# Unusual Dissolution Behavior Due to Film Formation

*Sir:*

We have recently studied the dissolution of salicylates in basic aqueous media employing a procedure described previously (1). Dissolution ordinarily takes place at a constant rate under the experimental conditions referred to, since surface area and concentration gradient across the diffusion layer remain essentially constant. Thus, a plot of amount of substance dissolved *vs.* time is linear as shown in the dissolution of acetylsalicylic acid (ASA) and aluminum acetylsalicylate (Al-ASA) in 0.1 *N* hydrochloric acid (1). While a similar linear relationship is obtained in the dissolution of ASA in basic aqueous media, the dissolution rate of Al-ASA does not remain constant but decreases with time until it becomes very low. This decrease in dissolution rate of Al-ASA is due to the formation of a basic, water-insoluble aluminum compound on the surface of the drug solids. Addition of EDTA to the dissolution medium prevents the formation of such a film by chelation of $Al^{+++}$ and, consequently, the dissolution rate in this medium remains constant under the experimental conditions. The weight loss of an Al-ASA pellet after partial dissolution in a basic aqueous medium containing EDTA is consistent with the amount of salicylate found in solution. In the absence of EDTA, the weight loss of an Al-ASA pellet is less than the theoretical weight loss (as calculated on the basis of the amount of salicylate in solution), the added weight being due to the deposited layer of the basic aluminum compound. A more detailed discussion of this phenomenon, its mathematics, as well as a description of the effect of variables such as pH, type and capacity of buffer, and stirring rate will be included in a future publication.

Our observations may have biopharmaceutical implications as indicated by a consideration of the gastrointestinal absorption pattern and dissolution behavior of Al-ASA. Salicylate given in the form of this drug is much more slowly absorbed than when given as ASA and is, in fact, not fully available to humans under the experimental conditions of a study described in a previous report from this laboratory (1). Despite the slow and incomplete absorption of salicylate after Al-ASA administration, the absorption peak occurred at the same time as after ASA administration, instead of being delayed as would be expected. The slower absorption of salicylate from Al-ASA can be explained on the basis of the slower dissolution of this drug, as compared with ASA, but the relatively early absorption peak cannot. The latter is apparently due to the deposition of the described film on Al-ASA solids in the small intestine. Thus, drug dissolution and absorption occur at a maximum rate during the early post-ingestion period when Al-ASA is in an acidic environment where no film formation takes place.

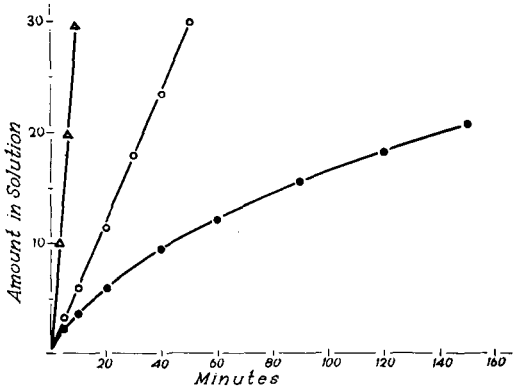


Fig. 1.—Dissolution of ASA and Al-ASA in 0.1 *M* Tris buffer of pH 8.0. △ ASA, ● Al-ASA, ○ Al-ASA with 1% EDTA added to dissolution medium. (Amount in solution expressed as mg. of salicylic acid.)

Film formation as a factor which may affect drug dissolution and absorption has, to our knowledge, not been described previously and is reported at this time in view of its biopharmaceutical implications.

(1) Levy, G., and Sahli, B. A., This Journal, **51**, 58(1961).

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