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) [1]; 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

flexibility in test method design is necessary, precisely because a single method or set of parameters may not be suitable for every TDS, particularly given the diversity of product design seen with the TDS dosage form.

The inclusion of well-organized and relevant drug product development information in New Drug Applications (NDA) and Abbreviated New Drug Applications (ANDA) is important to demonstrate that TDS product manufacturers have adequately researched and optimized their choice of adhesives and other excipients. Product development reports in NDAs and ANDAs can also help to demonstrate product optimization for release liner designs and packaging configurations, and/or to demonstrate the utility of non-rate controlling membranes within the transdermal matrix to add structural support and potentially decrease cold flow. Additionally, manufacturers are able to set product specific acceptance criteria for cold flow by providing a justifiable basis supported by product development research and statistical assessments of multiple product batches throughout the product's shelf life.

2.2. In Vitro Permeation Test

During the product development stage of the transdermal product lifecycle, an In Vitro Permeation Test (IVPT) using excised human skin is often utilized to evaluate the rate and extent of transdermal drug delivery. Because the skin of humans is structurally and functionally different compared with the skin of other mammals, animal in vivo models are of limited value to characterize the performance of TDS products because of substantial differences in permeability characteristics; porcine skin represents the closest human surrogate for estimating the performance of a transdermal product. Numerous literature references are available [12–21] which describe best practices in the design and performance of IVPT studies to characterize many aspects of TDS performance related to both, the safety and the efficacy of the TDS product. The importance of IVPT characterization of TDS performance is exemplified by its inclusion as an essential component of the EMA Guideline on quality of transdermal patches [22].

Briefly, IVPT studies are routinely performed using two common configurations of a diffusion cell system that allow the skin to be mounted and maintained at a physiological temperature of 32 °C and in a state of hydration. The two configurations include the vertical diffusion cell (VDC) and the flow-through diffusion cell, often referred to as a Franz cell [23] and the Bronaugh cell respectively. The Bronaugh flow-through diffusion cell is distinguished from the Franz diffusion cell by having a receptor compartment whose contents are not static, but rather, are a flowing stream of the receptor solution continuously replaced beneath the skin [24]. In this system, the flow rate, which allows the receptor solution to be eluted and collected for analysis, is optimized during IVPT method development. By contrast, the receptor compartment of the static Franz cell is continuously stirred, but the concentration of permeating compounds continues to build in the receptor compartment between time points, at which the receptor compartment is sampled via a sampling arm. In both configurations, the skin is mounted so that the outer, stratum corneum surface is dry and exposed to the air, and the drug product is dosed to the skin.

Well-conceived IVPT study designs are not necessarily a trivial matter, and it is valuable to report the careful considerations taken during IVPT model development to justify the validity of the methodology. For example, the barrier integrity of all skin sections must be verified prior to dosing, to ensure that the permeability of the skin is not abnormal and to eliminate aberrant skin sections with microscopic holes or tears. Before the barrier integrity test is conducted, the skin is typically mounted in the diffusion cell and allowed to equilibrate to physiological conditions. The barrier integrity is often evaluated using a pulse dose of tritiated water, or an instrument that measures transepidermal water loss (TEWL) or electrical resistance. Once the barrier integrity of a skin section has been verified, the TDS can then be dosed upon the skin.

Dosing (applying) the TDS to the skin section can be challenging once the skin has been mounted on the diffusion cell, as the pressure used to apply the TDS can cause significant deformation of the skin, if there is no support structure beneath it. The deformation is undesirable because it may damage the integrity of the skin barrier or affect the uniform adhesion of the TDS. However, if a support structure, like a mesh, is used when the skin is mounted, then the inertness of the support and its potential impact on the diffusion of drug substances is appropriate to evaluate. An obvious alternative is to dose the TDS while the skin is on the lab bench, so that conventional pressure can be applied during dosing and the skin could thereafter be mounted on the diffusion cell apparatus. However, this presents the logistical issue of verifying the barrier integrity which is typically performed prior to dosing. Applying a TDS to the skin in this scenario would require dismounting the skin for dosing on the lab bench, and then re-mounting it on the diffusion cell. If the TDS adhesion to the skin is not adequate, then certain portions of some TDS may peel or lift off the skin, leading to potential variability in transdermal drug delivery. Depending upon the intent of the study, this may be controlled by using a sparse non-occlusive mesh or gauze clamped upon the diffusion cell atop the TDS to prevent it from lifting. Effectively communicating the design considerations that were taken into account during IVPT method development, and justifying the validity of the optimized procedure are essential to support the validity of any results reported.

Whichever apparatus and technique is utilized for dosing the TDS, appropriate controls are typically utilized and care is taken during the manipulation of the system. Also, critical study design details are typically recorded and reported. These details include the number of skin donors and the number of replicate skin sections per donor per treatment group. A minimum of 3 donors with 3 replicate skin sections per donor per treatment groups is typical for a pilot study, because differences in the permeability of skin among individuals in the population can vary by as much as 10-fold and this corresponds to the variability that can be observed in human clinical studies. Specifically, the skin permeability between donors has been shown to follow a log-normal distribution [25,26]. Ultimately, the number of skin donors and replicates is typically selected to be sufficient to generate representative, interpretable results. For pivotal studies with statistical endpoints, 6 or more skin donors with 4 to 6 replicates per donor per treatment group may be necessary.

Furthermore, details such as the source and storage conditions of the skin prior to its use in the experiment, along with the species, age range, gender, race and anatomical region from which the skin was harvested would provide support and justify the validity of an IVPT study. While storage conditions, age, gender, and race have been investigated as potential sources for observed variability among donors, none have been definitively shown to be a predominant contributor. Conversely, regional variation in skin permeability between different anatomical sites is well documented [27–31]. As such, it is typically considered essential that all test groups compared in an IVPT study are dosed on skin from the same set of donors, and use skin from the same anatomical site from all donors.

Skin type and preparation methods can significantly influence the IVPT study results, thus TDS product manufacturers carefully consider the rationale for the type selected and preparation methods used. For example, full-thickness skin includes the stratum corneum, the viable epidermis, and the entire dermis, whereas split thickness skin is often prepared by dermatoming the skin at the level where the capillary beds would clear permeating compounds into the systemic circulation. Other epidermal preparations may be produced by heat separation, and include only the stratum corneum and the viable epidermis. Furthermore, the IVPT study duration typically captures the permeation profile including peak flux level and, ideally, the complete flux profile returning to the baseline, or a time period corresponding to the labeled period of wear. Deterioration of the skin after a few days in a diffusion cell was not uncommon in the early days of the technique; however the widespread

use of modern water purification systems and the use of antimicrobial agents in the receptor solution have facilitated studies of longer durations. The receptor solution composition is also typically selected to be physiologically compatible with the skin and its barrier, and optimized to provide adequate solubility and stability for the permeating drug(s).

