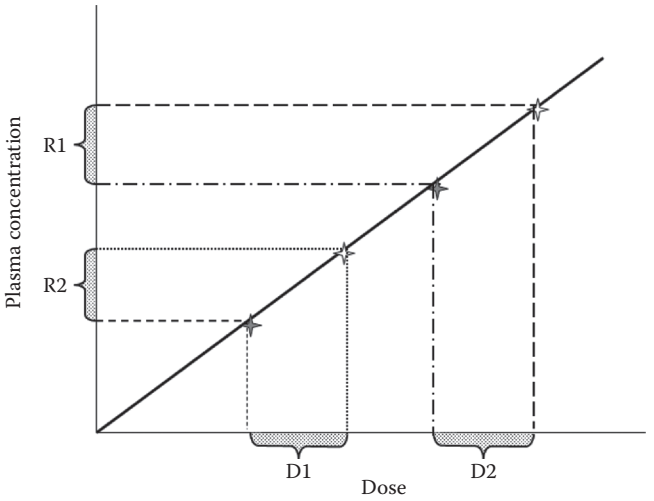

FIGURE 10.4 Blood concentration of a drug directly reflects the amount of drug delivered from the dosage form. The corresponding responses over a wide range of doses will be of adequate sensitivity to detect differences in bioavailability between two formulations. This is illustrated for two widely different doses, D1 and D2. Any differences in dosage form performance are reflected directly by changes in blood concentration (R1 and R2).

metabolite. Otherwise, if a metabolite is formed by presystemic or first-pass metabolism and contributes meaningfully to safety and efficacy, then FDA asks that metabolite plasma concentrations be measured and used to provide supportive evidence of comparable therapeutic outcome.

Urine measurements are not as sensitive as plasma measurements but are necessary for some drugs such as orally administered potassium chloride,[56] because serum concentrations are too low to allow for accurate measurement of drug absorbed from the dosage form. Both the cumulative amount of drug excreted (*Ae*) and the maximum rate of urinary excretion (R_{max}) are evaluated statistically in bioequivalence studies that rely on urine concentrations.

Bioequivalence Studies with Pharmacodynamic Endpoints

In situations where a drug cannot be reliably measured in blood, it may be appropriate to base bioequivalence evaluation on an in vivo test in humans in which an acute pharmacologic (pharmacodynamic) effect is measured as a function of time. The FDA accepts bioequivalence studies with pharmacodynamic endpoints for locally acting drug products. The pharmacodynamic response selected should directly reflect dosage form performance but may not necessarily directly reflect therapeutic efficacy. To be adequately sensitive to distinguish between two products that are not bioequivalent, the dose used in the pivotal bioequivalence study should be on the linear portion of the dose-response curve (Figure 10.5). A pilot pharmacodynamic study using the reference product can be conducted to determine the optimal dose for the pivotal bioequivalence study.