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Physicochemical and Fluid Mechanical Factors Related to Dissolution Testing

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Introduction

Dissolution resulting from a solid dosage form in a moving fluid flow field is linked with two mechanisms: shear at the dissolving surface created by the frictional effects of flow and diffusion. The former is a fluid mechanical property and the latter is a physicochemical one. For any given dissolution methodology, the fluid mechanical properties are intrinsic to the device and the physicochemical properties are intrinsic to the drug and the dosage form. A well characterized dissolution device is one which is calibrated, at least with respect to its intrinsic fluid mechanical properties, so that dissolution data can be correlated directly with the performance of the dosage form and the intrinsic physicochemical properties of the drug and are not confounded by unknown characteristics of the device.

While chemical calibrators, as currently used, give a measure of apparatus suitability, the data is a reflection of all the factors which affect dissolution performance. The contribution of specific factors, such as fluid flow and shear at the dissolving surface, cannot be identified and accounted for. Since fluid flow is common to all dissolution methods currently used and since fluid mechanical factors related to the system are critical to dissolution performance, this article will focus on the importance of fluid flow properties which are directly relevant to characterizing dissolution performance.

It would be useful if a given dissolution apparatus had the same design characteristics as other instruments, such as viscometers. In fact, viscosity measuring devices have much in common with dissolution methodology including dependence upon fluid flow characteristics governed by fluid mechanical principles, dependence on shear at a surface, and the need to be versatile enough to measure materials having a broad range of properties. A major difference is that viscometers have been specifically designed with explicit incorporation of fluid mechanical models whereas dissolution devices have not. In addition, both viscometers and dissolution devices are disarming in their simplicity but subtle in their complexity. The theme for this article is that these fluid flow properties if known a priori *or by measurement would enhance the ability to optimize performance criteria.*

Relationship of Performance Criteria to the Physicochemical and Fluid Mechanical Properties

Performance criteria of particular interest for any given methodology are sensitivity and reproducibility. Reproducibility to be able to replicate results and sensitivity to discern real differences between formulations when they exist. The premise is that these criteria will be affected by the fluid mechanical factors intrinsic to the method.

This premise derives from the fact that the fluid flowing over a dissolving surface is sheared as the liquid comes into contact with that surface. The resulting shear then affects the mass transport of dissolved material from the surface. This process can be visualized by reference to *Figure 1*, which shows the hypothetical dissolving surface immersed in a flowing stream (1). The free stream velocity, U, is uniform as the liquid approaches the dissolving surface. At the point of contact, the liquid velocity closest to the surface decreases due to shear while the liquid some distance from the surface, h1, maintains the original velocity, U, since it does not experience shear. Within a hydrodynamic boundary distance of h1 a velocity gradient occurs which is often functionally dependent upon the location from the initiation of fluid contact. The thickness of the hydrodynamic boundary layer is inversely proportional to fluid velocity and directly proportional to the kinematic viscosity. In general,

h1 = f(fluid velocity, kinematic viscosity, positional coordinates along the surface).

At the same time, the diffusion layer, h2, is a function of both the fluid mechanical and physicochemical properties of the dissolving material and in general

h2 = f(drug diffusion coefficient, fluid velocity, kinematic viscosity, positional coordinates along the surface).

In turn, the dissolution rate per square centimeter is dependent upon **both** h1 and h2. It is intuitive that as the fluid velocity increases, then the shear at the dissolving surface correspondingly increases. As a result both h1 and h2 decrease, and the dissolution rate increases.

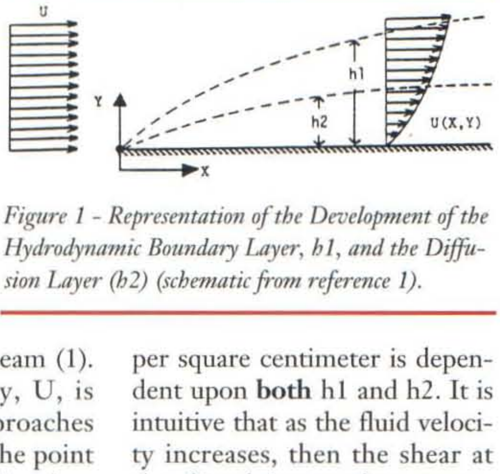

Figure 1 - Representation of the Development of the Hydrodynamic Boundary Layer, h1, and the Diffusion Layer (h2) (schematic from reference 1).

