Dissolution Rate Studies on Methylprednisolone Polymorphs

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Dissolution rates (DR) of methylprednisolone polymorphs I and II were determined by the rotating disk method as a function of rate of rotation (RR). The results show that the DR–RR relationship differs from that normally expected in the case of diffusion-controlled dissolution from rotating disks. The experimental data confirm the observations by Hamlin, *et al.* (5), that differences in DR between methylprednisolone polymorphs diminish at higher agitation intensities and indicate that this is due to an intrinsic property of the drug and is not caused by particular apparatus or methodology. From DR–RR data on methylprednisolone I, it was possible to determine the approximate agitation intensities, in terms of rotating disk r.p.m., obtained with five commonly used dissolution methods. These values are shown to be in reasonable agreement with those calculated independently from aspirin and salicylic acid data.

STUDIES OF intrinsic dissolution rates can be useful in evaluating the prospective absorption rate and physiologic availability of drugs which, when administered orally in solid form, are absorption-rate limited by the dissolution process (1, 2). Such studies are particularly pertinent to steroids because of the poor water-solubility of most of these and the difficulties encountered in determining their physiologic availability, due to the small doses customarily employed.

Recently (3), one of the authors (G. L.) has presented an equation (and experimental verification) evolved from an equation developed by Cooper and Kingery (4), which relates the effect of rate of rotation (RR) to the diffusion-controlled rate of dissolution (DR) of substances from the face of a rotating disk, *viz.*,

$$DR = K(RR)^{0.5} \qquad \text{(Eq. 1)}$$

Equation 1 assumes that (*a*) the surface area of the disk remains constant during dissolution, (*b*) the concentration of the dissolving substance in the bulk medium is very much less at all times than its solubility, and (*c*) the effective weighted average viscosity of the boundary layer and the effective weighted average diffusion coefficient of the dissolving species in the boundary layer are independent of rate of rotation (and thus independent of effective boundary layer thickness).

On the basis of Eq. 1 and our experimental data, we have shown (3) that the *ratio* of the dissolution rates of compounds is independent of rotation rate, provided that these compounds behave according to Eq. 1 or to a more general relationship

$$DR = K(RR)^{a} \qquad \text{(Eq. 2)}$$

where the value of the exponent a is the same for all the respective compounds.

The above relationships are useful since they permit one to compare the *in vitro* dissolution rate of a new drug with that of an older drug. In this way one may, in certain instances, deduce the relative *in vivo* dissolution rate of the new drug from absorption data obtained previously with the older drug. This is particularly so if pK's are similar or if the solubility of both drugs is independent of pH, but requires that dosage form properties (including particle size) be essentially the same in each case.

Hamlin, *et al.* (5), have reported recently results of experiments which show that differences in dissolution rates of methylprednisolone polymorphs I and II, observed at low agitation intensities, disappeared at higher agitation intensities. These results could be due to loss of sensitivity encountered with some of the apparatus and methodology used or it could be due to an intrinsic property of the polymorphs. The latter must be reflected by one of the following: (*a*) one or both polymorphic forms do not behave according to Eq. 1, (*b*) one or both forms do not behave according to Eq. 2, or (*c*) both forms behave according to Eq. 2 but differ in the value of exponent a. These possibilities have been investigated by the authors, and the results of the study are the subject of this report.

It was possible to make further use of the experimental data since they permitted an estimation of agitation intensities obtained with various apparatus and methods used in different laboratories. Independent estimations of these values were also made (using dissolution rate data obtained with other drugs), in order to check our methodology and treatment of data.

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EXPERIMENTAL

Materials.—Methylprednisolone polymorphs I and II were used in the forms in which they were obtained. Physicochemical descriptions of these two materials have been published previously by W. I. Higuchi, *et al.* (6). Acetylsalicylic acid and salicylic acid were of U.S.P. grade.

Dissolution Rate Determinations.—Pure methylprednisolone was compressed into flat-faced pellets of 1.27 cm. diameter at a pressure of 3570 Kg./cm.[2] with a modified Carver hydraulic press. Dissolution rate measurements were made in distilled water (methylprednisolone) and in 0.1 *N* hydrochloric acid (aspirin and salicylic acid) at 37 ± 0.1° by the rotating disk and beaker methods. Details of these methods and the respective apparatus have been reported in previous publications by Levy and Sahli (7) and by Levy and Hayes (8), respectively. Some of the rotating disk experiments (particularly the low-speed runs) were carried out with a newly developed precision apparatus (9). The duration of most runs was 2–4 hours, with sampling at 30 minute intervals. Data shown in Fig. 1 represent averages of three to five individual experiments. The beaker method, employed previously only for conventional tablets, was modified for intrinsic dissolution rate determinations by mounting the drug pellet with paraffin wax on a microscope cover glass (such that one face of the pellet remained exposed) and attaching the cover glass to the center of the bottom of the beaker with a water-insoluble adhesive. Samples of dissolution media were analyzed spectrophotometrically at 248 mμ (methylprednisolone) or 302 mμ (salicylic acid) after appropriate dilution with water (in the case of methylprednisolone), 0.1 *N* hydrochloric acid (in the case of salicylic acid), or alkaline hydrolysis followed by dilution with 0.1 *N* hydrochloric acid (in the case of aspirin).

