as white needles, 47 mg. (45%), m.p. 118–118.5°; $[\alpha]_D^{25}$ + 45°.

Anal.—Calcd. for $C_{28}H_{51}N$: C, 83.75; H, 12.80; N, 3.52. Found: C, 83.57; H, 12.72; N, 3.78.

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Method for Evaluating Dissolution Characteristics of Capsules

By M. PAIKOFF and G. DRUMM

A simple device is described which is useful for dissolution determinations of capsule formulations. It may be utilized in a visual inspection for capsule dispersion or disintegration, and also in the usual chemical dissolution rate determination for predicting possible problems of drug availability from capsules.

ON OCCASION it has been found difficult or almost impossible to devise biological assays to prove that the availability of a pure drug substance has not been altered when mixed with various adjuncts in a dosage form for clinical human testing. These adjuncts are included for weight adjustments and/or to allow mechanized filling of the capsule. Sometimes the drug can not be administered to the animal as the intact human dosage form, but the capsule must be opened, the contents mixed with some liquid carrier, and then administered *via* a stomach tube. This is obviously not the same dosage form intended to be administered to humans.

Dissolution rates of tablets may be determined by several procedures (1–5) employing various agitation intensities, dissolution media, and methods of sampling the solution for drug content assay. These procedures are possible because the tablet does not float to the surface of the dissolution media. Capsules do not behave in the same manner but will float to the top of the dissolution medium, unless the capsule is held under the surface. The use of lead shot or other devices to weigh down the capsule often react with the dissolution media and consequently yield nonreproducible results. Schroeter (6) described a very complex automated method of following the dissolution of tablets and capsules employing the U.S.P. disintegration apparatus and basket rack assembly.

The authors have devised a simple laboratory procedure for screening clinical supplies of new drugs which are prepared in the form of capsules.

EXPERIMENTAL

A capsule holder consisting of a two-bladed glass stirrer with an opening for the capsule is employed. The opening for the capsule is at the base of the stirrer between the two glass blades (Fig. 1). Variously sized orifices can be incorporated into the stirrer to accommodate differently sized capsules. The stirrer rod capsule holder is attached to a Heller stirrer model No. GT 21. The capsule, after being inserted into the holder, is located half-way down into the dissolution medium maintained at 37°. The stirring rate is varied easily, and the duration of mixing is most often 60 min. with appropriate time intervals scheduled therein for sampling.

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RESULTS AND DISCUSSION

This apparatus has been employed to accumulate two types of *in vitro* data.

Visual Dispersion or Disintegration.—The capsule containing formulation is checked for visual dispersion in 400 ml. of distilled water at 37° with a stirring rate of 60 r.p.m. During a period of 1 hr. the capsule is periodically inspected visually to determine if the ingredients of the capsule disperse following a lag period of several minutes for the gelatin capsules to dissolve. Dispersion or disintegration of the capsule ingredients usually indicates a satisfactory capsule formulation. However, if the ingredients of the capsule remain intact after the gelatin capsule has all dissolved (Fig. 2) and little or no dispersion of the capsule ingredients

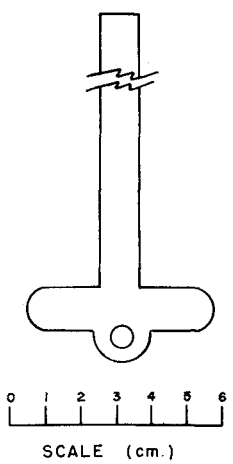

Fig. 1.—Scale drawing of stirrer capsule holder.

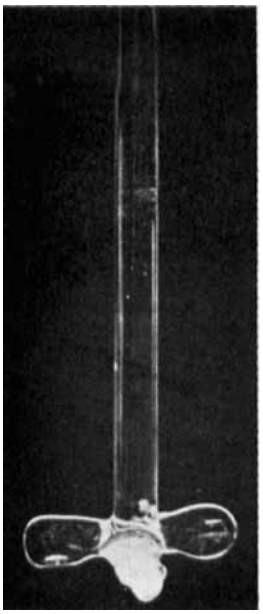

Fig. 2.—A capsule formulation which failed to disintegrate. The capsule ingredients and holder have been removed from the dissolution medium.

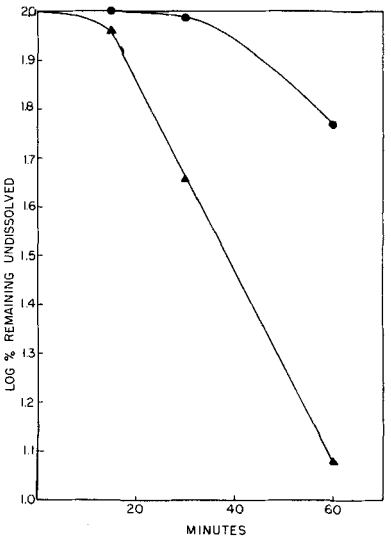

Fig. 3.—Dissolution test results. Key: ●, drug alone; ▲, drug plus additives.

has occurred, the formulation may be a candidate for poor drug availability. In questionable formulations of this type, the capsule ingredients may remain intact in the holder with a slight amount of swelling. When this lack of dispersion is noted, the formulation is changed or other methods of availability testing employed. However, one is made aware that there may be a drug availability problem with this formulation.

Comparative Dissolution.—To prove that the adjuncts added to a capsule formulation have not altered the drug availability in a capsule formulation that passes the visual dispersion test, this apparatus may be employed to compare the *in vitro* dissolution rate of the drug with and without additives. Because of solubility limitations, organic solvents have often been employed as dissolution media. Figure 3 is a typical graphic representation of the *in vitro* dissolution rate of a drug with and without adjuncts. These results would indicate that the availability of the drug has been improved by the addition of the capsule additives. A reverse picture would, of course, indicate that there may be a drug availability problem. These conclusions are, however, subject to confirmation by a suitable biologic assay of the intact capsule. In several cases where animal data have been available for comparative purposes, this method has exhibited satisfactory rank-order correlation.

CONCLUSION

A simple method is described for the determination of the dissolution behavior of drugs from capsules. The method utilizes the same basic equipment used for tablet dissolution studies employed by Levy and Hayes (1), except for the stirrer capsule holder.

This stirrer rod capsule holder apparatus possibly may have a role in the development of an official disintegration test for capsules.

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