With this pictorial representation in mind, two cases involving the underlying dissolution mechanisms can be defined. Case I occurs under condi-

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tions of low fluid velocity and leads to diffusion being the dominant dissolution mechanism. This situation can occur, for example, on the underside of the salicylic acid calibrator in apparatus II where the fluid flow is relatively stagnant and density gradients occur.

Case II occurs under conditions of increased fluid velocity where diffusion is coupled with the shear at the dissolving surface.

The important issue related to dissolution performance is the influence of fluid flow and the underlying fluid mechanical factors on the performance criteria of reproducibility and sensitivity. Information related to this issue was reported by Hamlin and coworkers (2) who measured the dissolution rate of two polymorphs of methylprednisolone. The results of their study are given in *Table 1*. Each test method is given along with the % difference in dissolution rate between the two methylprednisolone polymorphs. The % difference in dissolution rate is a sensitivity index which shows the ability to discern real differences. This sensitivity index will be affected by the variability of the data.

Test	**%Difference In Rates**	**Significance of Difference Between Rates by t Test**
Pellet Implants in Rats	**51.1**	**Significant 1% level**
Hanging Pellet *In Vitro Method*	**41.7**	**Significant 1% level**
***In Vitro Method* 1 lower agitation intensity**	**26.5**	**Significant 2% level**
***In Vitro Method* 1 higher agitation intensity**	**-0.4**	**No Significant Difference**

% Difference in Rates =

(Rate of I - Rate of II)/ (Average Rate of I and II)

Data taken form W.E. Hamlin et al., "Loss of Sensitivity in Distinguishing Real Differences in Dissolution Rates Due to Increasing Intensity of Agitation", *J. Pharm. Sci. 51*, 432-435 (1962).

Table 1- Sensitivity of Dissolution Tests to Agitation Intensity As Performed with Constant Surface Area Pellets of Methylprednisolone Polymorphs I and II By An In Vivo *and Several* In Vitro *Methods (data cited from reference 2).*

The *in-vivo* pellet implant and the *in-vitro* hanging pellet are examples of Case I dissolution. In this case real differences are discernable. Method 1 is an example of *in-vitro* Case II dissolution. The data for this method show that as agitation intensity increases, the ability to discern real differences between the two polymorphs decreases. The inference from these data is that the sensitivity decreases with increasing agitation rate.

Intrinsic Dissolution Testing As An Ideal Dissolution Method

With the idea that dissolution performance is linked with the fluid mechanical properties, one can define the characteristics of an ideal dissolution apparatus. In this context, predictable and known flow fields are the underlying factors of upmost importance. A known flow field is important because it leads to a predictable shear pattern at the dissolving surface; in turn a predictable flow field often leads to predictable dissolution performance via a quantitative relationship which relates the dissolution rate with all of the fluid mechanical and physicochemical factors of interest. In other words, the ideal device is self-calibrating.

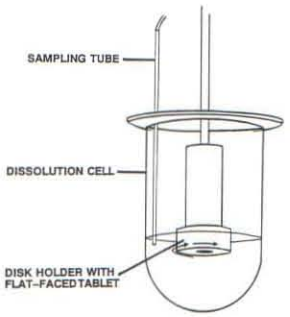

Figure 2 - Schematic of Wood's Intrinsic Dissolution Testing Method.