RESULTS AND DISCUSSION

Figure 1 shows the dissolution rates of methylprednisolone forms I and II, determined by the rotating disk method, as a function of rate of disk rotation. Polymorph I follows the relationship expressed by Eq. 2, but the slope value is 0.37 rather than 0.5 as might be expected (3). Polymorph II apparently does not obey either Eqs. 1 or 2, since

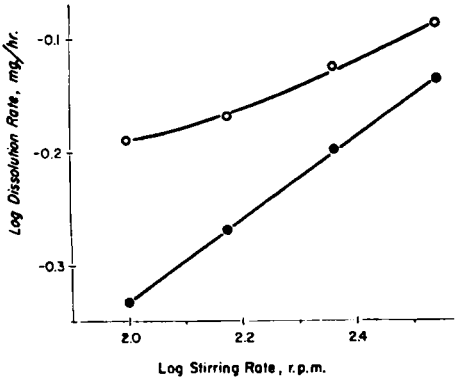

Fig. 1.—Dissolution rates of methylprednisolone polymorph I (●) and polymorph II (○) from rotating disks (1.27 cm.[2]) as a function of rate of disk rotation.

the log-log plot yielded a slight curve. The latter statement is made with reservations, since the reproducibility of dissolution runs with polymorph II was not as good as that with polymorph I.[1]

Figure 1 shows that differences in dissolution rate between forms I and II tend to disappear at higher agitation intensities.[2] This confirms the observations reported by Hamlin, *et al.* (5). In addition, since all measurements were made with the same apparatus, and since the utility of the method to yield proper data (0.5 slope values where applicable) has already been demonstrated (3), it may be concluded that the decrease in dissolution rate differences at higher agitation intensities is probably an intrinsic characteristic of the drug and not due to the apparatus or methodology used by Hamlin, *et al.* (5). The reasons for this unusual behavior are not readily apparent and are the subject of further investigations.

One important implication of the experimental results is that *in vitro* dissolution rate data obtained with compounds behaving like the methylprednisolone polymorphs may be misleading biopharmaceutically if the agitation intensity of the test procedure is either too high *or* too low. Thus, one would expect that very low agitation intensity procedures may yield good correlation with *in vivo* data obtained with pellet implants, but that correlation with data obtained from gastrointestinal absorption experiments may be better with *in vitro* data obtained at somewhat higher agitation intensities. It is certainly appropriate to characterize the dissolution-rate dependence of drugs on agitation intensity as part of their biopharmaceutical evaluation. Among the factors which are already known to account for unusual dissolution rate-agitation rate relationships are surface film formation (10, 11), interfacial reaction-controlled dissolution (5), surface effervescence (12), and surface-pitting (3).

The linearity of the log DR–log RR plot for methylprednisolone I and the good reproducibility of the data suggested to us the possibility of using our results as a "standard curve" to determine the relative agitation intensity encountered with other published dissolution procedures. The desirability of obtaining such information to permit comparison of dissolution data reported by different workers using different methodology has been emphasized strongly (13). Using the regression equation $y = 0.368x - 1.068$ which represents the straight line fitted to the methylprednisolone I data by the method of least squares [where x is log RR (in r.p.m.) and y is log DR (in mg./1.27 cm.[2]/hr.)], agitation intensities for the hanging pellet, Wruble 6 r.p.m., Wruble 12 r.p.m., and Souder and Ellenbogen 40 r.p.m. procedures were calculated from the data of Hamlin, *et al.* (5). Agitation intensity for the beaker procedure was calculated from data collected in our own laboratory. The agitation intensities are expressed in terms of rotating disk equivalent (RDE) r.p.m. This permits comparison of intensities derived from data obtained with different compounds without having to know their respective solubilities and diffusion coefficients.

[1] Similar differences in reproducibility are apparent from the data of Hamlin, *et al.* (5).

[2] It is possible that polymorph II may actually dissolve less rapidly than polymorph I at some sufficiently high agitation rate. Technical limitations prevented determinations of dissolution rates at such high rates of disk rotation.

