means (Lordi, 1986). The former is based on modification of those physical and/or chemical properties of the drug that affect bioavailability. These include the use of complex formation, ion-exchange resins to form drug adsorbates, and prodrug synthesis. The mechanism of sustained drug release is through decreased rate of dissolution of the altered drug and/or dissociation of the free drug into solution. In the case of prodrugs, a slow regeneration of the parent compound after absorption may provide an additional strategy for prolonging the drug action. The resulting drug modifications can thus be formulated as liquid suspensions, capsules or tablets. However, these methods can only be applied to drug moieties containing the appropriate functional groups (Yuen, 1991).

The second set of methods is based on modification of the drug release characteristics of the dosage form. Although products based on dosage form modification are of many designs and constructions, the mechanisms underlying the sustained release are few (Lee and Robinson, 1978). Drugs that are slowly dissolving are inherently sustained, but those

with rapid dissolution rates can be retarded by various means such as embedding them in a non-soluble, slowly soluble or hydrophilic matrix system, which may be then encapsulated in particulate form or compressed into tablets. Drug that is trapped in the channels of the porous insoluble matrix is released *in-vivo* upon penetration of fluids from the gastrointestinal tract. The dissolved molecules then diffuse out from these channels out from the matrix. The release mechanism of such system has been well studied by Higuchi in 1963. On the other hand, the drug release from the slowly soluble matrix system occurs through a combination of factors, such as permeation of the matrix by dissolution medium and erosion of the matrix material.

On the other hand, hydrophilic matrix consists of materials that swell and form gels upon contact with water or gastrointestinal fluids. Drug release in such system is controlled by the leaching/diffusion of the active substances through the swollen hydrated matrix, in addition to the erosion of the gelled layer.

An important class of the hydrophilic matrix former is hydrogel. It is defined as a natural or synthetic polymer that is capable of swelling in water and retaining a considerable amount of water without dissolving in it (Breimer *et al.*, 1985). For example, hydroxypropyl methyl cellulose (HPMC) has a unique ability to form hydrogel and thus offers a reliable method of regulating the drug release. The release of the drug from the gel can also be modified by the use of surfactant (Saito, 1960), varying the amount of the polymer in the formulation (Xu and Sunada, 1995), as well as using different viscosity grades of the hydrogel (Lapidus and Lordi, 1968; Daly *et al.*, 1984).

One new method for controlling the drug release is through osmotic pump, which utilizes osmotic pressure to control the release of active agents (Eckenhoff *et al.*, 1981; Theeuwas *et al.*, 1980). More recently, the osmotic pumps are small enough to be made implantable. The built-up of the osmotic pressure in the pump is attributed to the diffusion of water across a semipermeable membrane and dissolving the salt inside. The resulting solution pushes the active agent from the device. The rate of drug release will remain constant as long as the excess active drug remains within the device. Since the system is based upon osmotic pressure, the drug is delivered at a rate that is essentially independent on environmental pH and stirring rate. Example for a commercial oral osmotic pumping drug delivery system is OROS® which is being marketed by ALZA Corporation U.S.A. (Godbillon *et al.*, 1985a).

1.1.3 ADVANTAGES OF CONTROLLED RELEASE

Controlled release delivery systems offer four principal advantages over conventional formulations that deliver the entire active drug over a short period of time. The first advantage is that it provides a more constant drug level in the systemic circulation, and thus maintaining the concentration of the drug between the minimum effective and toxic levels. Such control is inherently difficult with conventional formulations, which tend to overdose initially and the subsequent blood levels fall below the minimum therapeutic levels. Thus, controlled release systems are designed in which the rate of drug delivery into the systemic circulation follows its rate of removal (Theeuwes, 1983).

Controlled release drug delivery systems are also capable of prolonging the therapeutic level of drug in the blood beyond that achieved with conventional dosage forms. The frequency of drug administration could be reduced to either once or twice daily; resulting in significantly improved patient convenience and compliance. The medical profession widely recognizes that a once-daily dosage regimen leads to significantly better patient compliance than multiple daily dosing, with a consequent improvement in the efficacy of the treatment (Brooks *et al.*, 1980).

