ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 44 (1997) 327–331

European Journal of Pharmaceutics and Biopharmaceutics

Workshop report

Scale-up of adhesive transdermal drug delivery systems[1,2,3]

Glenn A. Van Buskirk [a,*], Mario A. González [b], Vinod P. Shah [c], Scott Barnhardt [d], Colin Barrett [e], Stephen Berge [f], Gary Cleary [g], Keith Chan [h], Gordon Flynn [i], Thomas Foster [j], Robert Gale [k], Raymond Garrison [l], Scott Gochnour [m], Amanda Gotto [l], Sharad Govil [n], Vivian A. Gray [o], James Hammar [f], Samuel Harder [f], Charles Hoiberg [c], Ajaz Hussain [p], Carol Karp [g], Hector Llanos [q], Juan Mantelle [r], Patrick Noonan [s], David Swanson [k], Horst Zerbe [t]

[a] *Novartis Pharmaceuticals Corp., East Hanover, USA*
[b] *P'Kinetics Inc., Miami, FL, USA*
[c] *FDA, Center of Drug Evaluation and Research, Rockville, MD, USA*
[d] *Hercon Laboratories Corp., Emigsville, PA, USA*
[e] *Elan Corporation, Athlone, Ireland*
[f] *3M Pharmaceuticals, St. Paul, MN, USA*
[g] *Cygnus Inc., Redwood City, CA, USA*
[h] *University of Maryland, Baltimore, MD, USA*
[i] *University of Michigan, Ann Arbor, ME, USA*
[j] *University of Kentucky, Lexington, KY, USA*
[k] *Alza Corp., Palo Alto, CA USA*
[l] *Novartis Pharmaceuticals Corp., Suffern, NY, USA*
[m] *Theratec Inc., Salt Lake City, UT, USA*
[n] *Bertek Inc., St. Albans, VT, USA*
[o] *USP, Rockville, MD, USA*
[p] *FDA, Office of Pharmaceutical Science, Rockville, MD, USA*
[q] *Schering Laboratories, Miami Lakes, FL, USA*
[r] *Noven Pharmaceuticals, Miami, FL, USA*
[s] *Pharmaco International, Richmond, VA, USA*
[t] *Lohmann Therapeutic Systems, West Caldwell, NJ, USA*

Keywords: SUPAC; Adhesive transdermal systems; Scale-up; Post approval changes

1. Introduction

In order to control the scale-up of transdermal systems, the pharmaceutical scientist must understand the formulation and manufacturing attributes as well as variables present in the formulation components of the product that may affect the reproducibility of release of the active drug substance to the stratum corneum and epidermis. Changes in formulation composition involving adhesives, solvents, viscosity modifying agents and changes in the critical semipermeable films or laminates of the transdermal systems may have significant effect

* Corresponding author. Novartis Pharmaceuticals Corp., 59 Route 10, East Hanover, NJ 07936, USA. E-mail: Glenn.VanBuskirk@ pharma.novartis.com

[1] Notice to readers: This document represents a consensus of the personal views of the authors or presenters and does not necessarily represent the policies or guidelines of the American Association of Pharmaceutical Scientists (AAPS), FDA, USP, or any other organization.

[2] Based on the AAPS/FDA/USP Workshop held in Arlington, VA, 29 April–1 May, 1996.

[3] This article has previously been published in *Pharmaceutical Research* (Vol. 14, No. 7, 1997).

0939-6411/97/$17.00 Published by Elsevier Science Ireland Ltd.
PII S0939-6411(97)00138-0

on drug release. This requires that critical manufacturing process ranges be validated and that discriminating in-process and finished product tests be developed in order to assure control and reproducibility of the finished product. In addition, the influence of the variability in formulation components needs to be investigated and understood.

Transdermal Drug Delivery Systems (TDS) have differing release mechanisms based on differences in composition and fabrication. Unfortunately, there is little standardization of terminology to describe TDS type or release mechanism. The USP has begun to develop nomenclature and terminology based on TDS description and release mechanism but many systems appear to be hybrids of the proposed categories. In response to this, the workshop group proposed that all TDS systems be categorized broadly as: (1) liquid form-fill and seal, (2) peripheral adhesive, or (3) solid matrix systems (see Appendix A). The latter two categories include the subcategories of monolithic, matrix, multi-laminate and drug-in-adhesive systems. In all three major categories, the drug substance could be in solution or a suspension.