TABLE I.—AGITATION INTENSITY EQUIVALENTS (IN TERMS OF ROTATING DISK R.P.M.) OF VARIOUS DISSOLUTION METHODS

Method	Dissolution Rate (mg./cm.²/hr.)	RDE (r.p.m.)[b]
I. Based on Methylprednisolone Polymorph I[a]		
Hanging pellet	0.091[c]	2.3
Wruble apparatus, 6 r.p.m.	0.203[c]	20
Wruble apparatus, 12 r.p.m.	0.276[c]	46
Beaker	0.266	42
Souder and Ellenbogen apparatus, 40 r.p.m.	0.630[c]	435
II. Based on Salicylic Acid[d]		
Beaker	14.6	50
III. Based on Acetylsalicylic Acid[e]		
Wruble apparatus, 6 r.p.m.	12.8[f]	14
Beaker	18.9[g]	49

[a] Calculated from equation $Y = 0.368x - 1.068$, where x is log r.p.m. and y is log dissolution rate in mg./1.27 cm.²/hr. in water at 37°. [b] RDE = rotating disk equivalent. [c] Data from Hamlin, *et al.* (5). [d] Calculated from equation $y = 0.495x + 0.320$, where x is log r.p.m. and y is log dissolution rate in mg./cm.²/hr. in 0.1 *N* HCl at 37°. [e] Calculated from equation $y = 0.515x + 0.406$, where x is log r.p.m. and y is log dissolution rate in mg. salicylic acid equivalent/cm.²/hr. in 0.1 *N* HCl at 37°. [f] Data from Hamlin (14). [g] In terms of salicylic acid.

Table I shows the calculated RDE values for five published dissolution procedures. In view of a number of other imponderables related to the use of data collected in more than one laboratory, no attempt has been made to treat the results statistically. The RDE values listed in Table I should therefore be looked upon as reasonable approximations only.

The use of the regression equation to derive RDE values which fell beyond the range of experimental data from which the equation was calculated was based on the assumption that the linearity of the log DR *versus* log RR plot is maintained over a much wider range, particularly at lower rates. While extension of our rotating disk studies to very low rotation rates was impracticable due to the extremely low dissolution rate of the steroid, it was thought necessary to carry out at least one DR determination at a very low RR. Accordingly, the dissolution rate of methylprednisolone I was determined at 4 r.p.m. in a 6-hour run with 1-hourly sampling of medium. This yielded a dissolution rate of 0.12 mg./hour, compared with a theoretical value of 0.14 mg./hour calculated from the regression equation. Considering the extent of extrapolation and the experimental difficulties, this can be considered a very satisfactory agreement and justification for use of the regression equation over the indicated range.

An independent estimation of some RDE values was possible with data obtained from two other drugs, namely aspirin and salicylic acid. Using regression equations obtained in a previous study (3), an RDE value of 49 and 50 r.p.m., respectively, was obtained for the beaker method, which may be compared with a value of 42 r.p.m. calculated from the methylprednisolone I data. The agreement is quite good and also affords further support for extrapolation of the methylprednisolone data and the reasonable correctness of the slope value. RDE values for the Wruble 6 r.p.m. procedure were 20 and 14 r.p.m. from methylprednisolone and aspirin data, respectively. Considering the marked sensitivity of DR to changes in RR at the lower RR range, one may conclude that these RDE values are also in reasonably good agreement.

The RDE values obtained for the rotating bottle and tube methods may appear surprisingly high when compared with the rate of wheel rotation, but these high agitation intensities probably are due to the added agitation (and turbulence) caused by the to-and-fro movement of the void space in the containers. The RDE estimations for the Wruble and Souder and Ellenbogen methods apply only to instances where the solid drug is immobile (held rigidly in the container) and not where drug solids move freely in the dissolution medium. The latter case will usually involve much greater agitation (5) which varies with particle size and specific gravity of the drug, among others (1), and is probably not readily reproducible. It may seem unusual that an RDE value is provided for the hanging pellet procedure, since it involves an immobile object immersed in unstirred medium. However, solvent does flow over the pellet surface due to the difference in density of the drug-saturated boundary layer and the bulk medium. The rate of this flow is a function of the viscosity of the medium and the difference in density between the boundary layer and bulk medium (15). This difference is a function of the solubility of the drug and its effect in changing the density of the solvent. Thus, an RDE value for the hanging pellet is justified, but it is not a constant. It will differ with each drug, depending on the viscosity and density conferred by the drug on the boundary layer. Nelson has pointed out previously that dissolution from a hanging pellet and from stirred media represent different types of processes, with only the latter usually following Noyes-Whitney kinetics (15).

The experimental results described in this report clearly point up a new difficulty which may be encountered in dissolution rate studies pursued for biopharmaceutical purposes, and it appears prudent to obtain dissolution rate-agitation intensity profiles rather than to determine dissolution rates of substances at only one agitation intensity. Further studies in this and other laboratories may show whether the unexpected DR–RR relationship observed with methylprednisolone polymorphs is characteristic of steroids and certain other classes of compounds in general or whether it is a rare and unusual phenomenon.

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