Another important benefit is the elimination of local gastrointestinal irritation and erosion arising from exposure of the gastric mucosa to high drug concentrations released from the conventional dosage forms. Additionally, the systemic side effects could also be circumvented due to the absence of supra-therapeutic blood levels (Cowsar, 1974; Baker *et al.*, 1979).

Moreover, in view of the constant rate of drug delivery, controlled release systems require a smaller amount of drug to produce therapeutic blood level for a given duration. This, in turn, will improve the usage economics especially for drugs that are expensive and difficult to extract or to obtain (Brooks *et al.*, 1980; Tinkelman *et al.*, 1980).

1.2 IMPLANTS

1.2.1 GENERAL PRINCIPLES

Until the early 1970's, drugs were delivered into the human body mainly via oral and intravenous routes. These modes of drug delivery, although still the most common, have various disadvantages (Gombotz and Pettie, 1995). Since then considerable effort has been devoted into developing new methods for drug delivery. Some of the most recent modes of drug delivery include transdermal drug delivery, pulmonary drug delivery and polymeric implants. These polymeric drug delivery is the most extensively studied area as evidenced by the number of papers dedicated to this area (Chaubal, 2001).

A polymeric implant is a polymeric matrix imbedded with drug and is surgically planted into the body subcutaneously. The drug is then released for absorption into the blood or the affected site via diffusion or surface erosion to obtain controlled, predictable and localized administration of drugs. The key advantages of polymeric implants are:

1. Localized delivery of drugs: the preparation can be implanted directly at the site where drug action is required and hence systemic exposure of the drug can be reduced. This is important especially for toxic drugs, which are associated to various systemic side effects.

2. Sustained delivery of drugs: Since the drug is released over extended periods, it eliminates the need for multiple injections. This feature can improve patient compliance especially with drugs for chronic indications that require frequent injections.

3. Stabilization of the drug: The polymer can protect the drug from the physiological environment and hence improve its stability *in vivo*. This particular feature makes this technology attractive for the delivery of labile drugs such as proteins. (Gombotz and Pettie, 1995; Langer, 1998).

4. Implants offer an alternative mode for delivering drug into the systemic circulation especially with drugs that undergo extensive first pass metabolism. A higher amount of drug is capable of reaching the systemic circulation as compared to oral dosage forms (Langer, 1998).

Various synthetic as well as natural polymers have been utilized to form the matrix for the implant. The polymers employed should possess suitable characteristics listed below:

1. The polymer material is biocompatible and biodegradable. The degradation occurs *in-vivo* to smaller fragments, which can then be eliminated from the body either through enzymes present in the body (biodegradable polymers) or other chemicals (bioabsorbable polymers). Surgical removal is required to remove those non-biodegredable implants after they are depleted of drugs and thus resulting in increased cost and risk of multiple surgeries

2. The degradation products of the polymer are nontoxic, non cytotoxic and do not cause an inflammatory response.

3. The degradation should occur within a reasonable period of time as required by the application (Swift, 1993).

Some of the widely used biodegradable polymers for the fabrication of implants (Bick, 1983) are listed below.

Synthetic polymers	**Natural polymers**
Poly lactic acid	Collagen (Proteins)
- Poly-L-lactic acid	Chitin, Chitosan
- Poly-D, L-lactic acid	Polysaccharides
Poly glycolic acid	Fibrin
Poly-e-caprolactone	Albumin
Poly-p-dioxanon	
Tri-methylen carbonate	
Poly anhydrides	
Poly ortho ester	
Poly urethanes	
Poly amino acids	
Poly hydroxy alcanoates	
Poly phosphazenes	
Poly-b-malein acid	

Collagen, cellulose and chitosan are the most commonly used natural polymers in the implantable drug delivery system (Tanger, 1986).

1.2.2 CONTROLLED RELEASE MECHANISMS INVOLVED IN IMPLANTABLE DRUG DELIVERY SYSTEMS

An ideal implantable drug delivery system exhibits a zero order drug release, in which the release of drug is independent of time. However, a constant rate of release is difficult to achieve in most cases. As the amount of drug in the delivery system is depleted, the rate of release is also reduced. Thus, most drug delivery devices often show two phases of drug release: a rapid initial phase (which may or may not be linear) and a slower second phase of drug release which relates to the rapid depletion of the drug from the device.