It is essential to determine the solubility and stability of the drug substance(s) in the receptor solution prior to a pivotal IVPT study, experimentally if necessary. The receptor solution is typically selected to provide a minimum solubility that is ideally 10 times greater than the maximum sample concentration expected during the study [12]. Solubility enhancing additives in the receptor solution often include proteins like albumin [32,33] and surfactants like Triton-X100, or Oleth-20; the use of alcohol in the receptor solution is discouraged unless rigorously validated because alcohols in the receptor solution can compromise the skin barrier [34–36]. In addition, the receptor medium pH may alter the pH within the epidermis and influence the permeation of weakly ionizable drug substances from a TDS [37], hence a buffered pH of 7.4 is conventionally utilized for the receptor solution.

Additional study design details that are critical to consider, and report, include diffusion cell apparatus selection, the precise dose area (size of the diffusional area of the TDS), the temperature at which the skin surface (as opposed to the receptor fluid) is equilibrated prior to dosing, the rotational speed of any receptor stirring mechanism, and the method of sampling and/or flow rate for the diffusion cell system. Of course, care is routinely taken to avoid introducing air bubbles under the skin at any time during the experiment, as this may aberrantly decrease the effective diffusional surface area for the drug(s) [35,38]. In summary, TDS manufacturers routinely demonstrate and document the development of a well-controlled and physiologically relevant IVPT method, particularly for inclusion within their drug product applications. By including complete details of the study design, analytical method, and full permeation flux profile results (including summary parameters and raw data) from all studies conducted (i.e. pivotal or optimization), one can better support the study's scientific merits and the validity of the conclusions that can be supported by the results [39,40].

2.3. In Vitro Release Testing (IVRT)

IVRT is utilized as a quality control measure to help ensure the consistency of TDS performance from batch to batch but with minimal relevance to clinical use of the drug product. In a manner analogous to a dissolution test for a solid oral dosage form, an IVRT for a transdermal system is utilized for quality control purposes, but unlike its counterpart oral dissolution test, an IVRT has no physiological relevance and is not expected to exhibit any in vitro/in vivo correlation (IVIVC). The IVRT method and qualified apparatus are well-described in USP General Chapter <724> [41], however, considerations for the validation of this performance test (which is not addressed in USP <724>) are briefly discussed here along with special considerations for the IVRT method design.

Given the complexity of the dosage form, changes in release rate can result from a wide variety of scenarios. Routine issues addressed by this performance test may include detection of unintended variations in product quality and performance as a consequence of a change in manufacturing process, manufacturing site, batch size, or equipment. Sources for variability in drug release rate can arise from changes in the active and/or inactive ingredients, physical or chemical attributes of the final product (i.e. critical quality attributes), shipping, storage, and/or age of the drug product. Therefore, by identifying and facilitating a reduction in variability from these sources, IVRT can serve as a quality control test for product performance during both process development and manufacturing phases of the TDS life [39,42–44].

As detailed in USP chapter <724> [41], IVRT for TDS is typically performed using specific, qualified apparatus: Paddle over Disk (Apparatus 5), Cylinder (Apparatus 6), or Reciprocating Holder (Apparatus 7). Simplicity, reliability, reproducibility, discriminating capability, and

proportionality of release for different strengths (sizes) of a TDS are important considerations when IVRT methods are developed. The description of IVRT methods for TDS products is sufficiently detailed in NDA and ANDA submissions to facilitate an assessment of whether the method would be adequate to support a batch release specification [39,40]. Examples of such IVRT method parameters include the selection of the equipment or USP apparatus, the choice of dissolution/receptor medium, the speed of rotation or agitation employed, pH, analytical assay, sink conditions, use of a surfactant, and other such technical aspects of the test. Of particular importance, evidence validating the ability of the IVRT method to be discriminating is provided. Potential study designs to support an IVRT method's discrimination sensitivity may involve a comparison between drug release profiles of the target (reference) product and test products that have been manufactured by intentionally varying potentially critical manufacturing parameters by 10% to 20% outside the specified control limits [45].

The IVRT method validation report is not to be confused with the validation of the HPLC sample analysis method (which measures the concentration of the drug in the sample of dissolution medium taken during the IVRT). The IVRT method validation report, instead, focuses on the validation of the IVRT method itself (i.e., the measurement of the rate of drug release from the TDS). The report might describe the validation of the HPLC sample analysis method's linearity and range, reproducibility, specificity, sensitivity selectivity and robustness. However, it is equally important to demonstrate the validation of the range and sensitivity of the IVRT method, itself, across different strengths of TDS. The selectivity of the IVRT method to discriminate similar or different release profiles for equivalent and nonequivalent strengths of the TDS product, the reproducibility of the IVRT method across different runs, and the robustness of the IVRT method to changes in receptor medium temperature, paddle rate, or other method parameters are just a few items that assist in validation of the IVRT method.

IVRT method development includes multi-point drug release profiles for a duration until there is no increase over 3 consecutive time points. These release profiles are ideally characterized for the TDS lots used in the clinical trials, as well as each batch associated with stability studies. The release specification for a TDS product typically encompasses the initial, middle, and terminal phase of the complete drug release profile, thus requiring at least three sampling time points for the acceptance criteria. The acceptance criteria are conventionally based on the cumulative percentage or amount of drug released at these specified times. The percentage of drug release at the last time point is not less than the percentage of drug permeated based on residual drug analysis and/or pharmacokinetic data. Ultimately, an appropriately developed and validated IVRT provides a practical method to monitor for variations in product quality that may affect the performance of the TDS and to verify the consistent quality of each batch of the drug product [39,40].

2.4. Special considerations for stability and additional quality control

As previously discussed, comprehensive product development information has become increasingly critical in order for industry and regulatory scientists to assess whether post-approval batches of a complex TDS can be manufactured to reliably meet the needs of the patient. For example, it is recognized that the transfer of the in-process drug product from one stage to the next is not always immediate in any non-continuous manufacturing process. For a variety of reasons, adhesive mixes may be held for a period of time before being transferred to casting, drying and laminating. Similarly, after laminating, the bulk matrix may be rewound and stored for a period of time before being transferred to die cutting and pouching. Anytime there is an interruption in a manufacturing process, whether intended or not, it is important to characterize the effects that such hold times have on the finished drug product. Data from in-process sampling and other quality control measures can help support a conclusion that there is minimal or no impact

on the final drug product. Additionally, if individual products are held for a period of time prior to release to the marketplace, the product development studies and results justifying the selected hold time or equilibration period are important to report.

