

(containing the same amount of dicumarol) required larger doses in order to maintain prothrombin levels in the therapeutic range. Why? Laboratory tests showed that the rate of dissolution of the drug from the larger tablets was much slower than from the smaller tablets. Yet there was no change in the amount of drug but only in the amount of excipients used to produce this larger tablet. So the tablets were reformulated to increase this rate of dissolution of the drug. Yet it was discovered that some patients, who had their prescription filled with these new tablets still showed prothrombin levels below the therapeutic range. The only solution here was to have the physician retitrate the patients with respect to their dicumarol requirement for that tablet or dosage form.

It is quite likely that no two manufacturer's brands of dicumarol tablets will act alike in therapeutic activity and it is conceivable that a change from a slow release brand to a fast release may be extremely detrimental to the patient.

Every tablet obviously must disintegrate and release the medicament in a manner which makes the drug available for absorption. For the treatment of certain emergency conditions, such as an asthmatic attack, it is important that the tablet disintegrate rapidly and release the drug. On the other hand, where tablets contain drugs which may produce gastric irritation on rapid release of concentrated drug quantities, it is important that this disintegration and release of drug not be too rapid.

A study conducted by Chapman and co-workers (4) which appeared in the Canadian Medical Journal dealt with the disintegration time of twenty-nine tablets of two different drugs and found that sixteen of these took longer than sixty minutes to disintegrate. The tablets were still intact and the drug present in a form not available for therapeutic activity. The authors state that, "While it is relatively simple to assay a preparation and ensure that it meets labelled claim, it is more difficult to determine whether the drug is available to the patient once administered."

In a later study the same author (5) examined the absorption characteristics of riboflavin tablets. Generally speaking, the data showed that the riboflavin tablets showing the longest disintegration time were least absorbed—one to the extent of less than 14%. A drug must be absorbed in order that a therapeutic response be obtained.

An interesting study and one I want to mention here is one recently completed by the Food and Drug Directorate of Canada (6). This agency examined some ten different hydrochlorothiazide tablets produced by ten different manufacturers. They report that $t_{1/2}$, that is the time necessary for the tablet to dissolve and release 50% of its drug into solution varied from some two minutes to over five hours from these various tablets. The important point here was the fact that all of the tablets contained the same amount of drug and that all of the tablets disintegrated within the sixty minute time limit set down by the USP. Release of the drug from the disintegrated particle was another matter. The tablets here were equivalent—equivalent in the sense that they all contained the same amount of drug—but certainly not equivalent in their ability to release the drug to the patient for the required therapeutic response.

An increase in the pressure used in the compression of tablets, which is reflected by an increase in the disintegration time and medicament release, may markedly influence the intensity of the therapeutic effects and the availability of the drug. Again studies (7) have shown that substantially different blood levels vs. time curves were obtained when various penicillin V tablets compressed at different pressures and having different disintegration times were assayed in vivo. It should be noted here that at sixty minutes, which is the upper disintegration limit set by the U.S.P., only about 60% of the drug was available for absorption. Beyond sixty minutes the patient was in effect getting a placebo since the amount of drug released from these particles was below a therapeutic level.

Another rather dramatic example of marked potency difference involved Prednisone tables (8, 9). This is of particular interest to me in that we had a similar experience at the University of Iowa. Prednisone, as you are aware, has been one of the drugs which was the subject of much public discussion in Washington with respect to equivalency of product irrespective of the manufacturer.

Certain published reports involved prednisone tablets prepared by two manufacturers. Both showed the same prednisone content by laboratory analysis and both disintegrated into small particles in the time set forth by the U.S.P. Yet only one tablet gave the expected physiological response when administered to patients—the other was inactive. Why? The difference here was in a formula-