The mechanisms involved in controlling the release of drugs from the polymeric implants include either one or a combination of the followings:

a. Diffusion
b. Bioerosion
c. Osmosis

Of the three mechanisms, diffusion of the drug through the polymer matrix is the most common method involved in controlling the release of drug. The rate of diffusion is influenced by the size of the drug molecules, porosity of the polymer matrix (total void volume available), degree of crosslinking as well as the swelling characteristics of the polymer (Chaubal, 2001).

1. 3 DISSOLUTION OF SUSTAINED RELEASE DOSAGE FORMS

Drug dissolution is prerequisite to drug absorption and clinical response for almost all drugs. It is a process in which the drug is released and is available in solution ready to be absorbed. Various dissolution models have been developed over the years to simulate the conditions in-vivo and to predict the release of drug upon administration. The rate and extent of dissolution may influence the onset, rate, and extent of absorption, and hence could have a direct bearing on the pharmacological activity of a drug.

The earliest reference for dissolution testing was found in the article by Noyes and Whitney in 1897. At the middle of the 19^{th} century, the investigations were mainly focused on the dissolution behavior of a dosage form and its relation to the biological activity (Javaid, 1996). A wide variety of dissolution test systems have been described (Ridgway, 1975) and these have evolved into two distinct types: the stirred vessel and the flow- through column (Nelson and Miller, 1979). The stirred-vessel type is characterized by a relatively large volume of fluid with minimal liquid exchange (Langenbucher, 1977). Agitation is accomplished by stirring the liquid or by the motion of the vessel. Samplings at appropriate time intervals provide a direct measure of the rate and extent of release of the active ingredient. In contrast, the flow-through column method consists of a relatively small dissolution cell through which solvent flows through at a constant rate. No additional agitation is used.

The physiochemical characteristics of a sustained release dosage form can affect the rate of dissolution. These include wettability of a dosage unit, the penetration ability of the dissolution media, as well as the disintegration and degradation of the dosage form (Wagner, 1970). Certain dissolution process variables are also important and will affect the rate of dissolution (Smollen and Ball, 1984). An agitation rate capable of discriminating *in-vitro* conditions, which are important in-vivo, should be sought (Gupta and Robinson, 1992). The composition of the dissolution medium should preferably be aqueous in nature and capable of maintaining sink condition by keeping the concentration of dissolved drug in the bulk medium below 15% of saturation solubility (Swarbrick, 1970). A temperature of 37°C for the dissolution medium is favoured, being similar to our body temperature. In this regard, an allowance of ± 0.5°C is deemed acceptable by most compendia.

Although in-vitro technique offers a cheap and easy mean for evaluation during dosage form development, performing in-vivo studies on human or laboratory animals are necessary. The rate and extent of absorption of the dosage form can be determined by pharmacokinetic analysis. The in-vivo studies are necessary to ensure that satisfactory bioavailability is obtained without any dose-dumping.

1.4 TESTOSTERONE

1.4.1 GENERAL PHARMACOLOGY

Figure 1.1 shows the chemical structure of testosterone. Testosterone is the predominant sex hormone in males and is produced in the testes. In male, approximately 8 mg of testosterone is produced daily and about 95% is produced by the Leydig cells and the remaining 5% by the adrenal glands, adrenal cortex and adrenal medulla (Toft *et al.*, 1984).

1.4.1.1 PHARMACOLOGY

Testosterone is converted to dihydrotestosterone by the enzyme 5α-reductase in target tissues, such as the hypothalamus, and may be of importance in regulating gonadal function (Goldfien, 1995). Testosterone promotes growth of the genitalia and the development of male secondary sex characteristics. It is necessary for the maintenance of libido and potency. Moreover, its presence within the seminiferous tubules is required for spermatogenesis. Circulating testosterone, on the other hand, inhibits gonadotrophin production by the anterior pituitary, resulting in the suppression of spermatogenesis during testosterone therapy. Testosterone also possesses anabolic activity, such as developing and maintaining muscle mass. It also helps to prevent osteoporosis (Goldfien, 1995). Testosterone or its derivatives are transported to the target tissues, where testosterone enters the cell. Circulating testosterone is bound tightly to a serum glycoprotein of hepatic origin, called sex hormone binding globulin, and weaklt to albumin. Less than 1% to 2% of the circulating testosterone is thought to be unbound. Together the free and weakly bound testosterone can enter target tissues (Goldfien, 1995).

