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Letter to the Editor

Dear Editor:

In in earlier commentary, D'Arcy and Worthen (1988) raised the issue of assuming that inactive ingredients have no or minimal effect on the performance of a pharmaceutical dosage form. The authors pointed out it is the innovator, or brand name, product which establishes the performance profile for the entire pharmaceutical preparation. Current regulations require generic copies to test the equivalence of the active ingredient. However, inactive ingredients typically are not considered in the review process.

We are reporting the effect that a dye can make on a modified release dose form to demonstrate that inert ingredients can influence final product attributes in ways that may not be anticipated or tested for in generic products.

In 1988, Procter & Gamble Pharmaceuticals (formerly Norwich Eaton Pharmaceuticals) changed the physical appearance and characteristics of Entex LA®, a delayed release tablet containing guaifenesin 400 mg and phenylpropanolamine 75 mg in a Carbopol™ (carboxypolymethylene) matrix. The marketed product was uncoated and contained a blue dye. A film coating was developed to increase patient acceptability, such that the film coating would hydrate quickly when ingested to facilitate swallowing and mask the unpleasant taste associated with guaifenesin. The original tablet contained 3 mg of FD&C Blue no. 1 Aluminum Lake dye which represented $< 0.5\%$ of total tablet weight. When the dye was removed from the tablet in initial experiments, the dissolution was shown to be faster than the upper dissolution specification limit at 1.5 h. There was an increase of 27% dissolution of phenylpropanolamine at 1.5 h; the dissolution rate for guiafenesin increased by 39% at 1.5 h when the dye was removed. The blue lake dye appeared to interact with the Carbopol matrix to significantly delay the dissolution rate of the active ingredients. Lake dyes are pigments formed by the precipitation and adsorption of a dye onto an alumina hydrate insoluble base. In this case, the low level of lake dye enhanced the polymer hydration rate necessary for acceptable dissolution. In the development and testing of the orange film-coated Entex LA, a yellow lake dye was added to the core tablet to reduce the dissolution rate to the extent that the final tablet met established dissolution specifications for both active ingredients.

This example underscores the need for caution when changing dose form excipients generally considered to be inert. This caution is especially critical in modified release dosage forms which are designed to retard delivery or provide consistent sustained delivery.

Sincerely,

Richard J. Dansereau, Ph.D.
Dennis B. Worthen, Ph.D.

Reference

D'Arcy, P.F. and Worthen, D.B., The product is the sum of its parts. *J. Clin. Pharm. Ther.*, 13 (1988) 313–315.