Because transdermal matrices are not rigid structures, a variety of developmental investigations or even post-market explorations may be necessary to assure high pharmaceutical quality over the life of the product. Just as pressure sensitive adhesives must have a degree of flow in order to adhere to the skin, the extent of rigidity may also impact the migration of drug substances and excipients within the matrix. Many TDS formulations include multiple non-miscible adhesives, solubilizers, permeation enhancers, internal membranes, or many other possible excipients, and the physical and chemical properties of these components may induce characteristic microstructures. For example, certain drug substances may have an affinity to form adsorbates with crospovidone, a commonly used excipient. While this may be advantageous to limiting crystal formation in some formulations, it can significantly impact drug delivery in a number of ways ranging from variations in molecular dispersity, to increased water uptake into the matrix. If the inherent molecular dispersity changes over time, drug delivery or adhesion properties may be influenced [46].

A similar set of issues can potentially occur in TDS products utilizing two non-miscible adhesives, one for solubilizing the drug and the other for adhesion of the TDS. Should rearrangements of the emulsion-like system occur over time within the matrix, adhesion issues or changes in drug delivery and release are possible. As such, it may be critical to develop a well-characterized understanding of the drug product, characterizing where the pharmaceutical ingredients are within the adhesive matrix, and what changes the matrix may undergo from the time of manufacture until product expiry. Therefore, it can be highly informative to visually assess the surface and cross-sectional changes in drug product matrix via high-powered microscopy, elemental mapping, or other scientific means [45]. The goal of this intensive product and process understanding is to ensure the development of a consistent, safe and effective drug product. Specifically, one that can be manufactured and marketed throughout its intended shelf-life with a mitigated risk of product quality related recalls.

Another common concern with the long-term stability of TDS is the crystallization of the drug substance in the matrix. In 2008, Schwarz Pharma Manufacturing recalled its rotigotine transdermal system, Neupro®, for crystal formation of the drug substance in the drug product [47]. More recently, Ortho-McNeil-Janssen Pharmaceuticals recalled lots of its Duragesic® (fentanyl transdermal system), due to crystals observed in the TDS matrix [48]. Given that the majority of drug substances used in TDS formulations are solids, and must be dissolved into adhesive matrices or other delivery vehicles, the potential for drug recrystallization is significant. Microscopic methods can be employed to monitor for the presence of crystals, and acceptance criteria for the batch release and stability specifications can be established that are scientifically justified and clinically relevant. In order to develop an appropriate level of product and process understanding surrounding crystallization, manufacturers perform stability challenging studies such as crystal seeding, temperature cycling, photostability, freeze/thaw, and may be able to predict the likelihood that crystallization will occur in individual TDS formulations during storage.

TDS products may be intentionally designed to contain solid drug substance particles, forming a suspension-like matrix. Despite the desired presence of some amount of solid drug substance in such formulations, a degree of quality control is required in order to assure that the TDS drug product performs the same from batch to batch and throughout stability. Establishing regular tests, justified acceptance criteria and a body of evidence that describes the proliferation of crystals with regard to the number of crystals, their size, and their polymorphic form are an essential part of the overall control of TDS product quality.

Also, stability studies need to consider the impact of the identifying label on the backing membrane, itself, as well as on the stability of the TDS product. In general, TDS backing membranes are labeled with, at minimum, the drug product name and strength, and are designed to be visible throughout the duration of wear as well as after product disposal [49]. Regardless of the actual marketed wording, it is prudent for TDS manufacturers to incorporate a representative identifying label using the desired labeling technique into the manufacturing process in the early phases of clinical trials, in order to adequately assess the impact of that label on stability. Methods of applying the identifying label can be unique to the individual product. Ink printing, embossing, debossing, or laser etching, are just a few of the techniques that have been explored over the history of TDS manufacturing; each exhibiting advantages and disadvantages. In a manner similar to the characterization of the backing membrane, any inks utilized are assessed for leachables and extractables since the inks are expected to not interact with the drug product throughout the duration of shelf-life. Embossing, debossing, and laser etching are physical methods to label a backing membrane, which if applied after the drug/adhesive matrix has been laminated, may introduce physical stress to the matrix and lead to crystal formation or other undesirable issues associated with the TDS product quality. As such, choosing an appropriate labeling technique and evaluating the incorporation of a representative label early in development is important to assess its compatibility. Additionally, the regulatory acceptability of an identifying label often requires a multidisciplinary decision making process to account for the quality of the drug product as well as the readability of the label and concerns for medication errors.

2.5. Quality by design

For several years, regulatory agencies have been encouraging pharmaceutical product manufacturers to embrace Quality by Design (QbD) principles as part of a strategy to mitigate many quality related issues across the field of pharmaceutics [50]. While it is recognized that complex dosage forms present several challenges limiting the adoption of a comprehensive QbD manufacturing process, it may be feasible and beneficial to incorporate several aspects of QbD discussed in ICH Q8, Q9 and Q10 throughout product development and manufacturing. A well-designed QbD approach to product development can facilitate the identification of critical quality attributes (CQAs) that can affect product purity, strength, drug release, drug delivery and stability. Furthermore, systematic risk assessments and QbD characterizations can support identification of appropriate controls for manufacturing process variables in order to produce TDS products with acceptable CQAs. Risk assessments can also help to define the sensitivity or robustness of raw material characteristics, hold times, equilibration periods, and other manufacturing considerations that may be relevant to TDS products. Conceivably, CQAs for a particular transdermal product may encompass everything from the traditional aspects of adhesion properties and in vitro release to attributes that have more recently become evident due to quality related deficiencies in the marketplace such as cold flow, residual solvents, residual drug, and reservoir seal. Similarly, quality target product profiles (QTPPs) may touch on in vivo and in vitro delivery rates, residual drug in the TDS, adhesion to skin, lack of irritation to the skin, and avoidance of dose dumping. Ultimately, the incorporation of QbD into the transdermal development program helps to manage the risk of failures in product quality that can arise due to the complexity of the dosage form and its manufacturing. By defining CQAs and QTPPs during pharmaceutical development, and by developing a control strategy based upon a comprehensive product and process understanding, TDS manufacturers may be able to better control the quality of these complex dosage forms [8].