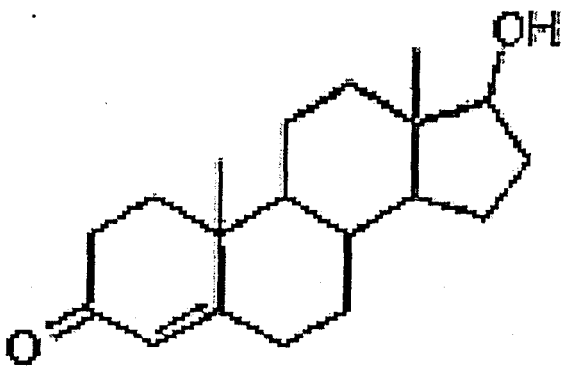

FIGURE 1.1 : CHEMICAL STRUCTURE OF TESTOSTERONE

1.4.1.2 PHARMACOKINETICS

Although testosterone is readily absorbed orally, considerable first-pass metabolism occurs in the liver where inactivation of testosterone occurs. Approximately 80% of the drug is metabolized, thus minimal amount of testosterone reaches the systemic circulation after oral administration (Gillies *et al.*, 1981; Lipsitt, 1983). Testosterone is normally administered as an oily intramuscular injection, which is released slowly to obtain a prolonged effect (Paton *et al.*, 1969). A half-life of 4.5 hours has been reported after administering testosterone orally, while a half-life of 11 days has been reported after intramuscular injection (Paton *et al.*, 1969).

1.4.1.3 PREPARATIONS

Oral. Oral preparations of testosterone and its synthetic analogues are minimally absorbed due to its extensive first pass metabolism. However, oral administration of fluoxymesterone 10-20 mg per day is suffice in the middle-aged or elderly patients to alleviate minor symptoms of testosterone deficiency and prevent osteoporosis.

Intramuscular. For testosterone replacement therapy, intramuscular preparations are the most effective. Dosage should provide about 10 mg per day; with testosterone propionate this is met by giving 25 mg three times weekly. With the longer acting esters, the dose is about 200 mg every 2 to 3 weeks.

Implants. Testosterone pellets 400-600 mg are inserted subcutaneously every 4-6 months into the anterior abdominal wall by means of a trocar and cannula under local anaesthesia. (Toft *et al.*, 1984).

Transdermal. A preparation of testosterone for transdermal use has been developed in which a testosterone-loaded film is applied each day to the scrotal skin. This preparation permits maintenance of plasma concentrations of testosterone within the normal male range (Toft *et al.*, 1984).

1.4.1.4 INDICATIONS

Testosterone is mainly used in the treatment of male hypogonadism, a clinical syndrome due to reduced testosterone secretion and may delay puberty in children. However, the administration of testosterone should be monitored closely, especially in children, since it can cause premature epiphyseal closure, resulting in stunting of growth and short stature. Thus, not more than half the adult replacement dose should be used for the first year. Moreover, if there is co-existing growth hormone deficiency, testosterone therapy should be withheld until an acceptable height is reached with human growth hormone therapy (Toft *et al.*, 1984).

Testosterone replacement therapy is also used to alleviate minor symptoms of testosterone deficiency (e.g. tiredness, lack of concentration and depression) and to prevent

osteoporosis. Large doses of testosterone have also been used in the treatment of refractory anemias, resulting in an increase in reticulocytosis and hemoglobin levels.

1.4.1.5 ADVERSE EFFECTS AND CONTRAINDICATIONS

The side effects observed with testosterone therapy are salt and water retention, hypertension, cholestatic jaundice (especially with methyltestosterone and fluoxymesterone) and premature closure of the epiphyses if given in early puberty.

