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Review article

Navigating sticky areas in transdermal product development

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ABSTRACT

The benefits of transdermal delivery over the oral route to combat such issues of low bioavailability and limited controlled release opportunities are well known and have been previously discussed by many in the field (Prausnitz et al., 2004 Prausnitz et al. (2004) [1]; Hadgraft and Lane, 2006 Hadgraft and Lane (2006) [2]). However, significant challenges faced by developers as a product moves from the purely theoretical to commercial production have hampered full capitalization of the dosage forms vast benefits. While different technical aspects of transdermal system development have been discussed at various industry meetings and scientific workshops, uncertainties have persisted regarding the pharmaceutical industry's conventionally accepted approach for the development and manufacturing of transdermal systems. This review provides an overview of the challenges frequently faced and the industry's best practices for assuring the quality and performance of transdermal delivery systems and topical patches (collectively, TDS). The topics discussed are broadly divided into the evaluation of product quality and the evaluation of product performance; with the overall goal of the discussion to improve, advance and accelerate commercial development in the area of this complex controlled release dosage form.

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1. Introduction

Since the arrival of the first TDS to the market in 1979, this dosage form has established an important niche route of administration in the pharmaceutical industry [1,2], despite a smaller market share for the dosage form when compared with the broader pharmaceutical market [3]. Slow growth, in terms of the number of transdermal products entering the market each year as compared to other routes of administration, can be attributed to a number of specific factors including:

- A limited number of drug substances for which delivery through the skin is the optimal route of administration;
- Scientific and engineering challenges associated with the design of TDS products;
- A need for specialized knowledge and experience to manufacture and control the quality of these complex dosage forms;
- A lack of clarity regarding certain regulatory expectations for these dosage forms.

Even experienced drug product manufacturers with approved TDS sometimes struggle to maintain the quality of these complex dosage forms. Since 2000, nearly 20 years after the first TDS was introduced, the number of batches of TDS recalled from the market has continued to increase primarily for quality issues such as drug crystallization, reservoir leakage, and adhesive issues [4]. Many common TDS defects can be ascribed to outmoded technologies for product development, manufacture and control. The goal of this review is to provide an overview of common deficiencies and industry best practices for product quality and performance characterization through appropriate design considerations. Mechanisms of drug delivery using TDS are well understood in the literature and therefore not included in great detail in this review [5,6].

2. Product development and quality aspects of transdermal systems

2.1. Raw material qualification and adhesives

Innovation has led to great diversity in the formulation and manufacturing design of TDS. Passive systems can be as simple as a single drug substance dissolved in a single adhesive, or can be highly complex, multi-component, multi-adhesive, multi-laminate matrices. Excipients can include various adhesive systems, permeation enhancers, rate controlling or non-rate controlling membranes, solubilizers, plasticizers/softeners, or tackifiers, all which can influence the quality and performance attributes of the TDS. As such, the characterization and control of key functional excipients like adhesives are critical to support the safety, efficacy and quality of the drug product [7].

Rigorous qualification of adhesives, as well as other key excipients, during the product development stages is exceptionally important. A well-developed knowledge base of the critical parameters and characteristics of adhesives and excipients, both before and after the incorporation of the drug(s) into the matrix, supports the optimization of drug product quality attributes for transdermal formulations. This product and process understanding also facilitates future changes in the manufacturer or manufacturing process of the raw materials [8].

Adequate qualification for the adhesive component of a TDS often includes an assessment of the adhesive at three main stages; (1) as a readily available polymer, (2) as a lamina, and (3) in the final drug product. Qualifying the adhesive as a raw material provides insight into potential differences that may exist for the same adhesive supplied by different manufacturers, or by an altered manufacturing process. Examining the adhesive as a lamina, or in the absence of the drug substance or other drug product excipients, can verify the functional parameters of adhesion and may also assist in identifying the potential impact of any differences in impurity profiles. Finally, assessing the adhesive in the final drug product can help identify unanticipated interactions of TDS components that might affect product performance.

When the adhesive is a readily available polymer, its qualification may include molecular weight distribution, polydispersity, infrared (IR) spectroscopic analysis, thermal analysis, intrinsic or complex viscosity, and measurement of residual monomers, dimers, solvents, heavy metals, catalysts and initiators. When the adhesive is a lamina (without drug or other formulation-specific excipients) its qualification may include IR identification, measurement of residual solvents, extractables and leachables, and an evaluation for peel, tack, shear, and adhesion. When the adhesive is in the final drug product its qualification may include measurement of residual monomers, dimers and solvents, viscosity, loss on drying, impurities, and content uniformity. Functionality parameters to be assessed may include (but are not limited to) peel, shear, adhesion, tack, in vitro release testing (IVRT) with a dissolution apparatus, and in vitro permeation testing (IVPT) with excised human skin mounted in diffusion cells [9].

The United States Pharmacopeia (USP) General Chapter <3> Topical and Transdermal Drug Products briefly highlights four in vitro adhesion tests; peel adhesion, release liner peel, tack and shear. There are multiple methods and technical nuances for each of the tests. For example, characteristics of the method such as the conditioning time, angle of peel, peel rate, or substrate to which the product is adhered for a given test method can significantly impact the results obtained from each test or the meaningfulness of the result. Ultimately, the TDS manufacturer determines which methods and what acceptance criteria are most suitable for a given product, and justifies them accordingly [10].

In addition to the adhesive characterizations described above, manufacturers increasingly address common issues with product quality and with patient use difficulties observed in the post-marketing setting through rigorous in-process controls and specifications. Cold-flow, the creep or oozing of the adhesive matrix beyond the perimeter of the backing membrane or through the release liner slit, is one example of a product quality issue that is now closely monitored by pharmaceutical and regulatory scientists. Its recent inclusion to USP General Chapter <3> reflects the shared concern of both manufacturers and regulators that adequate control of cold flow is necessary in order for a TDS product to be of acceptable quality for patients. It is generally understood that pressure sensitive adhesives (PSA) used in TDS products routinely exhibit a certain amount of plasticity and flow in order to facilitate adhesion; however, the presence of excessive cold flow may cause a "tacky" ring around the perimeter, make it difficult for the patient to remove the TDS from the pouch and/or release liner, and may result in unintentional exposure to the drug [11]. There is no single metric for assessing cold flow that adequately characterizes dosing, usability, and product stability. A quantitative method of assessing cold flow can provide a meaningful measurement, but it does not necessarily describe the difficulty in removing the TDS from the pouch or the protective films from the TDS. A qualitative assessment by visual observation can describe cold flow in the context of usability, but it may be subjective and might not adequately identify dosing or stability-related issues.

In order to adequately assess cold flow at release and throughout the stability period for a drug product, manufacturers typically use a combination of quantitative and qualitative methods. For example, in the product specification, appearance criteria can assess potential patient use issues caused by cold flow by monitoring whether TDS are difficult to remove from their pouches, whether release liners detach from the adhesive matrix of the TDS, whether backing membranes adhere to the pouch, and whether adhesive residue is transferred to the pouch after removal of the TDS. A complementary quantitative cold flow method can characterize the degree to which cold flow extends beyond the perimeter of the backing membrane, or flows through the release liner slit or is transferred to the pouch lining. Because of the diversity in components and product design associated with this complex dosage form, the onus remains on the manufacturer to determine the most suitable cold flow assessment methods for the individual product. This