2.6. Biowaivers for the transdermal products

The term biowaiver refers to a regulatory waiver of the requirement for evidence of in vivo bioavailability (BA) or bioequivalence (BE) in

accordance with Title 21 of the Code of Federal Regulations (CFR) Part 320 Section 320.22 (i.e., 21 CFR 320.22). For most TDS systems, the BA of a drug molecule is typically limited by the permeability of the skin to that molecule (in the context of the TDS formulation's interaction with the skin), and as such a biowaiver may not be applicable for all transdermal systems [22]. For example, reservoir systems in which varying strengths of a product are dependent on differing concentration of drug in the reservoir rather than a change in surface area may not exhibit dose proportionality. Conversely, for matrix-type systems, one or more lower strengths can sometimes be granted a waiver as long as the different strengths of the transdermal products can be manufactured from the same laminate and the strengths are proportional to surface area. In this case, various strengths are considered proportionally similar in their active and inactive ingredients and it is assumed that the transdermal bioavailability of the drug at a given point in time is consistent per unit area of skin and that the change in bioavailability is therefore proportional to the change in the TDS size. Acceptable results from the proposed pivotal BA/BE study for the highest strength in combination with in vitro drug release profile comparison studies demonstrating similarity (using the f2 approach) to the highest strength typically support such biowaiver requests. The principles of modified-release dosage forms are typically applied for matrix type transdermal products in terms of demonstrating in-vitro release profile similarity requirements [51]. An obvious caveat to the latter is that a discriminating IVRT method has been properly developed and that all batches manufactured are of adequate and consistent quality.

A biowaiver may be applicable for pre- and post-approval site and minor process changes. Formulation changes, such as a change in adhesive or adhesive supplier, require special consideration as even slight modifications in a formulation can change adhesion, irritation and potentially the delivery of the drug substance. Studies to establish comparable BA/BE between two transdermal products after site, process or adhesive changes are important elements in support of INDs, NDAs, ANDAs and their supplements. In comparative BA/BE studies, the systemic exposure profile of a reference drug product (before the change) is compared to that of a test drug product (after the change). For the products to demonstrate equivalent BA or BE, the active drug ingredient or active moiety in the test product must exhibit the same rate and extent of absorption as the reference drug product. The regulatory definitions and the procedures for determining the BA or BE of drug products are provided in Subparts A and B, respectively, of 21 CFR 320.

In the case of INDs and/or NDAs, BE information can be useful to establish links between (1) early and late clinical trial formulations; (2) formulations used in clinical trial and stability studies, if different; (3) clinical trial formulations and to-be-marketed drug product; and (4) other comparisons, as appropriate. In each comparison, the post-change product is the test product and the original is the reference product.

In case of a new site, process change, changes in components or composition, and/or change in adhesive supplier after approval, BE is typically demonstrated in vivo. Typically for approved products, the drug product after the change is compared to the drug product before the change. Post-approval changes requiring completion of studies in accordance with 21 CFR 320 are typically submitted in a supplement and approved by FDA before a drug product made with the change can be marketed in the United States (also see Section 506A(c)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) under Title 21 of the United States Code Section 356a(c)(2)(B)).

3. Evaluation of transdermal system performance

3.1. In vivo skin adhesion

Skin adhesion is critical to deliver the intended dose and therefore provide a consistent efficacy and safety profile. The lack of adequate adhesion can cause an adhesive surface to get caught on clothing and be further detached, and may also result in a safety concern due to potential person-to-person transfer when a transdermal system is partially or fully detached. Optimizing skin adhesion is a challenging balance between the need for secure adhesion to the skin during the application period and the need to prevent skin irritation during wear or damage to the skin upon removal. The patient would also prefer that the TDS is easily separated from the release liner at time of application and is easily removed from the skin at the end of application period.

Regulatory Agencies recommend adhesion testing to support the approval of TDS and generally recognize that in vivo skin adhesion studies provide the greatest prediction of adequate adhesion for the proposed commercial drug product during use. Typically, clinical investigators are encouraged to allow subjects to freely conduct their daily activities to simulate real world conditions. The effect of water on in vivo adhesion is also of interest, particularly if the product is intended to be a multi-day or a chronically worn TDS. The adhesion study conducted typically utilizes a TDS product representative of the to-be-marketed formulation, as changes in design, excipients, or even manufacturing process can impact the adhesion properties of a TDS. In general, during the in vivo adhesion evaluation the TDS is used as proposed and product reinforcement such as taping the edges, use of overlays or occluding the product from water during bathing is not recommended during the in vivo adhesion evaluation [52].

3.2. Ex vivo TDS residual drug analysis

Materials science, engineering and chemistry also contribute to key design considerations during product development, such as minimizing the drug load of the TDS, and minimizing the amount of drug remaining in the TDS following patient use. This residual drug amount is an important safety consideration, even if the TDS is not retained on the patient beyond the labeled period of wear. Environmental safety concerns such as abuse of previously used products or the unintentional and potentially fatal exposure of a child to the residual drug in the TDS are of considerable concern [53]. The measurement of residual drug in the TDS is not only associated with the safety of the drug product; it is also a methodology by which the potential efficacy of the TDS can be characterized. Residual drug analysis following TDS wear is a common method by which to quantify the amount of drug delivered during the dosing period, and to calculate the rate of drug delivery, and the strength of the TDS drug product. As such, the residual drug content is a characteristic of TDS product performance that is associated with both product safety and efficacy.

Conventionally, TDS are designed to contain a significant amount of excess drug at the end of the wear period to ensure sufficient thermodynamic activity for zero order delivery at a clinically effective rate during the period of wear [22]. Theoretical calculations based on information available in labeling for commercial products indicate that residual drug in transdermal systems can range from 10 to 95% depending on the product design [54]. While a certain amount of excess drug load may be necessary to facilitate a sustained drug delivery rate, TDS manufacturers are expected to make reasonable efforts to minimize this drug excess.

The FDA Guidance for Industry-Residual Drug in Transdermal and Related Drug Delivery Systems [54] was issued by the FDA in 2011 to address some of the issues pertaining to residual drug in the TDS from a safety perspective. The guidance recommended methods to minimize residual drug by using appropriate scientific approaches during product development and manufacturing. The guidance recommends the use of good product and process understanding and QbD to minimize the residual drug in a TDS.

Generic TDS are not required to be qualitatively (Q1) and quantitatively (Q2) similar to the reference listed drug (RLD) product. Instead, generic TDS are required to demonstrate BE to the RLD in vivo and thus are expected to deliver drug at essentially the same nominal rate as the RLD, but to achieve this often despite using excipients (e.g.

adhesives, permeation enhancers, etc.) that differ from the RLD. Innovative TDS designs can leverage advances in TDS science and technology to reduce the drug load, as compared to the RLD or to mitigate any safety concerns that might arise from having a residual drug load that exceeds the RLD [44].