Testosterone is contraindicated in the presence of prostatic carcinoma or breast carcinoma in men. It causes virilization in women and suppresses spermatogenesis in men. The use of testosterone is also contraindicated in pregnant women or women who may become pregnant during the course of the therapy. Care should be exercised in the administration of testosterone to patients with renal or cardiac disease who are predisposed to edema. If sodium and water retention occurs, it is responsive to diuretic therapy (Toft *et al.,* 1984).

1.4.2 EVOLUTION OF TESTOSTERONE REPLACEMENT THERAPY

Testosterone is administered through a wide variety of modalities over the six decades since its introduction into clinical usage (Hamilton, 1937). However, the clinical applications of testosterone are limited due to their negligible oral bioavailability and extremely short half-life when they are administered parenterally (Foss, 1939; Parkes, 1938). On the other hand, orally active synthetic testosterones, mostly based on the 17-α alkyl substituents, are required at high doses with multiple daily dosing, which is

unsatisfactory for life-long testosterone therapy. Nevertheless, they are now considered obsolete due to their hepatotoxicity. Thus, the main focus of research now is to develop effective depot formulations of testosterone (Handelsman *et al.*, 1997). In recent years, injections containing ester derivatives of testosterone in oily vehicle have been regarded as the standard testosterone replacement therapy (Nieschlag & Behre, 1990). However, this form of treatment requires deep, painful intramuscular injections (Mackey et al., 1995) at regular intervals of approximately 2 weeks (Snyder & Lawrence, 1980). Moreover, oily intramuscular injections of testosterone exhibits prominent fluctuations in the blood concentrations (Behre *et al.*, 1990), making this regimen far from ideal for life-long testosterone replacement therapy (Lisser *et al.*, 1942; Stuenkel *et al.*, 1991).

Subdermal implants, originally developed by Deansley and Parkes (1937 and 1938), were the first true depot formulations of testosterone and were rapidly accepted into clinical practice (Biskind *et al.*, 1941; Hamilton and Dorfman, 1939; Howard and Vest, 1939). The original testosterone pellets were formulated by high-pressure compression of testosterone mixed with cholesterol. However in the early 1950s, an alternative manufacturing method was developed in which the testosterone was melted and cast into a solid cylindrical shape on cooling without any excipients (Handelsman, 1990, 1991). Fused crystalline implants were available 4 decades ago but has since declined in popularity and by 1980, they had fallen largely into disuse (Handelsman *et al.*, 1997). However, over the last decades, subdermal implants have again saw an increase in popularity due to fewer side effects (Cantrill *et al.*, 1984; Conway *et al.*, 1988; Handelsman *et al.*, 1990; Jockenhovel *et al.*, 1988). Cantrill *et al.*, in 1984, showed that testosterone implantation generally remains as

the most acceptable form of androgen replacement therapy to both the patients and the doctors.

1.5 EXPERIMENTAL SCOPE OF THIS STUDY

The study was undertaken to develop a matrix controlled release formulation of an implantable system using testosterone as a model drug. Various polymers were evaluated as the matrix forming material.

The study was sectioned into various stages with the following objectives.

- To develop a matrix controlled release implantable system for testosterone.
- To evaluate various polymers as matrix forming material.
- To evaluate the in-vivo performance of the formulations using male Sprague-Dawley male rats.

CHAPTER TWO

PREPARATION OF TESTOSTERONE CONTROLLED RELEASE IMPLANT SYSTEMS AND IN-VITRO STUDIES

2.1: INTRODUCTION

One of the most commonly used methods for fabricating controlled release dosage forms is through incorporating the drug substance into a hydrophilic matrix system. Generally, modulation of the drug release is achieved through using different types of polymers (Beraja *et al.,* 1987), different viscosity grades of polymer (Nakano *et al.,* 1983) as well as soluble and insoluble fillers (Ford *et al.,* 1987; Rao *et al.,* 1990).

Hydrophilic matrix systems containing water-soluble polymers, such as hydroxypropyl methylcellulose (HPMC), were introduced in the early 1970s. The hydrophilic matrix system is the most simple sustained release technology, consisting essentially of a drug and water-soluble polymer with high viscosity. HPMC has been widely approved for use in controlled release systems (Hogan, 1989; Wichterle, 1960; Padley, 1980; Graham, 1984; Vazquez *et al,* 1992) as well as implants, transdermal drug delivery systems and oral-controlled release systems (Ford *et al.,* 1987). HPMC is inert, stable against microbial attack (Nakano *et al.,* 1983) and has good biocompatibility, thus, making it one of the most prominent carriers in drug delivery systems (Colombo, 1993).