The rotating disk or Wood's device (3) shown in *Figure 2* is an example of a desirable dissolution method since it leads to a predictable flow field and to predictable and sensitive dissolution performance. In this configuration, the dissolving material is held in a flat faced tablet die, with a single face presenting for dissolution. The fluid motion is generated by turning the shaft holding the single faced tablet at a known speed. From a fluid mechanical standpoint, this situation is known as flow generated by a rotating disk in a stationary fluid. From a dissolution point of view, this would be a Case II situation.

Figure 3 shows an idealized representation of the flow field for the rotating disk (4). Note that the fluid is drawn toward the center of the dissolving surface as the surface rotates. The fluid nearest the surface is sheared and travels radially outward. This system is similar to a ceiling fan where the fluid air is drawn to the center and then exits radially.

This device leads to reproducible and sensitive dissolution data. The device is available commercially with a shaft size which is compatible with current dissolution instrumentation.

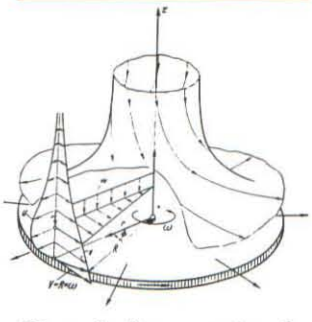

Figure 3 - Representation of the Flow Field for the Rotating Disk (from reference 4)

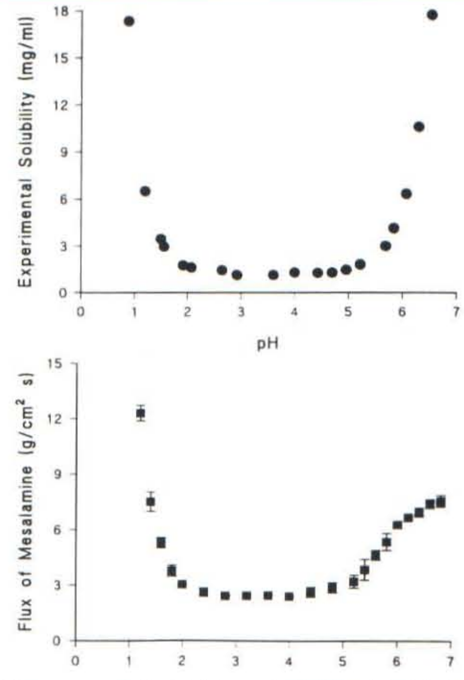

Figure 4 - pH/Solubility and pH/Flux Profiles for Mesalamine As Measured by the Rotating Disk (data cited from reference 5).

Shown in *Figure 4* is the solubility and dissolution rate/pH profile for mesalamine (5 amino- salicylic acid), which is an amphoteric species having an amine and carboxyl group (5). At low pH values where the amine group is ionized and the solubility is increased, the dissolution rate is correspondingly increased. At pH values between 2 and 5, the solubility and dissolution rate is minimized. The solubility and dissolution rate increases at pH values above 5 where the carboxyl group is ionized. These data demonstrate that the rotating disk method is sensitive to the underlying physicochemical occurrences in the diffusion layer. At pH values above 6 the solubility continues to increase, but the dissolution rate begins to plateau. This outcome is due to the self-buffering capacity of the drug. Thus, this method is sensitive to the micro-environmental pH, which may be different from that in the bulk. The important point is that it is possible to identify the physicochemical properties of interest since the fluid mechanical properties are known; the dissolution results are not confounded by unknown apparatus related factors.

It should be emphasized that the rotating disk is self-calibrating since there is a formal relationship between the dissolution rate, R, and the variables of interest where:

$$R = C_S D^{2/3} \nu^{-1/6} \omega^{1/2} A$$

This relationship quantitatively links the phyicochemical factors (drug solubility and drug diffusion coefficient) and the fluid mechanical factors (kinematic viscosity and rotation rate of the disk) with the dissolution rate. It also includes the geometric influence by including the physical surface area, A. Therefore, if these factors are known from independent measurements, then the dissolution rate can be calculated *a priori* and the method is self-calibrating. By knowing this relationship, the sensitivity of the dissolution rate to each of the parameters alone or in combination can also be evaluated.