Of course, the amount of residual drug in a transdermal system may also provide a measure of its maximum drug delivery rate and strength. Based on the EMA guidance [22], the strength of a TDS is the mean dose delivered per unit time, e.g. mass delivered in vivo per hour. The EMA guidance specifically recommends characterization of drug product strength (proportionality of strengths, if necessary) and residual drug based on pivotal clinical studies. Although the FDA has not published a similar Guidance for Industry regarding the characterization of strength/rate for transdermal systems, manufacturers of transdermal products have typically utilized one or both of two different methods to characterize the nominal strength of their products: 1) determination of strength (drug delivery rate) for a transdermal system by using pharmacokinetic data or 2) determination of strength for a transdermal system by residual drug [55–57]. The first involves deriving a clearance (Cl) value from absolute BA of the drug and multiplying that by the concentration (C_{ss}) at steady state [58]. The second approach involves measuring the amount of drug left in the TDS at the end of the wear period and dividing the consumed amount of drug by the period of wear. Both approaches have different advantages and disadvantages based upon the assumptions that are employed in the calculation of rate. The pharmacokinetic approach provides a rate measured in the systemic circulation however, it assumes that the clearance of the drug is constant between the TDS and the intravenous product that was used to estimate the clearance value. The residual drug approach, while perhaps less burdensome clinically, assumes that the amount of drug depleted from the TDS is the delivered amount. This assumption may not be true if there is, for example, drug metabolism in the skin, drug metabolism by bacteria on the skin, drug loss due to sweat, or other unaccounted drug losses.

In the absence of well-defined standards, or a widely accepted protocol for conducting residual drug studies to characterize strength or performance, TDS manufacturers adopt a variety of approaches which may vary in their degree of robustness. Industry best practices for a well-designed residual drug study are described below:

1. Pivotal in vivo studies are conducted in humans. It is not considered adequate to establish the delivery rate or product strength based upon in vitro studies, or upon a calculation of a theoretical delivery rate based upon known drug load and nominal delivery rate.
2. Tape or overlays are not used in studies where the TDS will be used to calculate residual drug, unless the use of an overlay is necessitated by the product label.
3. TDS adhesion assessments are conducted over the entire period of wear to evaluate whether the TDS diffusional surface area remains in full contact with the skin during the entire period of the study.
4. In an attempt to calculate and report mass balance, drug is quantified in every component of the drug product (e.g. the release liner, original packaging) as well as articles that may have come into contact with the active matrix during the study procedure such as clinician gloves and post-study packaging components.
5. Drug in the adhesive residue on the surface of the skin following removal of TDS is collected using appropriately valid methodologies to swab the skin and to quantify the drug in the cleansing swabs.
6. Sample storage conditions before and after application of the TDS on the skin are validated. The photostability and thermal stability of the active ingredient(s) in the TDS are also considered when selecting appropriate storage conditions.
7. The amount of residual drug in the TDS is utilized to calculate the amount of drug depleted from the system, estimated in relation to the total drug content measured in other TDS units from the same

lot of the product. Appropriately sensitive, valid analytical methods are used to assay the residual drug content for the purpose of calculating drug depletion and delivery. A drug extraction method with a target extraction efficiency of close to 100% is utilized to minimize error when estimating the amount of residual drug in the TDS.

3.3. Impact of heat on product performance

Another performance consideration during TDS product development is the influence of elevated temperature on the transdermal drug delivery profile [55,56]. Exposure of TDS to heat during product use can arise from hot baths or showers, sunbathing, saunas, hot tubs, heating pads, electric blankets, heated waterbeds, tanning lamps, or other sources. Depending upon the TDS product qualities relating to design, formulation, and/or the manufacturing process, the drug delivery from a TDS may increase significantly following initial exposure to elevated temperature, resulting in serious unintended consequences impacting product safety. Since an accelerated rate of drug delivery also depletes the drug load more rapidly than the TDS product was designed for, the TDS may thereafter deliver drug at a substantially lower rate during the later period of wear, even under continued heat exposure, which may alter the efficacy of the drug product. As such, heat effects that often impact TDS product performance can affect both, product safety and efficacy.

In certain cases, where the potential for higher than expected plasma levels of the drug is a potential concern, cautionary notes have been included with the drug product labeling to warn against the exposure of the TDS to elevated temperature during product use. Such concerns have been supported by in vivo studies performed to evaluate the effect of elevated temperature during product use with methylphenidate, buprenorphine, and fentanyl TDS, as specified in the labeling. Specifically, results from a Daytrana® (methylphenidate transdermal system) study indicated that when heat was applied to the TDS, both the rate and extent of drug delivery increased significantly; C_{max} and AUC increased by 2-fold and 2.5 fold respectively [59]. Changes in lag times (T_{lag}) and time to maximal concentration (T_{max}) were also associated with this heat effect. Similarly, a buprenorphine TDS study indicated that application of a heating pad led to a 26% to 55% increase in blood levels [55]. Likewise, a fentanyl TDS study indicated that, overall, the patient exposure to fentanyl increased by 120%, and the average maximum fentanyl levels increased by 61% following heat application [56,60].

Drug delivery from a TDS may not only be influenced by an external heat source such as an electric blanket but also by the internal source of elevated body temperature during fever or exercise [55] Therefore, the relative influence of heat on the TDS product, itself, compared with the influence of heat on the skin may not be the same under different elevated temperature scenarios, and different techniques have been used to evaluate the effect of heat on TDS drug delivery rate in vivo. For example, buprenorphine TDS study results indicated that while using a heating pad led to enhanced blood levels, induction of a mild fever did not lead to increased delivery [55]. A study using an ethinyl estradiol/norelgestromin TDS evaluated the effects of exposure to sauna, immersion in cool water, and exercise on a treadmill. No significant changes in plasma levels of either ethinyl estradiol or norelgestromin were observed in connection with exposure to elevated external or internal temperature for that TDS [61]. However, significant increases in nitroglycerin plasma concentration was observed for a nitroglycerin TDS, when it was exposed to a high external temperature and used while exercising [62].