2. Compositional variables

TDS typically contain, in addition to the drug(s), vehicles such as oils, alcohols, glycerin, water, fatty acid esters, surfactants and may also contain other fillers or excipients such as lactose, silicon dioxide, cellulosics and cross-linking agents. During scale-up, adjustments in the levels of these components may be made in order to maintain proper drug release and/or product adhesion/wear characteristics while minimizing irritation.

In addition, the TDS platform will contain several materials such as backing film, peelable liner, etc. which have inherent lot to lot variability and may influence drug release, product wearability or product stability. Thus, the pharmaceutical scientist must understand the relationship between product components and product excipients in order to reproducibly perform scale-up of the product.

Special attention is required of the adhesive composition since there is often intimate contact of the adhesive with the drug or other excipients that may alter the properties of the adhesive and/or may influence the release of drug. There are data to show the effect of adhesive type, e.g. silicone rubber or polyisobutylene on the solubility of the drug in the adhesive and on the diffusion coefficient of the drug within the adhesive matrix. This interaction can affect the rate and extent of drug release from the transdermal system. The adhesive/drug interaction is not the only formulation parameter which can affect drug release. Others are vehicle and filler composition and the porosity, tortuosity and thickness of the matrix layer.

No a priori allowable range in excipients or platform materials was established by the workshop group. Instead emphasis was placed on knowledge of the interplay between each product component and product performance. This knowledge should reside in a formulation development report which establishes a working range of system components/composition based upon their impact on key product characteristics such as wearability, adhesive properties, and drug release/stability.

The workshop concluded that for each TDS, the development report should identify those excipients/components which have minor impact on system functionality or performance and those that are critical. An allowable operating range for non-critical excipients/components should be documented. Critical components and/or excipients should be tightly controlled and the allowable range should be clearly defined by experimental data showing the impact of change on some performance or system attribute such as drug crystallinity, solubility, wearability/adhesion, drug release or system stability.

3. Process variables

Manufacture of transdermal systems typically involves several unit operations. Drug, excipients and polymers are often mixed, then coated on a platform substrate before being 'dried' to remove excess solvent. Alternatively, in some systems a drug/excipient/solvent mixture is dispensed for a form, fill and seal type system. Many systems are laminated to form their multi-layer structure. Large rolls of bulk transdermal film components are slit and converted to final rollstock prior to punching and pouching.

For each unit operation a series of key variables to control and key properties to measure (to assess control) have been delineated and are found in Table 1.

Even seemingly unimportant components of a transdermal delivery system can impact on system performance and thus need to be well characterized. Similarly, the interplay of solvents/liquids and excipients needs to be evaluated as variability may impact the degree of plasticization, cross-linking or cause the formation of a eutectic mixture or crystallization thereby causing a significant impact on drug delivery, system adhesion or wearability.

TDS, like other pharmaceutical drug products, benefit greatly from use of in-process controls as an assurance mechanism of finished product consistency. A TDS should be well controlled through a series of rapid, simple limit tests that correlate to a known performance parameter. These tests should be used in conjunction with calibrated equipment with documented Installation Qualification, Operational Qualification and Performance Qualification (IQ/OQ/PQ).

Table 1
TDS unit operation

Unit operation	Key variables	Key properties	Potential issues
Mixing	Mixing speed	Drug content (% basis)	Shear stress
	Mixing temperature	Homogeneity	Correct formulation ratio (drug/carrier)
	Mixer type/size	Viscosity	
	Mixing time	Solids content	
	Blade size (diameter)		
Coating/drying/lamination	Coating method	Appearance	Drug loss
	Temperature	Coating weight and uniformity	Excipient loss
	Residence time in oven	Residual solvent	Cost/energy consumption
	Air velocity		Lane width
	Surface tension	Viscosity	Rollstock quality, static electricity
	line speed		
	web tension		lane registration
Liquid/Gel dispensing (for form/fill/seal)	Dispensing mechanism	Weight of dose	Shear stress
	Temperature	Content uniformity	Gel in heat seal
	Web registration	Viscosity	Solvent evaporation
		Solids content	
		Solvent levels	
		Stringing	
Converting process	Die configuration	Dimensional accuracy	Yield/wastage/cost
	Sealing temperature	Pouch integrity	Roll tension
	Sealing pressure	Appearance	Storage time
	Dwell time		Detection of defects