Measurement of Fluid Mechanical Characteristics

In most practical cases, a quantitative relationship between the dissolution rate and the physicochemcial and fluid mechanical variables is not known *a priori*. In this case, experimentally determined fluid flow properties are a useful surrogate.

Visualization Technique

Visualization studies are important to understanding the flow patterns and the underlying shear pattern at the dissolving surface. Nondisintegrating salicylic acid tablets containing phenolphthalein and dissolving in 0.1 N sodium hydroxide solution as the dissolution medium are a convenient probe for this purpose (6). These tablets clearly show the presence or absence of a shear pattern at the dissolving surface via the red color resulting from the dissolution process. For example, the shear pattern is clearly visualized as being rotational when the dominate fluid flow is primarily rotational. The shear pattern will also demonstrate whether density gradients are present or whether dissolution is occurring evenly across the tablet surface. The visualization studies shown in *Figures 5 a, b,* and *c* resulted from this technique at three stirring speeds using a device where fluid flow is generated by a rotating cylinder. Shown in *Figure 5 (a)* is visualization resulting from relatively low stirring speeds. In this case there is no well defined shear pattern, as evidenced by the non-uniform color distribution across the dissolving surface. The visualization in *Figure 5 (b)* resulted from intermediate stirring speeds. In this case, the color distribution shows that there is a well defined and uniform shear pattern across the surface. The material is dissolving uniformly across the surface and the dissolved material is carried away from the center of the dissolving tablet. At higher stirring speeds, as shown in *Figure 5 (c)*, the color is absent on part of the dissolving surface, indicating that dissolution is not uniform across the surface. These findings suggest that the dissolution performance will be affected as the transitions between Case I and Case II dissolution occur. The data also suggest that there is an upper bound to the agitation intensity where dissolution sensitivity may be adversely affected. Using this technique it is possible to determine a range of agitation intensities or fluid flow velocities where the shear pattern is stable and does not substantially change. The technique is also sensitive enough to visualize where Case I dissolution predominates over Case II. Thus, the resulting information is qualitatively useful in predicting whether the dissolution performance will be reproducible and sensitive within a range of agitation intensities.

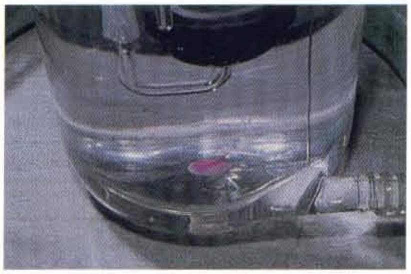

Figure 5a - Visualization Study Under Conditions of Low Agitation Intensity.

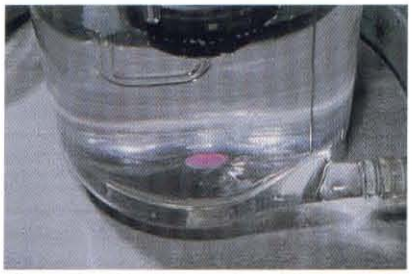

Figure 5b - Visualization Study Under Conditions of Moderate Agitation Intensity.

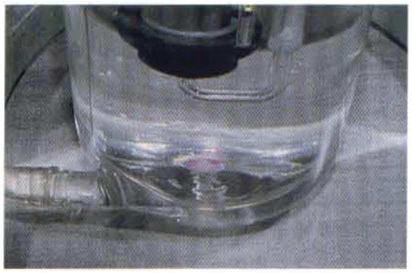

Figure 5c - Visualization Study Under Conditions of High Agitation Intensity.

Direct Flow Measurement

Visualization studies provide indirect information about the actual fluid velocities and resulting flow fields. Direct flow measurements can be made using laser Doppler anemometry techniques (7). However, the instrumentation for this flow measurement method is expensive. A technically feasible alternative method is a mechanical anemometer which is rugged, reasonably priced, capable of measuring average fluid velocities in the range of interest, and able to measure the degree of fluid fluctuation. This latter fluid flow characteristic is possibly most important since local fluctuations in fluid flow will inevitablly lead to perturbations in the shear pattern. It is possible that when local fluctuations are large enough, then the reproducibility and sensitivity of the dissolution data will be affected.

