Increasing K, with all other parameters kept constant, increases the absolute rate of delivery, whereas increasing the thickness of application slows the *relative* clearance of the drug from the film. (Relative clearance is in terms of the fraction of the total drug present. This should not be confused with the absolute rate of release, which is always equal to, if not greater than, that of a thinner film.) Experimental verification of some of the basic dependencies has been provided by Addicks and co-workers (17).

III. APPLICATIONS OF THEORY: IN VITRO RELEASE STUDIES

A. Experimental Designs

According to Gemmell and Morrison (18), *...in vitro methods may be of limited predictive value but they are the means of assessing the ability of a vehicle or base to liberate medicament under the conditions of the test.* This statement very accurately describes the usefulness of in vitro release studies. In vitro studies have invariably involved release from applications that are much thicker than those seen clinically. Additionally, the chemical nature of the receptor phase used in such studies often bears no resemblance to the skin, and is usually configured as a thick slab. Overall, the conditions are such that the release kinetics reflect features of diffusion from a semi-infinite medium into a semi-infinite medium. If the receptor phase is rate-controlling, and if this phase bears little chemical resemblance to the skin, then it is foolishly unproductive to make extrapolations to in vivo situations (4).

Among the first experiments performed on the release of drugs from ointments were those developed 60 years ago by Reddish (19, 20). The procedure involved the measurement of the antiseptic properties of ointments containing various drugs. The experiments were carried out by applying ointment to agar that had been inoculated with *Staphylococcus aureus*. After incubation, the agar plates were assessed to determine the presence of a zone of inhibition. Thus, a crude measure of the ointment's ability to liberate a drug was achieved. A variation of this method was introduced by Clark and Davies (21) in which the minimum time required for an ointment to cause inhibition of bacterial growth was used as an index of ointment efficacy.

The practice of gauging the bioavailability of a drug from an ointment from the drug's ability to diffuse from the ointment into agar was extended by Lockie and Sprowls (22). The drugs used in their experiments were sulfathiazole and iodine, both of which can be detected colorimetrically. The procedure consisted of placing a tube filled with agar (containing an appropriate colorimetric indi-