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Formulation of protein drugs into products using this type of preformulation data base is well documented [72] in the literature. It is also a subject of a separate chapter of this book.

VI. PREFORMULATION SCREENING OF PARENTERAL PACKAGING COMPONENTS

One of the more difficult and often time-consuming requirements during parenteral product development is the selection of compatible packaging components, generally comprised of glass, elastomeric closures, and plastics. Although the dividing line between where preformulation stops and where formulation and package development studies begin may be defined differently among industrial organizations, preformulation work done toward package selection is often critical to the early smooth development and progression of a parenteral product. In many cases extension of expiration dates of parenteral products are limited to a physical incompatibility involving elastomeric closure and/or glass interaction with the formulation.

For example, the investigation for a compatible elastomeric closure and multiple-dose vial can be approached by screening studies initiated at a later stage of preformulation or, if need be, initially for those requiring the use of multiple-dose vials throughout the development program.

A. Closure Selection Process

Basic considerations for the selection of a compatible closure formulation are based on numerous factors. Those of high importance at the preformulation stage are physical and chemical compatibility of the closure with the formulation as well as the rate of water vapor permeability, oxygen permeability (if oxidation is a problem), sorption of active and preservative, level and type of extractives, pH change, color change, and particulate matter formulation. These criteria as well as others have been reviewed [83] and presented as guidelines [84] for closure selection. The reactivity of the formulation and presence of certain excipients, such as preservatives, buffers, antioxidants, and chelating agents may influence the general type of elastomer required.

Several general properties of elastomeric closures useful for initial closure screening studies are:

1. Oxygen permeation through butyl rubber is almost 20 times less than natural rubber [83], and is therefore of choice in circumstances where oxidation is likely to cause color formation, color change, or chemical loss.
2. Swelling characteristics of neoprene in oil at 160°C is 7 to 10 times less than for natural rubber or butyl [85], therefore making neoprene a prime choice for oil products.
3. Butyl closures have been shown not to absorb the preservatives benzyl alcohol and methylparaben from solution, whereas natural rubber and neoprene absorbed approximately 10% after 12 weeks of storage at 60°C [86]. Significant loss of preservative in a multiple-dose vial could result in serious microbial contamination following multiple entries.

4. Elastomeric closures contain metallic salts which may be incompatible with certain excipients in a formulation. The presence or absence of closure-derived incompatible ions should be determined by an extraction procedure [87] using distilled water or the formulation vehicle. Should certain metallic ions be present that appear to be incompatible with the product, such as zinc for a phosphate-buffered product, procedures can be designed to remove the surface excess zinc and other group II ions by an appropriate washing and autoclaving procedure using edetate disodium [88].
5. Other tests relating to performance and identity characteristics as well as a list of potential elastomeric closures in use for various product applications is available [89].

B. Closure Screening Experiment

Assuming that the investigator has developed general information as described above and has previous experience with a similar drug product, a series of closures can be identified for screening with appropriate input by the closure manufacturer. For example, if five closure formulations are identified for trial with a solution of drug in water at the appropriate pH, the following types of tests can be run:

1. Place 400 ml of formulation into each of five 1-liter type-I glass bottles or flasks. Into each flask place a sufficient number of whole closures to provide a total exposed surface area of approximately 200 cm^2. The closures should have been previously washed. An example procedure is to wash the closures in a detergent solution such as benzalkonium chloride followed by adequate rinsing and autoclaving for 30 min at 121°C with an appropriate vacuum drying cycle. This will ensure an equal pretreatment for all closures. A blank using the formulation alone is prepared similarly. The flasks are appropriately sealed with either Teflon-lined screw caps or ground-glass stoppers.
2. The containers are placed at room temperature and 35°C on a shaker set at a low rpm rate so that the solution movement is obtained with minimum discernible closure movement to avoid abrasion. Samples are examined at 1- and 2-week intervals for the following:

    a. pH change from initial reading.
    b. Visual comparison of color: Each flask should stand for at least 5 min to allow for settling. A 10 ml sample is withdrawn from the top portion of the sample and placed into an appropriately sized test tube. These tubes are then placed onto a white background and viewed from the top of the test tube down onto the paper. A color ranking is then recorded for each closure formulation versus the water, such as: no change from initial, slight color, pronounced color, and so on. If appropriate, APHA color can be determined as described previously.
    c. Solution clarity: Visual solution clarity is determined from the supernatant liquid of each flask using descriptions such as: clear

with no precipitate, clear with precipitate, cloudy without precipitate, cloudy with precipitate, very cloudy. Samples are ranked in accordance to degree of clarity.

d. Particulate matter: A determination is made by shaking each flask and quickly withdrawing a 50 ml aliquot by pipet and transferring onto a prewashed, preweighed 0.45 μm membrane. The precipitate is washed with 10 ml of fresh distilled water and dried to constant weight. Each membrane is weighed and viewed under a stereoscopic microscope at a 10× magnification. A rank order of sample cleanliness and weight of precipitate is determined.

e. Physical dimensions: Physical dimensions of the closures are checked versus untreated samples to detect swelling, color change, and so on, and hardness.

f. Chemical assay: The chemical assay for active and preservative is determined by the appropriate procedure.

Test parameters are checked at weekly intervals for at least 2 weeks, at which time each closure is ranked and selection of the best two performing candidates is made. If all closures are judged unsatisfactory, additional selections must be made. Experiments using two or more closure manufacturers at the same time may increase changes of success since factors involved in closure product compatibility are still unpredictable. Alternatively, a more rigorous extraction procedure [87] can be employed where closures contained in extraction flasks covered by beakers are autoclaved for 2 hr at 121°C. Following this procedure, tests are run on the extract after cooling to room temperature.

The goal of the screening process should be to identify at least two closures that can be recommended to the formulator for long-term product evaluation.

C. Glass Selection

When possible, glass ampuls should be used during preformulation studies. The work necessary to identify suitable vial and closure systems usually takes much more time than available at this stage. Studies done in ampuls can usually be directly carried over to the formulation stage for use in toxicological and early clinical trials. Ampuls provide the best seal to either exclude oxygen or retain an inert atmosphere if required, and their reactivity with formulations is relatively low compared to glass vials and elastomeric closures, particularly over a wide pH range.

Type I glass, as defined in USP XXII, refers to borosilicate glass, which is generally used for preparations intended for parenteral administration. Type II glass, soda-lime glass that is treated with an agent such as ammonium bisulfite to remove surface alkalinity, is usually used for packaging acidic and neutral preparations. To be classified as such, type I and type II glass must pass a test related to alkalinity of an aqueous extract.

Although such a test defines type I glass, there are subtle differences in the manufacture of type I glass which may affect compatibility [90,91]. Some type I glass is made without added barium ions, and is highly preferred for use with drug solutions containing sulfate ions since leaching of barium from the glass matrix can often result in microprecipitates in the form of very in-

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