As noted in Table 1, parameters which may need to be controlled include solids content, drug content, residual solvent level, viscosity and dimensional accuracy. These are affected by mixer type, mixing time, coating rate, drying rate and temperature, line speed and tooling accuracy (wear). Hence, these latter parameters should be well controlled and monitored as determined by product and process characterization.

4. In vitro tests for transdermal systems

In vitro drug release testing is commonly used to characterize transdermal systems and is a basic quality control tool used along with stability data to control scale-up and post-approval changes. The USP has established three different in vitro drug release tests. These are (1) Paddle over disk (apparatus 5), (2) Cylinder method (apparatus 6) and (3) Reciprocating disk method (apparatus 7) [1].

The Paddle over disk method is the most widely used based on its simplicity and reproducibility, but any of the remaining apparatus can be used if justified with data to show discrimination and reproducibility. Typically, any in vitro release test should be conducted for a duration sufficient to exceed 100% total drug delivered in vivo and a minimum of three to four test points to reflect the release profile. Three levels of acceptance are specified with each level requiring an increased sample population similar to level 1, level 2, and level 3 testing for oral dosage forms. It is acknowledged that these tests typically do not correlate to in vivo drug release but help in quality control of the finished TDS.

In vitro skin permeation is an important tool for characterizing drug release from a transdermal system and has been shown, in some cases, to provide a correlation with biologic response. This test has been shown to be sensitive to skin variability which differs between anatomical sites within an individual and from individual to individual. Therefore, a good experimental design would require an adequate number of replicates (taken from a single piece/sample of skin) and should include a test to evaluate the integrity of the skin sample. Additionally, for each drug product, the in vitro permeation system should be validated to provide both intra-day and inter-day (which may be confounded with inter-subject skin) variability. Such a validation should provide a minimum of 12 replicates during each of 6 days. Variability caused by differences in donor skin are best characterized by running a 'reference formulation' head-to-head with the test formulation.

5. In vitro/in vivo correlation (IV/IVC) for transdermal systems

Using in vitro release and/or in vitro permeation, it is possible to evaluate a possible correlation with in vivo bioavailability. Three possible correlations can be investigated.

- In vitro release/in vitro skin permeation
- In vitro release/in vivo bioavailability
- In vitro permeation/in vivo bioavailability

Although there are few recorded in vitro/in vivo correlations for transdermal systems, these techniques have nonetheless proven to be useful in guiding SUPAC issues and it is expected that as the body of data grows a number of IV/IVC will be demonstrated.

When a bioavailability study for a TDS is conducted, the parameters to measure should include:

$AUC_{0-\tau}$ (τ = dosing interval), $AUC_{0-\infty}$, apparent dose (calculated as the difference between the TDS initial potency and final potency), C_{max} and C_{ss} (at steady state); where

$$C_{ss} = AUC_{ss}/\tau$$

6. Level 1, 2 and 3 SUPAC changes

Based on the science currently available, the Workshop concluded that TDS SUPAC issues could be dealt with in three levels based on the significance of the change and the potential impact of the change on TDS performance (Fig. 1).

The lowest level of change and the category which covers the largest proportion of changes is in level 1 and is described as 'minor' changes that can be handled within an Annual Report for the affected NDA or ANDA. Justification and data supporting the change need to be filed and may include stability data (release and/or limited data on aged or accelerated samples) to show consistency with the control product. The database should also include in vitro release and/or permeability data.