Several additional literature reports indicate that the application of heat could lead to enhanced drug delivery for other TDS products. An evaluation of the heat effect with a fentanyl TDS using the controlled heat aided drug delivery (CHADD) device as the external heat source indicated that fentanyl delivery was significantly enhanced during the period when heat was applied [63,64]. A testosterone TDS also exhibited a

sustained increase testosterone C_{max} when heat was applied in a similar fashion [65]. As a notable exception to this observed heat effect, when a granisetron TDS was evaluated using a heating pad, the results indicated that although there was a small enhancement in flux, no significant changes were noted in the pharmacokinetics [66].

It is evident that not all TDS products may be susceptible to significant heat effects, and even those that can exhibit significant heat effects are not necessarily unsafe, particularly when used responsibly and in accordance with their label. Nonetheless, a growing body of evidence forms the basis for a valid concern about how heat affects a TDS product as a function of its quality, and TDS manufacturers routinely consider this issue during product development. The identification of critical factors in the design of TDS heat effects studies, such as appropriate elevated test temperatures, heat exposure durations, cycles of heat exposure, and mechanisms of heat exposure, enables a thorough evaluation of this aspect of TDS product performance.

Given the complexity of composition and construction for TDS, it is reasonable to anticipate that different TDS formulations might respond differently to elevated temperature, and that the release of drug from a TDS that was engineered to deliver drug at a controlled rate at a normal skin temperature of 32 °C might change substantially under conditions of elevated heat [63–65,67]. As manufacturing changes are made to a TDS over its product lifecycle, the impact of that change on the performance of the TDS in the context of exposure to heat may also need to be considered [68]. Generic TDS, which may have a different TDS formulation from the RLD, are expected to be bioequivalent to the RLD under conditions of use described in the product label. Also, generic TDS, which are required to use similar labeling to the RLD, rely upon both the safety and efficacy findings for the RLD. Therefore, because of potential formulation differences, and consequently, the potentially differing heat effects, TDS manufacturers have begun to utilize IVPT studies to characterize the performance of their generic TDS at elevated temperatures in a parallel comparison to that of the RLD [69,70]. The FDA has supported research to evaluate whether such in vitro evaluations of TDS heat effects by IVPT methodologies correlate with in vivo results [71]. These research efforts aim to characterize the relationship between TDS surface temperature, skin surface temperature, and the corresponding drug release profile from a TDS, both in vitro using IVPT studies with excised human skin and in vivo with a parallel clinical study involving human subjects.

3.4. Skin irritation and sensitization

Either or both the active drug and/or the excipients in a TDS may cause skin irritation and sensitization, hence manufacturers assess the irritation and sensitization potential during development of new and/or generic TDS formulation, as well as when significant raw material changes occur in the post marketing setting. Animal models are generally used initially to assess the skin irritation potential, but this is then followed by a dedicated clinical study in humans [52,72,73]. The clinical skin irritation and sensitization studies are performed under conditions of maximal stress with the aim of capturing the worst case scenario.

Skin irritation and sensitization can be assessed in separate studies (or can sometimes be combined in a single study) as described in product specific Guidances [72,73]. Briefly, the relevant study design is similar for both new and generic TDS products with the exception that for generic drugs, in addition to the test TDS, the RLD TDS is included for a comparative analysis of skin irritation and sensitization potential. When comparing between the test and reference products, special precautions may be necessary to avoid overdosing the subject in instances where lower strengths of the test and reference product are not available for investigation. The assessment of the skin reactions is performed using a pre-defined scale and observations for adequate adhesion are also typically included.

4. Conclusion

Ultimately, transdermal delivery systems are complex dosage forms with multiple potential failure modes that may impact safety and efficacy. As such, it is necessary to demonstrate the consistency of product performance through first, a well-characterized understanding of the product and second, a studied understanding of the influence that the manufacturing process and the quality attributes can have on the final performance of the TDS. The various considerations described in this review highlight some of the challenges in development and regulation of TDS. Regulatory agencies have been increasingly engaged with industrial and academic partners, participating in collaborative projects, consortia, meetings, and publications, with the shared goal of advancing the science in the field as well as the quality of TDS products. In the end, the ultimate goal is to utilize sound scientific principles to explore new and improved ways to protect and promote the health of the people who use TDS drug products.

Disclaimer

This article reflects the views of the authors and should not be construed to represent United States Food and Drug Administration's views or policies.

References

[1] M.R. Prausnitz, S. Mitragotri, R. Langer, Current status and future potential of transdermal drug delivery, Nat. Rev. Drug Discov. 3 (2) (2004) 115–124.
[2] J. Hadgraft, M.E. Lane, Passive transdermal drug delivery systems, American Journal of Drug Delivery 4 (3) (2006) 153–160.
[3] M.R. Prausnitz, R. Langer, Transdermal drug delivery, Nat. Biotechnol. 26 (11) (2008) 1261–1268.
[4] 2000–2010 Recalls by dosage form and problem area, The Gold Sheet 45 (5) (2011).
[5] P. Karande, S. Mitragotri, Enhancement of transdermal drug delivery via synergistic action of chemicals, Biochim. Biophys. Acta 1788 (11) (2009) 2362–2373.
[6] K.S. Paudel, et al., Challenges and opportunities in dermal/transdermal delivery, Ther. Deliv. 1 (1) (2010) 109–131.
[7] G.A. Van Buskirk, et al., Passive transdermal systems whitepaper incorporating current chemistry, manufacturing and controls (CMC) development principles, AAPS PharmSciTech 13 (1) (2012) 218–230.
[8] J.S. Eglovitch, Use QbD to get through rough Patch, FDA tells transdermal makers, The Gold Sheet 45 (10) (2011).
[9] C. Strasinger, Regulatory challenges: gaps and future consideration for transdermal systems, DIA: Regulatory Challenges: Gaps and Future Consideration for Transdermal Systems, 2011 Arlington, VA.
[10] U.S. Pharmacopeia general chapter <3> topical and transdermal drug products - product quality tests, USP 36-NF 31United States Pharmacopeial Convention, United States, 2013.
[11] A.M. Wokovich, et al., Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute, Eur. J. Pharm. Biopharm. 64 (1) (2006) 1–8.
[12] Jerome P. Skelly, V.P.S., Howard I. Maibach, Richard H. Guy, Ronald C. Wester, Gordon Flynn, Avraham Yacobi, FDA and AAPS report of the workshop on principles and practices of in vitro percutaneous penetration studies: relevance to bioavailability and bioequivalence, Pharm. Res. 4 (3) (1987) 265–267.
[13] S.W. Collier, R.L.b.a., Preparation of human and animal skin, in: R.L.B.a., H.I. Maibach (Eds.), In Vitro Percutaneous Absorption: Principles, Fundamentals and Applications, CRC Press, 1991.
[14] R.G. Doug Howes, Jonathan Hadgraft, Jon Heylings, Ulla Hoeneck, Fritz Kemper, Howard Maibach, Jean-Paul Marty, Hans Merk, Jose Parra, Dimitrios Rekkas, Ivano Rondelli, Hans Schaefer, Ulrich Tauber, Nicole Verbiese, Methods for assessing percutaneous absorption: the report and recommendations of ECVAM workshop 13, Altern. Lab. Anim 24 (1996) 81–106.
[15] W. Diembeck, et al., Test guidelines for in vitro assessment of dermal absorption and percutaneous penetration of cosmetic ingredients. European Cosmetic, Toiletry and Perfumery Association, Food Chem. Toxicol. 37 (2–3) (1999) 191–205.
[16] Opinion on basic criteria for the in vitro assessment of dermal absorption of cosmetic ingredients, European Commission, Health & Consumer Protection Directorate-General, Scientific Committee on Consumer Products (SCCP), 2006.
[17] OECD Series on Testing and Assessment: Guidance Document for the Conduct of Skin Absorption Studies, 2004 [cited 2016 March 02]. (Available from:) http://www.oecd-ilibrary.org/environment/guidance-document-for-the-conduct-of-skin-absorption-studies_9789264078796-en.
[18] OECD Guideline for Testing of Chemicals, Section 4, No. 428: Skin Absorption: In-Vitro Methods, 2004 [cited 2016 March 02]. (Available from:) http://www.oecd-ilibrary.org/environment/test-no-428-skin-absorption-in-vitro-method_9789264071087-en.
[19] In vitro dermal absorption rate testing of certain chemicals of interest to the occupational safety and health administration, United States Environmental Protection