HPMC is capable of swelling in water and retaining a considerable amount of water without dissolving in it (Breimer *et al.,* 1985). The release of drug from the HPMC matrices generally involves the simultaneous absorption of water and desorption of drug via a swelling-controlled diffusion/erosion mechanism (Lee, 1983; 1984). As water penetrates the glassy matrix containing a dispersed drug, the polymer swells and thus, lowering the glass transition temperature, leading to the diffusion of drug through this swollen rubbery region into the external medium.

A number of variables can alter the release of drug from the matrix containing HPMC. The release of drug is, to a great extent, controlled by the viscosity of the polymer used. Huber and Christensin (1968) found that tablets containing a higher viscosity grade of HPMC released tetrazine at a significantly slower rate than that of a lower viscosity grade. According to Ford and co-workers (1985a; 1985b; 1985c) and Xu and Sunada (1995), the most important factor affecting the release rate from HPMC matrices is the drug: HPMC ratio. Nakano *et al.* (1983) indicated that the release of theophylline from HPMC matrices decreased as the viscosity grade of the HPMC was increased. The sustained drug release from these two systems is achieved through polymer swelling to a gel-like consistency at the tablet periphery, thus forming a barrier to drug diffusion. Harwood and Schwartz (1982) also found that the release of drug was slower from an ophthalmic matrix preparation which contained higher viscosity grades of HPMC. A similar observation was also reported by Lapidus and Lordi (1968) and Daly *et al.* (1984).

The release of drug from HPMC matrix could also be modified through the incorporation of additional exipients. Saito (1960) reported that the viscosity of non-ionic polymers could

be increased by the addition of anionic surfactants. A similar observation was also observed by Walker and Wells (1982) who found that a combination of anionic sodium carboxymethyl-cellulose with cellulose produced a synergistic increase in viscosity. Daly *et al.* (1984) also showed similar results when investigating the effect of sodium lauryl sulfate (SLS) on the release of chlorpheniramine from HPMC matrix.

The present study was conducted to develop a controlled release implant system of testosterone. Polymers such as starch, HPMC and polyvinyl pyrrolidone (PVP) were used (either individually or in combination) to prepare the implant systems and their *in-vitro* drug release characteristics were evaluated. Moreover, implant systems with increasing HPMC content; different viscosity grades of HPMC and those with anionic surfactant, sodium lauryl sulphate (SLS), were also evaluated. The above polymers were chosen based on their inertness as well as biocompatibility, being important pre-requisites in the formulation of implant systems.

2.2 MATERIALS AND METHODS

2.2.1 MATERIALS

Testosterone, Schering, Germany.

HPMC K100, HPMC K4M, HPMC K15M and HPMC K100M, Colorcon Company, Singapore.

Polyvinyl pyrrolidone, BASF Company, Germany.

Maize starch, BDH Chemiclas, England..