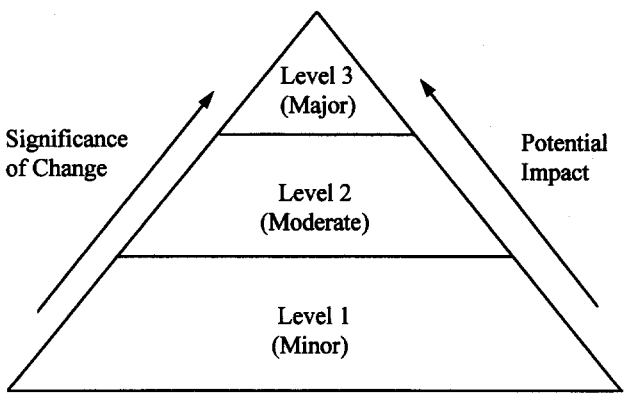

Fig. 1. The hierarchy of scale-up and post approval changes and their significance on TDS performance.

'Moderate' changes or level 2 changes should include all of the above data including one batch with 3 months of stability data but need to be filed as a 'Changes Being Effected' submission in order to allow for possible dialog with the FDA prior to implementation.

'Major' or level 3 changes require a prior approval supplement and typically may contain a bioavailability study or suitable in vivo / in vitro correlation with comparative stability on three batches for 3 months in support of the proposed change.

Table 2 contains guidance on the process of establishing the significance of the change and hence the corresponding SUPAC approach. It should be used in conjunction with actual data for the affected TDS system and in consultation with the FDA in making the final determination.

7. Summary

The Scale-up of Adhesive TDS presents unique challenges to the pharmaceutical scientist. This is because this dosage form lacks a well-established bioavailability surrogate and must therefore rely on in vivo testing as well as reproducible physico-chemical parameters, in vitro testing and stability in order to assure control of product 'sameness' during scale-up and post approval changes. This requires a substantial database of information on key unit operations and final product quality control. A proposed approach to satisfy this requirement is outlined in this report of the AAPS/FDA/USP SUPAC Workshop on this subject.

Appendix A. Glossary of terms

The following definitions of terms commonly used in the scale-up of TDS products have been generated for the purpose of creating a better understanding of the concepts and points raised within the workshop report. This glossary of terms represents only the opinion of the workshop participants and does not have any statutory significance.

A.1. Functional elements

Parts of a system that provide drug release characteristics and wear properties.

- Matrix layer: an adhesive or non-adhesive polymer layer that contains and modulates drug release.
- Monolithic layer: same as matrix.
- Multilayer matrices: two or more functional layers that provide a particular drug release profile and/or appropriate wear properties.

Table 2

Type of change	Criticality of change	Level		
		1 (Minor)	2 (Moderate)	3 (Major)
Manufacturing scale change ≤ 10 ×	N	X		
Manufacturing scale change > 10 ×	N		X	
Change in order of addition	N		X	
Site change				
Same campus	N		X	
New site/same equipment	Y		X	
New site/equipment/process	Y			X
Change in composition				
Non-critical components	N	X		
Critical components	Y			X
Change in components				
Backing film	N	X		
Release liner	N	X		
Adhesive	Y			X
Peripheral adhesive	Y		X	
Processing aids	N	X		
Preservatives	N	X		
Flux/penetration enhancer	Y			X
Cross-linking agent	Y		X	
Rate-controlling membrane	Y			X
Source of active ingredient	Y	X		
Non-rate controlling membrane	N		X	
Excipients	N	X		

- Rate control layer: a layer that provides a rate limiting step for the delivery of a drug or enhancer.
- Permeation modulating excipients: materials that can increase, decrease or change the release profile of a drug or enhancer from a matrix (e.g. solubilizer, enhancer, or other additives.)

A.2. Structural elements

Parts of a system that make up a platform for delivery of drug(s) through the skin. These elements are common to all transdermal system designs.

- Backing material: the layer that protects the system during wearing or provides integrity to the system.
- Drug layer or reservoir: the layer or layers which contain the drug substance.
- Skin adhesive layer: the layer which attaches the system to the skin.
- Protective liner (Release liner): a removable film that protects the adhesive layer while the system is in the package.
- Adhesive system: a pressure sensitive adhesive that adheres the system to the skin or various laminate structures to each other.

A.3. Transdermal design types

- Liquid form-fill and Seal-system with a liquid or gel drug reservoir.
- Peripheral adhesive systems: system with an adhesive overlay on top of an adhering or non-adhering matrix or reservoir.
- Solid matrix systems: system with drug in a three dimensionally stable polymer matrix.

References

[1] USP 23, Drug Release 724 (1995) 1796–1799.