Agency, 40 CFR Parts and 799, [OPPT-2003-0006; FRL-7312-2], RIN 2070-AD42, U.S. Federal Register 2004, pp. 22402–22441.

[20] R.C. Hans Raabe, Sherry Ward, John Harbell, In vitro percutaneous absorption expert users workshop, Report From an In Vitro Dermal Absorption Assay Workshop, 2005.

[21] S.M.-K. Janet Kielhorn, Inge Mangelsdorf Fraunhofer, International programme on chemical safety, WHO, ILO, UNEP, Environmental Health Criteria 235, Dermal Absorption 2006, pp. 1–185.

[22] European Medicines Agency: Guideline on quality of transdermal patches (EMA/CHMP/QWP/608924/2014), 2014 [cited 2016 March 02]. (Available from:) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/12/WC500179071.pdf.

[23] T.J. Franz, Percutaneous absorption on the relevance of in vitro data, J. Investig. Dermatol. 64 (3) (1975) 190–195.

[24] R.L. Bronaugh, R.F. Stewart, Methods for in vitro percutaneous absorption studies IV: The flow-through diffusion cell, J. Pharm. Sci. 74 (1) (1985) 64–67.

[25] G.B. Kasting, et al., Improving the sensitivity of in vitro skin penetration experiments, Pharm. Res. 11 (12) (1994) 1747–1754.

[26] P.A. Cornwell, B.W. Barry, Effects of Penetration Enhancer Treatment on the Statistical Distribution of Human Skin Permeabilities, Int. J. Pharm. 117 (1) (1995) 101–112.

[27] R.J. Feldman, et al., Regional Variation in the Percutaneous Penetration of 14C Cortisol in Man, J. Investig. Dermatol. 48 (1967) 181–183.

[28] H.I. Maibach, et al., Regional variation in percutaneous penetration in man. Pesticides, Arch. Environ. Health. 23 (3) (1971) 208–211.

[29] R.C. Wester, P.K. Noonan, H.I. Maibach, Variations in percutaneous absorption of testosterone in the rhesus monkey due to anatomic site of application and frequency of application, Arch. Dermatol. Res. 267 (3) (1980) 229–235 Archiv fur Dermatologische Forschung.

[30] A. Rougier, et al., Regional variation in percutaneous absorption in man: measurement by the stripping method, Arch. Dermatol. Res. 278 (6) (1986) 465–469 Arch. Dermatol. Forsch.

[31] C. Lotte, et al., In vivo relationship between transepidermal water loss and percutaneous penetration of some organic compounds in man: effect of anatomic site, Arch. Dermatol. Res. 279 (5) (1987) 351–356 Archiv fur Dermatologische Forschung.

[32] I.P. Dick, et al., Improved in vitro skin absorption for lipophilic compounds following addition of albumin to the receptor fluid in flow-through cells, in: B.K.e. al. (Ed.), Prediction of Percutaneous Penetration, STS Publishing, 1996.

[33] E.S. Cross, et al., Bovine-Serum-Albumin-containing receptor phase better predicts transdermal absorption parameters for lipophilic compounds, J. Investig. Dermatol. 120 (2003) 589–591.

[34] R.L. Bronaugh, Methods for in vitro percutaneous absorption, Dermatotoxicology Methods, CRC Press, Washington, DC, 1998.

[35] Keith R. Brian, K.A.W., Adam C. Watkinson, Methods for studying percutaneous absorption, Dermatological and Transdermal Formulations, CRC Press, 2002.

[36] R.L. Bronaugh, R.F. Stewart, Methods for in vitro percutaneous absorption studies III: hydrophobic compounds, J. Pharm. Sci. 73 (9) (1984) 1255–1258.

[37] J.H. Kou, et al., Effect of receiver fluid pH on in vitro skin flux of weakly ionizable drugs, Pharm. Res. 10 (7) (1993) 986–990.

[38] S.F. Ng, et al., Validation of a static Franz diffusion cell system for in vitro permeation studies, AAPS PharmSciTech 11 (3) (2010) 1432–1441.

[39] T.G.a.P Ghosh, Biopharmaceutics and clinical pharmacology aspects of microneedle product development, 3rd International Conference on Microneedles, 2014 Baltimore, Maryland.

[40] C. Strasinger, Scientific considerations for microneedle product development, 3rd International Conference on Microneedles, 2014 Baltimore, Maryland.

[41] U.S. Pharmacopeia General Chapter <724> Transdermal Delivery Systems - General Drug Release Standards, Vol. USP 31-NF 26United States Pharmacopeial Convention, United States, 2008.

[42] U.S. Pharmacopeia General Chapter <725> topical and transdermal drug products – product performance tests, 35(3)United States Pharmacopeial Convention, United States, 2009.

[43] L.X. Yu, Advisory Committee for Pharmaceutical Science and Clinical Pharmacology – Dissolution Testing and Quality by Design, 2012.

