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TALKING POINTS

Determination of Micro-pH in Solid Drug Delivery Systems

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Pharmaceutical formulators have used the term *micro-pH* for many years to define the environment present within a solid drug delivery system at loci close to drug particles. There is, of course, some difficulty in applying the term *pH* to a solid pharmaceutical drug delivery system such as a compressed tablet. However, with the exception of effervescent tablets of the Alka-Seltzer type, most tablets contain about 1–3% of total water, as may be quantified by Karl-Fischer titration. In many instances, most of this total water is probably ''bound'' rather than ''free.'' It is only the ''free'' water that is immediately available for chemical interactions such as hydrolysis of drugs (an alternative way of regarding this situation is by considering the activity of water in the tablet as being very much less than is observed in an aqueous solution).

For drugs susceptible to hydrolysis, it is common to observe that the rate of hydrolysis in aqueous solution is quite sensitive to pH since either one (or both) of the hydronium and hydroxyl ion species may catalyze degradation. Determination of the degradation rate/pH profile of the drug in aqueous solution will often reveal a minimum point or pH plateau at which it may be desirable to formulate an aqueous solution of the drug.

The degradation rate/pH profile in the solid drug delivery system is likely to be of the same shape as that determined in aqueous solution if the reaction mechanism and kinetics are the same. However, because of the greatly reduced water activity, the absolute magnitude of the degradation rate will be greatly reduced. Even so, for drugs that are very liable to decompose in the presence of water, there may well be an advantage to including in the drug delivery system a moiety with the function of adjusting the pH of the environment in the immediate vicinity of the drug so that the micro-pH is believed to be optimal for the stability of the drug.

Consider the example of a drug that degrades very rapidly at pH values below neutrality, but is much more stable in the pH region 7 to 10. For such a drug, there may be good reason to formulate a tablet or capsule so that the micro-pH is within the range 7 to 10. Thus, we might decide to include some pharmaceutically acceptable alkaline material in the product.

The question may then arise: How do we measure the micro-pH of such solid systems? Clearly, it would be quite invalid to add a relatively large volume of water to the tablet (say, 10 ml) and measure the pH of the resultant solution/suspension. The diluting effect of this vast excess of liquid water would obviously greatly reduce the hydroxyl ion activity by several orders of magnitude. Such an exercise would indicate a micro-pH that could easily be 1 to 3 pH units lower (i.e., closer to neutrality) than the true value.

It seems to me that there may be at least three possible approaches that could lead to a valid—although probably not very precise—estimate of micro-pH.

The first method, termed the *catalytic effect method*, relies on measurement of the amount of drug degraded in tablets containing the same amount of drug and of the same general formula, made on the same press with identical compaction settings, varying only in (*a*) the amount of total water and (*b*) the amount of alkaline reacting substance. It would be desirable to use a fractional factorial design for such a study. Suppose we examined systems with a total water content of 0.1%, 0.5%, 1.0%, 1.5%, 2.0%, 2.5%, and 3%, and we were able to demonstrate that, at 25°C, the rate of drug decomposition in the systems with 0.1% total water was not significantly different from zero, then we could reasonably conclude that the degradation observed in the other systems was due to free water. If we decided to formulate our products at 1.5% total water, we could then estimate the micro-pH in tablets of this water percentage, but with varying amounts of alkaline material, by a comparison of the drug degradation rates observed in such products with the pH stability profile observed in aqueous solution. This method would require quite a large amount of experimental work—such as might be acceptable for a graduate student working in a university—but that would probably be regarded as excessive by formulators working in the pharmaceutical industry. Also, if the pH stability profile for the drug in aqueous solution showed a plateau, this method would not be able to determine the exact micro-pH value on the plateau. It is possible that all that we might be able to conclude is that the micro-pH was somewhere on the stable plateau region.

The two direct methods of measuring micro-pH that many pharmaceutical analysts might prefer to use are spectrophotometry or potentiometry. Using microsurface reflectance spectroscopy, for example, it might be possible to estimate micro-pH after adding a very small amount of a concentrated solution of an indicator to the cut surface of a tablet. However, this method makes two modifications to the system, namely, adding an indicator and adding water. Thus, many analysts might prefer to use a potentiometric method for which only one type of perturbation is applied to the system (i.e., the addition of water).

Using a microcombined electrode system, it may be possible to measure the micro-pH on the fractured surface of tablet using a volume of added water as small as 50 μl. After gentle agitation of the system (which should be kept under a blanket of nitrogen to prevent the ingress of carbon dioxide), a stable pH value should be obtained. Because the buffer capacity of the microenvironment may be very limited, it is essential to take all practical steps to exclude carbon dioxide. Measurements of micro-pH made without the protection of nitrogen (or some other suitable inert gas) will tend to be too low. In other words, the measured micro-pH will be *lower* than the true micro-pH.

The obvious limitation of the potentiometric method, as outlined above, is that it does require the addition of a finite (albeit very small) volume of water to the system. The addition of *any* water to the system will reduce the hydroxyl ion activity, and thus even with a blanket of nitrogen, the observed micro-pH will be *lower* than the true micro-pH.

A possible way of allowing for this dilution effect would be to use the extrapolation to infinite dilution strategy commonly used in physical chemistry (e.g., determination of weight-average molecular weight of proteins by light scattering). To use this approach, we perform a number of potentiometric measurements of micro-pH using different volumes of added water (say 50, 80, 100, 120, 150, and 200 μl). We would probably discover that, as δV (the volume of water added) increased, the observed pH decreased. A plot of measured pH on the ordinates as a function of δV on the abscissa (linearized if necessary using an acceptable polynomial non-lin program) allows the estimate of the true micro-pH, that is, the value that obtains in the absence of any added water.

Of course, even for tablets stored at USP controlled room temperature, some excursions of temperature up to 30°C are permitted. For each excursion, there will be changes in the ratio of free to total water, the solubility of the drug and the degradation rate constant of the drug. Predicting the effect of such changes would be very complex.