Correlations Which Relate Fluid Mechanical and Physicochemical Properties with Intrinsic Dissolution Performance; Defining An Intrinsic Calibration Procedure

The historical development of calibrators and their purpose as viewed from an industrial perspective has recently been addressed (8,9). Morgan (9) noted that there is a current need to determine what role chemical calibrators should play in standardizing dissolution testing. One role, which is as important now as it was at the beginning of the use of calibrators, is the determination of the sensitivity of the data to real differences in dissolution rates and the evaluation of the reproducibility of these data.

The value of the Wood's device in dissolution testing is related with the intrinsic dissolution rate and self-calibrating features of the method. The value of this concept can be generalized to the intrinsic dissolution performance for any specific dissolution device. It is proposed that the sensitivity index of Hamlin *et al.* be used as a quantitative indicator of the intrinsic dissolution performance, which could then be correlated with the test conditions of interest, such as agitation intensity.

A protocol involving visualization coupled with dissolution using physicochemically different calibrators, such a polymorphs, is proposed as being useful in this regard. The protocol would involve visualization studies as a first step in determining the range of agitation intensities where there is a transition from Case I to Case II dissolution. Then, dissolution rate studies would be carried out using both chemical calibrators within a specified range of agitation intensities. The sensitivity to detect real differences at a given agitation intensity would then be evaluated by comparing the percent difference between the resulting dissolution rates. Results from this test would also reveal the variability associated with these data.

A chart *(Table 2)*, similar to the original data presentation given by Hamlin *et al* . (2), would provide information about the resulting reproducibility and sensitivity of the dissolution as a function of the test condition (agitation intensity) for a given device.

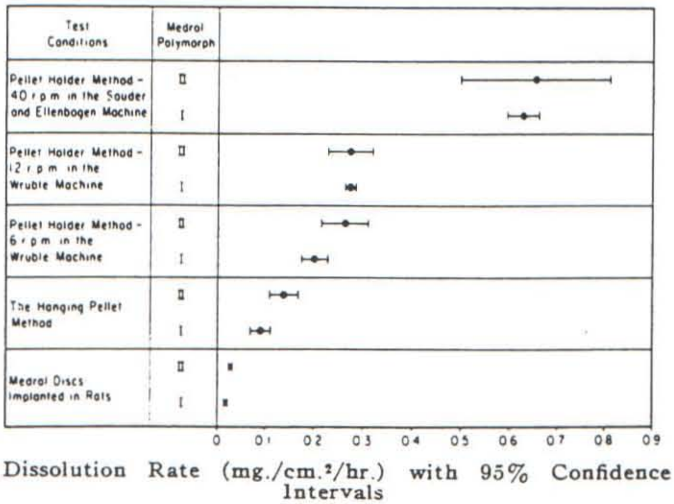

Table 2 - Dissolution Rates and Their 95% Confidence Intervals for Methylprednisolone Polymorphs I and II determined Under Various Conditions (data cited from reference 2).

Unlike the current defined system suitability test, this proposed protocol would establish the intrinsic dissolution performance characteristics of the device. These data could then be used as a benchmark for measuring the intrinsic performance of the device and the range of agitation intensities where both sensitivity and reproducibilty can be achieved when either Case I or Case II dissolution is dominant.

Follow-up mechanical anemometry studies could then be made to correlate the agitation intensity with a measured average fluid velocity and to determine the degree of local fluid flucuation at a given agitation intensity.

Summary

Adolph Fick's laws of diffusion were confirmed using a method where a funnel shaped device held a dissolving material. Fick's innovative method, which included criteria for sensitivity and reproducibiliy, was critical to the successful experimental confirmation of his premise about diffusional processes. There is a need for equally creative solutions for the efficient and effective use of calibrators in connection with dissolution testing.

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