1. INTRODUCTION

Endocrine control of both male and female reproductive function in mammals involves many common mechanisms. Prominent differences arise mainly at the level of steroid hormones produced by the gonads: estrogens and progestagens by the ovaries and androgens by the testes. A more subtle yet very important difference lies in the pharmacokinetics of the various hormones produced endogenously by different elements of the neuro-endocrine axis controlling reproduction. In effect, these differences result in the establishment of ever-varying blood levels of peptide and steroid hormones. These variations are more evident as physiological phenomena in the human female, in the form of menarche, a menstrual cycle and a discernible menopause, but are also prevalent in the male. The administration of sex steroids for pharmacological intervention in reproductive processes in both males and females should therefore ideally seek to take into account the biorhythms that these hormones show in normal physiology.

The present work directly addresses transdermal (TD) delivery of testosterone (T) as a model of this general problem. Male subjects deprived of endogenous T need androgen supplementation therapy. The administration of a contraceptive vaccine against the gonadotropin-releasing hormone (GnRH) to males results in a decline in serum T levels. Such subjects also require T supplementation to maintain anabolic and psychological parameters. Greatest therapeutic benefit may be expected if the "normal" rhythm of the hormone is restored. Another application of T administration is in contraception. Exogenously administered androgens are envisaged to render the subject infertile by means of feedback inhibition of the biosynthesis of T. It is possible that pulsatile activity can be inhibited by imposing a pulsatile inhibitory signal rather than by maintaining high, constant amounts of the inhibitor. This could be specially advantageous with T, which is known to have dose-dependent anabolic as well as psychotropic effects. An understanding of the pulsatile nature of the physiology of sex steroids may help in better implementation of the above objectives.
To do that, however, it is necessary to prepare a reliable delivery system that can mimic the diurnal profile of the hormone. Testosterone is not orally bioavailable, so that alternative routes must be sought. The frequency of dosing needs to be high since it has a short serum half life of about 12 minutes. It is a lipophilic steroid with well-defined skin permeation characteristics. These properties make it a suitable candidate for TD delivery. A skin patch intended for application to the scrotum has recently been introduced in the USA and another has received approval from the US FDA. Testosterone delivered by these TD systems mimics the pattern of blood concentrations observed during a 24 hr period in normal adult males. What they fail to address, nevertheless, is the prevalence of pulses of T subsumed within the diurnal profile.

Delivery systems seeking to release a large number of pulses require some degree of sophistication in design and engineering. They need to have a delivery portal that can be opened and shut by a control mechanism. Iontophoretic delivery systems are a case in point. However, such sophistications in design lead to escalation in costs, thereby limiting the reach of the delivery system. This is illustrated by the fact that a simple TD system based on passive diffusion for nitroglycerin delivery costs as much as Rs. 55 a unit in our country today (1995). It has therefore been an important concern of this work to formulate a purely "mechanistically" controlled system for delivering more than one pulse of the drug without resorting to expensive control mechanisms.

TD delivery methodology developed over the past 25 years has been focused at providing constant blood levels of the delivered drug. Consequently, it has been customary to minimize variations in the delivery profile. The ideal TD system is posited to release the incorporated drug with zero order kinetics. The experiments reported here, on the other hand, seek to maximize the variations in the delivery rate during the delivery period, so that more complex profiles of the drug may be arrived at.

The phenomenon of "burst release" or "loading dose" from a controlled delivery system has been almost invariably observed. It refers to the release of a significant amount of the incorporated material very soon after the delivery system is exposed to the release medium. It is possible to deliver an early peak of the drug by enhancing rather than attenuating the burst release. The shape of this peak in vivo would of course be determined
by the elimination kinetics of the drug. In the case of T, this peak has been found to rise and fall rapidly. Subsequent release of T can be adjusted by varying formulation factors associated with the rate-controlling materials making up the device. Sustained diffusion of T, controlled by a polymer matrix is capable of generating a pharmacokinetic profile with at least one well-defined maximum. It can thus be seen that more than a single maximum can be generated by a single application of a TD system designed along these lines. To increase the number of pulses, one would need to divide the incorporated drug into fractions sequestered in individual compartments of the device, each releasing its payload either after different lag times or at different rates that superimpose to generate a pulsatile profile.

This objective is beyond the scope of this work, being at best an elaboration of the principles demonstrated by the reported experiments. Instead, it has been thought appropriate to develop TD formulations of T that can generate biphasic profiles of delivery and pharmacokinetics, to optimize the preparation and evaluation procedures for these and to undertake preliminary investigations into their applicability as androgen replacement or contraceptive systems in animal models. Further, efforts have been made to establish the causes of the dichotomy between the kinetics of release during the early and later parts of the delivery period.

Two different series of formulations were prepared. The first set comprises of liquid formulations that are intended for application on the skin using a dispenser such as a micropipette or a simpler device such as a dropper. The alcoholic vehicle in these formulations evaporates and deposits a tacky film on the surface of the skin. The film is made up of a blend of poly(vinyl pyrrolidone) and poly(vinyl alcohol), and entraps T within its matrix. The second set of formulations are presented as adhesive-dispersion controlled TD patches, which are prepared by knife coating various pressure-sensitive adhesive formulations incorporating T on to a fabric backing. The formulation and preparation procedures as well as the evaluation of these systems in terms of physico-chemical properties, release characteristics and bioavailability in the castrated rat and GnRH immunized monkey models is described.