[44] B. Rege, Review Considerations for Transdermal Patches, GPhA FDA CMC Workshop June 4–5, 2013, 2013 [cited 2016 March 02]. (Available from:) http://www.gphaonline.org/media/cms/Bhagwant_Rege_1.pdf.

[45] C. Strasinger, NDA 203752 Chemistry Review, 2012 [cited 2016 March 02]. (Available from:) http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203752Orig1s000ChemR.pdf.

[46] M. Schulz, B. Fussnegger, R. Bodmeier, Drug release and adhesive properties of crospovidone-containing matrix patches based on polyisobutene and acrylic adhesives, Eur. J. Pharm. Sci. 41 (5) (2010) 675–684.

[47] U.S. Food and Drug Administration, Enforcement report for May 14, 2008, U.S. Food and Drug Administration, 30 APR 2009, 2012 Web. 4 NOV 2012. [cited 2016 March 02]. (Available from:) http://www.fda.gov/Safety/Recalls/EnforcementReports/2008/ucm120506.htm.

[48] U.S. Food and Drug Administration, Enforcement report for June 6, 2012, U.S. Food and Drug Administration, 07 JUN 2012, 2012 Web. 4 NOV 2012. [cited 2016 March 02]. (Available from:) http://www.fda.gov/Safety/Recalls/EnforcementReports/ucm307229.htm.

[49] FDA Drug Safety Communication: FDA Requiring Color Changes to Duragesic (fentanyl) Pain Patches to Aid Safety-emphasizing That Accidental Exposure to Used Patches can Cause Death, 2013 [cited 2016 March 02]. (Available from:) http://www.fda.gov/downloads/Drugs/DrugSafety/UCM368911.pdf.

[50] B. Aksu, et al., Strategic funding priorities in the pharmaceutical sciences allied to Quality by Design (QbD) and Process Analytical Technology (PAT), Eur. J. Pharm. Sci. 47 (2) (2012) 402–405.

[51] Draft guidance for industry: bioavailability and bioequivalence studies submitted in Ndas and Inds - general considerations, 2014 [cited 2016 March 02]. (Available from:) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf.

[52] Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms, 2014 [cited 2016 March 02]. (Available from:) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177884.pdf.

[53] Fentanyl PATCH can be DEADLY to CHILDREN, 2014 [cited 2016 March 02]. (Available from:) http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm300803.htm.

[54] Guidance for Industry Residual Drug in Transdermal and Related Drug Delivery Systems, 2011 [cited 2016 March 02]. (Available from:) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220796.pdf.

[55] Butrans (Buprenorphine Transdermal System) Approved Label, 2014 [cited 2016 March 02]. (Available from:) http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021306s015s019lbl.pdf.

[56] Duragesic-100 (Fentanyl Transdermal System) Approved Label, 2014 [cited 2016 March 02]. (Available from:) http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019813s063lbl.pdf.

[57] Climara (Estradiol) Approved Label, 2013 [cited 2016 March 02]. (Available from:) http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020375s027lbl.pdf.

[58] L.S. Abrams, et al., Pharmacokinetic overview of Ortho Evra/Evra, Fertil. Steril. 77 (2 Suppl 2) (2002) S3–12.

[59] Daytrana (Methylphenidate Transdermal System) Approved Drug Label, 2013 [cited 2016 March 02]. (Available from:) http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021514s017lbl.pdf.

[60] K.T. Moore, et al., Randomized 5-treatment crossover study to assess the effects of external heat on serum fentanyl concentrations during treatment with transdermal fentanyl systems, J. Clin. Pharmacol. 52 (8) (2012) 1174–1185.

[61] L.S. Abrams, et al., Pharmacokinetics of norelgestromin and ethinyl estradiol delivered by a contraceptive patch (Ortho Evra/Evra) under conditions of heat, humidity, and exercise, J. Clin. Pharmacol. 41 (12) (2001) 1301–1309.

[62] T.F. Barkve, et al., Increased uptake of transdermal glyceryl trinitrate during physical exercise and during high ambient temperature, Am. Heart J. 112 (3) (1986) 537–541.

[63] T.S. Shomaker, J. Zhang, M.A. Ashburn, Assessing the impact of heat on the systemic delivery of fentanyl through the transdermal fentanyl delivery system, Pain Med. 1 (3) (2000) 225–230.

[64] M.A. Ashburn, et al., The pharmacokinetics of transdermal fentanyl delivered with and without controlled heat, J Pain 4 (6) (2003) 291–297.

[65] T.S. Shomaker, J. Zhang, M.A. Ashburn, A pilot study assessing the impact of heat on the transdermal delivery of testosterone, J. Clin. Pharmacol. 41 (6) (2001) 677–682.

[66] Sally T. Haislip, J.W.G., Julian D. Howell, Results from four pharmacokinetic studies of the granisetron transdermal system, Research and Reports in Transdermal Drug Delivery 2013, pp. 19–26.

[67] K.K. Petersen, et al., Effect of local controlled heat on transdermal delivery of nicotine, Int. J. Physiol. Pathophysiol. Pharmacol. 3 (3) (2011) 236–242.

[68] Soo Hyeon Shin, P.G., Brian Newman, Sam Raney, Hazem Hassan, Audra Stinchcomb, Influence of Heat on Reference and Generic Transdermal Drug Delivery Systems, 2014 [cited 2016 March 02]. (Available from:) https://2014aapsam.zerista.com/poster/member/22481.

[69] Citizen Petition, Requirement for a Usability Study Before Approving ANDAs for Generic Daytrana (Methylphenidate) Transdermal System, 2012 [cited 2016 March 02]. (Available from:) https://www.pharmamedtechbi.com/~/media/Supporting%20Documents/The%20Pink%20Sheet%20DAILY/2014/January/12114%20noven%20citizen%20petition.pdf.

[70] FDA response to Citizen Petition for Daytrana (Methylphenidate)Transdermal System, 2013 [cited 2016 March 02]. (Available from:) https://www.pharmamedtechbi.com/~/media/Supporting%20Documents/The%20Pink%20Sheet%20DAILY/2014/January/12714%20fda%20denial%20of%202012%20noven%20petition.pdf.

[71] Funding opportunity title: in-vitro release tests for transdermal drug delivery systems, 2013 [cited 2016 March 02]. (Available from:) https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-015.html#_Section_IV._Application_1.

[72] Draft Guidance on Ethinyl Estradiol; Norelgestromin, 2009 [cited 2016 March 02]. (Available from:) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM162407.pdf.

[73] Draft Guidance on Fentanyl, 2010 (Available from:) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM162427.pdf.