

Abstract

Historically, primary packaging materials utilized for Transdermal Drug Delivery Systems (TDDSs) have been successful in protecting long term stability. Recent discoveries have been made for particular drugs in Drug-In-Adhesive (DIA) TDDSs that a dual packaging system comprising primary and desiccated secondary enclosures is required to provide the necessary protection for long term stability. Furthermore, the primary packaging system can be comprised of materials that meet the current Code of Federal Regulations (C.F.R.) Title 16, Part 1700 for Poison Prevention Packaging.

1. Purpose

During the development of a Methylphenidate DIA TDDS, it was noted that once the finished product was packaged into moisture impermeable primary packaging material, relatively high amounts of related substances were formed at both the 25°C/65%RH and 40°C/75%RH formal ICH storage conditions. Further investigation suggested that relatively finite amounts of moisture entrapped in either the TDDSs and/or the sealed impermeable primary packaging environment provided the catalyst for related substances formation. Hence, the solution was to create a packaging system that would allow moisture to be transmitted through the primary packaging material by a desiccant material held within a secondary packaging system that does not allow ambient moisture to transfer through its composition. Finally, the primary packaging material would have low drug absorption and pass requirements for Poison Prevention Packaging.

2. Materials, Sample Preparation, Analytical Methods

2.1 Materials

Methylphenidate DIA TDDS

Methylphenidate Base; Mallinckrodt, Inc
Polysiloxane Adhesive; Dow Corning Corp.
Polyacrylate Adhesive; Cytec
Ethyl Cellulose; Dow Chemical Corp.
Scotchpak™ 1022 Release liner; 3M™
Scotchpak™ 9732 Backing; 3M™

Primary Packaging Material

Example 1 : 1.25mil Barex®/Foil/Paper
Example 2 : 1.25mil Barex®/2mil PET
Example 3 : 1.25mil Barex®/0.92mil PET
Desiccant Salt : Calcium Sulfate

2.2 Sample Preparation

The Methylphenidate DIA TDDS wet blend was produced to render a dry laminate containing 20% Methylphenidate Base, 50% Polysiloxane Adhesive, 15% Acrylate Adhesive and 15% Ethyl Cellulose. Laminate was produced by casting the wet blend on Scotchpak™ 1022 release liner, drying for 7 minutes at RT, then 7 minutes at 85°C in a convection oven. The dried matrix was laminated to Scotchpak™ 9732 backing and had a coat weight of $11.0 \pm 0.5\text{mg/cm}^2$. Units were die-cut from the laminate at 10cm^2 for the subsequent aging studies. The primary packaging material was sealed Barex® to Barex® with a 10cm^2 unit enclosed.

2.3 Analytical Methods

After sealed units were removed from their respective aging conditions, the units and primary packaging materials were placed into separate extraction solutions of acidified methanol. The extraction solution was sonicated for 45 minutes at room temperature. Aliquot samples were then analyzed by HPLC to determine potency, related substances and drug absorption by the primary packaging materials.

3. Results

3.1 Case Study I : 80°C Aging of 10cm² Units

The 10cm^2 units were sealed in primary packaging Examples 1, 2 and 3 at n=3. The packaged units were placed in an 80°C convection oven for 4 days. Packaged units in Example 1 were held at room temperature as a control. After 4 days of accelerated aging, the units and primary packaging materials were analyzed for related substances (%) and drug absorption (mg).

Table I

Example	Total Related Substance	Drug Loss	Absorption
1 (RT)	0.1	0.0	0.108
1 (80)	15.0	14.1	0.209
2 (80)	8.7	7.9	0.176
3 (80)	8.7	6.6	0.107

When the 80°C samples are compared, the results indicate that primary packaging materials utilized in Example 1 had the highest amount of related substance when compared to Examples 2 and 3 as a result of the Foil layers impermeability for allowing transmission of moisture through the material.

3.2 Case Study II : 40°C/75%RH Aging of 10cm² Units

To further investigate the findings of Case Study I, Example 3 primary packaging material was utilized in a long term desiccated and sans desiccated environment. The 10cm^2 units were sealed in Example 3 primary packaging material and placed in desiccators with and without Calcium Sulfate. Subsequently, the desiccators were placed in a 40°C/75%RH incubator for one month storage. Packaged units, n=3, were removed after one month from each desiccator and analyzed for related substances (%). Control units were stored at 8°C/2%RH for one month.

Table II

Example	RS 1	RS 2	Total
3 (8°C)	0.33	0.32	0.65
3 (40°C Des.)	0.34	0.68	1.02
3 (40°C Sans Des.)	2.58	2.27	4.85

The analytical results indicate that the use of a moisture permeable primary packaging material, along with a desiccant, can enhance the long term stability of the Methylphenidate DIA TDDS. Although the choice of the secondary packaging for this study was a Polycarbonate desiccator, with a large headspace, the use of a desiccant to remove the moisture from the environment and packaged units reduced the total related substances by 79% at the 40°C/75%RH storage condition.

4. Conclusion

The experimental design to determine a permeable primary packaging material, high Moisture Vapor Transmission (MVTR), and an impermeable secondary packaging material, low MVTR, along with the use of a desiccant has allowed for long term stability for the Methylphenidate DIA TDDS. The selection criteria of proper packaging materials can be optimized to enhance this two part packaging system. Although the secondary packaging system described in Case Study II was a desiccator, utilizing a flexible or stiff secondary packaging material is possible as a replacement as long as a low MVTR material is selected. Desiccant selection is available in a wide range of designs for convenience of use in the secondary packaging system. Finally, by selection of the proper primary packaging material composition, Poison Prevention Packaging can be attained. The Example 3 primary packaging material was tested as per Consumer Product Safety Commission Protocol and Standards and was shown to pass C.F.R. requirements.