Historically, preformulation evolved in the late 1950s and early 1960s as a result of a shift in emphasis in industrial pharmaceutical product development. Up until the mid-1950s, the general emphasis in product development was to development elegant dosage forms, and organoleptic considerations far outweighed such (as yet unheard of) considerations as whether a dye used in the preparation might interfere with stability or with bioavailability.

In fact, pharmacokinetics and biopharmaceutics were in their infancy, and although stability was a serious consideration, most analytical methodology was such that even gross decomposition often went undetected.

It was, in fact, improvement in analytical methods that spurred the first programs that might bear the name "preformulation." Stability-indicating methods would reveal instabilities not previously known, and reformulation of a product would be necessary. When faced with the problem of attempting to sort out the component of incompatibility in a 10-component product, one might use many labor hours. In developing new products, therefore, it would be logical to check, ahead of time, which incompatibilities the drug exhibited (testing it against common excipients). This way the disaster could be prevented in advance.

A further cause for the birth of preformulation was the synthetic organic programs started in many companies in the 1950s and 1960s. Pharmacological screens would show compounds to be promising, and pharmacists were faced with the task of rapid formulation. Hence they needed a fast screen (i.e., a preformulation program) to enable them to formulate intelligently. The latter adverb implies that some of the physical chemistry had to be known, and this necessitated determination of physicochemical properties, a fact that is also part of preformulation.

1. PREFORMULATION'S PLACE IN THE STABILITY FUNCTION

The approach of preformulation was so logical, indeed, that it eventually became part of the official requirements for INDs and NDAs (Schultz, 1984):

> New drug substances in Phase I submission. For the drug substance, the requirement includes a description of its physical, chemical or biological characteristics. We in the reviewing divisions regard stability as one of those characteristics. The requirement of NDA submissions ... of the rewrite stability information is required for both the drug substance and drug product. A good time to start to accumulate information about the appropriate methodology and storage stations for use in dosage form stations for use in dosage form stability studies, therefore, is with the unformulated drug substance.... Stress storage conditions of light, heat and humidity are usually used for these early studies, so that the labile structures in the molecule can be quickly