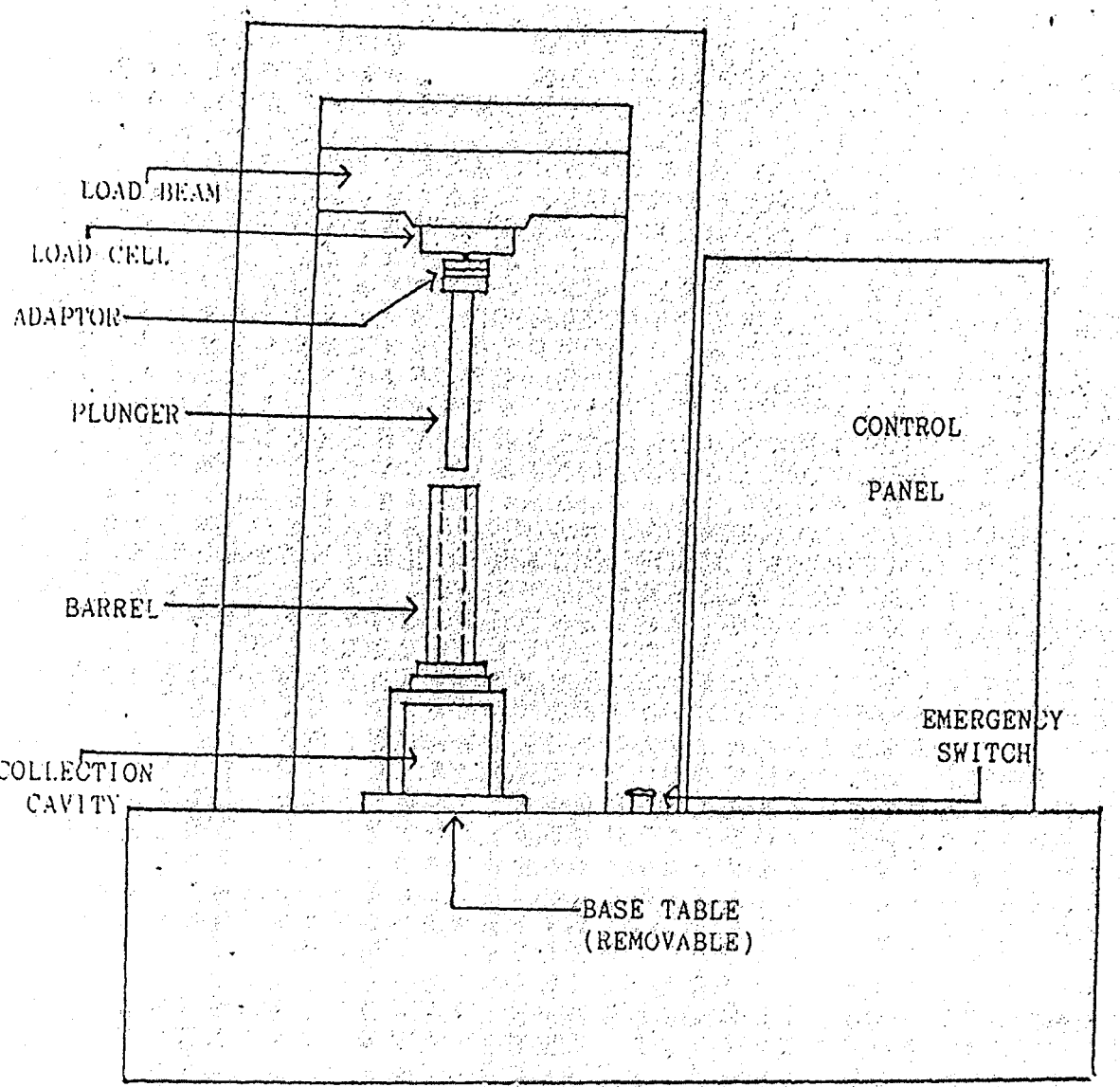

Figure 2.1 : Front view Illustration of the extruder

Sodium lauryl sulphate, Shin Poong Phrmaceuticals, Seoul, Korea.

2.2.2 METHODS

2.2.2.1 PREPARATION OF TESTOSTERONE IMPLANT SYSTEMS

Testosterone implant systems were prepared by first mixing the testosterone with polymeric materials in a planetary mixer (Kenwood Chef, UK) for 10 minutes. This was followed by the addition of sufficient amount of water until a suitable wet mass was formed which was then mixed for 15 minutes. The mixture was extruded using a ram extruder (SDX, Malaysia) yielding cylindrical implant systems with an outer diameter of 1 mm. The extruder was set to move downwards at a speed of 235 mm/min. For sterilization of the final extrudates, the extruded implant systems were then heated at 60°C for 4 hours in an oven (Carbolite, England) (BP, 1988).

An illustration of the ram extruder is shown in Figure 2.1. The mixture to be extruded was inserted into the barrel, which was then hand tightened to the die that contained one or more holes with a diameter of 1 mm. The barrel was then placed onto the table above the collection cavity. The plunger started to move downwards into the barrel when the power is on, thus pushing the mixture through the hole yielding short cylindrical implant systems.