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PACKAGING DRUGS AND PHARMACEUTICALS

Wilmer A. Jenkins
Formerly Director
Packaging Products Division
Polymer Products Department
E. I. du Pont de Nemours & Company, Inc.

Kenton R. Osborn
Formerly Technology Manager
Packaging Products Division
Polymer Products Department
E. I. du Pont de Nemours & Company, Inc.

TECHNOMIC PUBLISHING CO., INC.
LANCASTER · BASEL

Packaging Drugs and Pharmaceuticals
a TECHNOMIC® publication

Published in the Western Hemisphere by
Technomic Publishing Company, Inc.
851 New Holland Avenue, Box 3535
Lancaster, Pennsylvania 17604 U.S.A.

Distributed in the Rest of the World by
Technomic Publishing AG
Missionsstrasse 44
CH-4055 Basel, Switzerland

Printed in the United States of America
10 9 8 7 6 5 4 3 2 1

Main entry under title:
Packaging Drugs and Pharmaceuticals

A Technomic Publishing Company book
Bibliography: p.
Includes index p. 347

Library of Congress Catalog Card No. 93-60377
ISBN No. 1-56676-014-3

The Relative Importance of Product Protection in Package Selection

In theory, product protection is the most significant determinant. The drug manufacturer's primary concern is that the drug product gives the consumer all of its benefits when it is used. Adding to this motivation are federal regulations and concerns about lawsuits stemming from product failures. In practice however, the vast majority of drugs do not have demanding protection requirements (such as an absolute barrier) as seen in Table 8.1. Also, there is usually a variety of alternative package possibilities for the level of protection required. Therefore, in practice, meeting product protection needs is generally not highly restrictive in determining package choice. This is reflected in the growing use of plastic packaging for all dosage forms but especially for oral solids, where 70–80% are in plastic bottles [12]. The exceptions to this generality are noteworthy, however, in that much attention has been given to them in packaging studies reported in the literature.

Compatibility

For product protection, *USP* recommendations are specific about package type since they depend only on the properties of the drug. By contrast, specific compatibility recommendations cannot usually be made since interaction of a drug with a package depends on the chemistry of both the drug and the package. But there are exceptions; for some injectable fluids, *USP* recommends "glass only" or "Type I glass only," etc. Among the 33 drugs that did not fall into one of the 35 general categories in Table 8.1, there are a few cases where specific restrictions related to compatibility are given: glass or PE, nonmetallic, plastic container and collapsible lined or coated tube.

Thus the packager has the responsibility to be certain that "the container does not interact physically or chemically with the article placed in it so as to alter the strength, quality, or purity of the article beyond the official requirements" [13]. While there are a few compatibility problems with glass (a prominent case being with nitroglycerine preparations) and with metal containers for corrosive drugs, the concern has been primarily with plastic packages. Beginning in the early 1970s many compatibility studies of

drug/packaging systems were conducted. For sterile dosage forms, an excellent summary was published in 1984 by Wang and Chien. They summarize in one table the results of sorption studies on 115 different drugs [14]. A significant change (discoloration or 10% or greater absorption of the drug) occurred in 36% of the systems studied. While compatibility problems are considerably less common for other dosage forms, they have been encountered, and quantitative analysis of the problem is not always easy.

The term compatibility encompasses three different consequences of chemical interaction between the package and any of the components of a drug product formulation. The first results in actual reduction in drug availability or potency through sorption—the removal of the drug by the package. The second results in contamination as the formulation extracts substances from the package. The third causes breakdown of the package by deterioration of its strength, stiffness or barrier properties as the formulation chemically attacks the package.

Sorption

When formulation components are removed by a package two different processes are involved: adsorption onto the surface and absorption into the package wall by diffusion. A component may also desorb from the outer surface of the package and pass into the atmosphere if it is volatile enough. Strong adsorption or absorption requires a strong chemical interaction between the component and the packaging material. In addition, for a high level of absorption the packaging material must be permeable to the component. Glass has a chemically active surface but is an absolute barrier so that while adsorption can be strong, no absorption occurs. For plastics, on the other hand, both adsorption and absorption are possible. In the literature, when adsorption and absorption occur together, there is rarely a distinction made between the two and therefore the term sorption will be used to indicate both are taking place.

The usual method for measuring sorption is to soak a known quantity of the packaging material, usually a thin film or section of the container wall, in a solution of the drug product or in the formulation if it is a liquid. Either the amount of a component lost from the solution or the weight gain by the packaging material is measured. Of course, sorption studies of actual product/package

systems have also been made. When a multicomponent formula is involved, separation of the interaction of the different components is much more complicated. In one example of a sophisticated technique used for this purpose, phenylephrine, a decongestant, was labeled with radioactive carbon and placed in PE nasal spray bottles. Concentration changes of the active drug alone were followed using internal liquid scintillation spectrometry which distinguished the phenylephrine interaction from those of the other components in the formulation [15].

There have been many studies of sorption kinetics leading to a number of different mechanisms and equations aimed at predicting rate of sorption and its dependence on key variables such as drug composition, plastic type, and temperature. However, as Wang and Chien conclude: "Given the conflicting results in the literature, it is difficult to predict sorption activity. It seems more appropriate, at this stage of knowledge, to study such activity, rather than try to predict it" [16].

Leaching

Leaching is primarily a problem with IV fluids and large volume parenterals. Widely studied examples are the leaching of plasticizers from PVC IV bags, extraction of additives from rubber closures and corrosion of glass surfaces. Most leaching problems occur with plastics because of the presence of additives such as fillers, activators and plasticizers. Leaching can cause discoloration, precipitation, change in pH, and contamination that can lead to increased toxicity or instability of the drug.

The *USP* describes several tests for leaching [17]. For glass, a powdered sample in purified water is autoclaved at 121°C and the water is then tested for the amount of alkali present. This test is used to confirm that a container intended for injectable fluids is made of the appropriate type of glass. For plastics, purified water at 70°C is used as the extracting medium for containers. The water is then examined for volatile, nonvolatile and heavy metal residues as well as acidity and alkalinity. In addition biological tests are performed in two stages: *in vitro* tests on cultures of mammalian fibroblast cells and *in vivo* tests on small animals. Materials that fail to meet the requirements of the *in vitro* tests must undergo *in vivo* testing. For the *in vitro* tests, plastic samples are extracted with saline solution at either 50°, 70°, or 121°C de-

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