Available online at www.sciencedirect.com
SCIENCE DIRECT
European Journal of Pharmaceutics and Biopharmaceutics 60 (2005) 309–314
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Note

IV–IVC for topically applied preparations–a critical evaluation☆

Vinod P. Shah*

Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, USA

Received 10 May 2004; accepted in revised form 25 September 2004
Available online 18 March 2005

Abstract

In vitro–in vivo correlation (IV–IVC) is the relationship between an in vitro parameter (drug release or other rheological properties/measurement such as viscosity and spreadability) and an in vivo parameter (pharmacodynamic (PD) or dermatopharmacokinetic (DPK) or other measurement). In a true sense of correlation, in vitro measurement should predict in vivo performance of the product. For topically applied preparations, one of the in vitro measurements is the drug release from the formulation and in vivo measurement is the drug concentration in the stratum corneum, DPK or the PD measurements. The in vitro release of the drug is the property of the dosage form and is a measure of product quality and 'sameness', especially after certain Scale-UP and Post Approval Changes after initial drug approval.

To obtain an IV–IVC for a topically applied drug product is a difficult challenge. However, some success has been achieved in showing a relationship between the drug release and PD and/or DPK measurement. Interestingly, one of the in vitro rheological properties was found to relate to the observed PD and DPK response for Clobetasol dipropionate products. Different rheological properties of the two formulation products explained the difference in DPK results obtained by two laboratories for the same tretinoin gel products. In the scientific arena, it is difficult to obtain a classical IV–IVC even for orally administered products and is more so difficult for topically administered drug products.

Keywords: In vitro–in vivo correlation; In vitro release; Rheological properties; Spreadability; Dermatopharmacokinetics; DPK; Pharmacodynamics

1. Introduction

The term of in vitro–in vivo correlation (IV–IVC) has a different meaning to different investigators. In the present discussion, the term IV–IVC is applied to the finished topical dermatological dosage form. IV–IVC is the relationship between in vitro parameter such as drug release or other rheological properties/measurements like viscosity and spreadability and in vivo parameter like a pharmacodynamic (PD) response or a dermatopharmacokinetic (DPK) measurement or a clinical end point in humans. For a good correlation, a minimum of three products varying in in vivo and in vitro measurements are desired. With two products, only a rank order relationship may be achieved. In vivo measurements represent the product response and are generally invariable whereas in vitro measurements are physical attributes of the product and are method dependent and thus are variable. In vitro test conditions can be altered to 'achieve' correlation with in vivo measurements. In general, to obtain IV–IVC is difficult, especially with topical dermatological drug products.

For approval of a new (pioneer) drug product, a new drug application (NDA) is required in US with documentation of safety and efficacy along with appropriate in vivo and in vitro test measurements. For approval of a generic product, an abbreviated new drug application (ANDA) is required with documentation of in vivo bioequivalence (BE) and in vitro test measurements. Determination of BE is important from both the clinical and regulatory standpoints. For topical dermatological drug products, bioequivalence can be determined by comparative clinical trials or by comparative pharmacodynamic measurements, e.g. for glucocorticoids. Comparative DPK method has been suggested as a means of determining bioequivalence of a generic product [1].

☆ Presented at 5th International Conference on cell culture and in vivo models for drug absorption and delivery, Saarbrucken, Germany, February 25–March 5, 2004.

* Address: Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD 20852, USA.
E-mail address: shahvi@cder.fda.gov

0939-6411/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2004.09.015

2. In vivo measurements

2.1. Dermatopharmacokinetic (DPK) method

The DPK methodology includes measurement of drug concentration in stratum corneum (SC) as a function of time. The method involves application of test and reference product on the same subject at the same time at multiple sites on the forearm with each site yielding a single drug concentration. Using the drug uptake and elimination phases, AUC and C_{max} of the test and reference products can be calculated. These metrics can then be used to determine 90% CI limits for BE of the test product [2]. Advantage of this approach is that both test and reference products can be studied on the same subject at the same time, thus reducing the variability.

2.2. Pharmacodynamic (PD) measurements

Topical glucocorticoids produce a skin blanching (vasoconstriction) at the site of application. This has been correlated with the clinical potency of the glucocorticoid. This phenomenon has been employed in the development of BE guidance for corticosteroids [3]. In skin blanching studies also, the test and reference products can be studied in the same subject at the same time, thus reducing the variability. Before conducting BE study, a pilot study is recommended for selecting appropriate time intervals [3]. Transepidermal water loss is another PD measurement that has been employed to determine barrier function of SC. However, its application in BE studies needs more work.

3. In vitro measurements

In vitro drug release is measured using vertical diffusion cell system with a synthetic membrane. The synthetic membrane serves as an inert support membrane separating the cream from receptor phase. A simple procedure has been developed to measure drug release from topical dermatological dosage forms [4]. The method can be automated, and it has been used to measure drug release rate from several therapeutic classes of topical drug products. The method is formulation sensitive and can detect significant differences in formulation. For, e.g. when nine marketed miconazole nitrate cream products were studied for their in vitro release properties, data fell into two distinct groups. Formulation details (obtained from Physicians' Desk Reference book and product labeling) also revealed that these nine miconazole drug products fall into two groups, again lining up with the release rate data (Fig. 1). Further studies also suggest that in vitro release is concentration and manufacturing process dependent [5]. The value and application of in vitro release testing of topical dermatological drug products is well described in a workshop report [6]. The report also concluded that in vitro release should not be used to compare distinct and different types of drug formulations, such as comparing in vitro release rate between a cream and an ointment.

In vitro release is the property of the dosage form and is used to assure product sameness after minor compositional changes, manufacturing process and site changes after drug approval under SUPAC guidance [7].

Another in vitro characteristic that has been observed with some of the topical cream preparations relates to one of the rheological properties of the formulation, and is the lateral 'spreading'. This characteristic of the product can easily be observed when the formulation is applied as a spot on the filter paper. The 'firm and viscous product' stays at its place whereas 'less viscous and fluid product' disperses and spreads in the surrounding areas. This lateral spreading property of the dosage form has been correlated with the PD response and DPK measurement in SC [8].

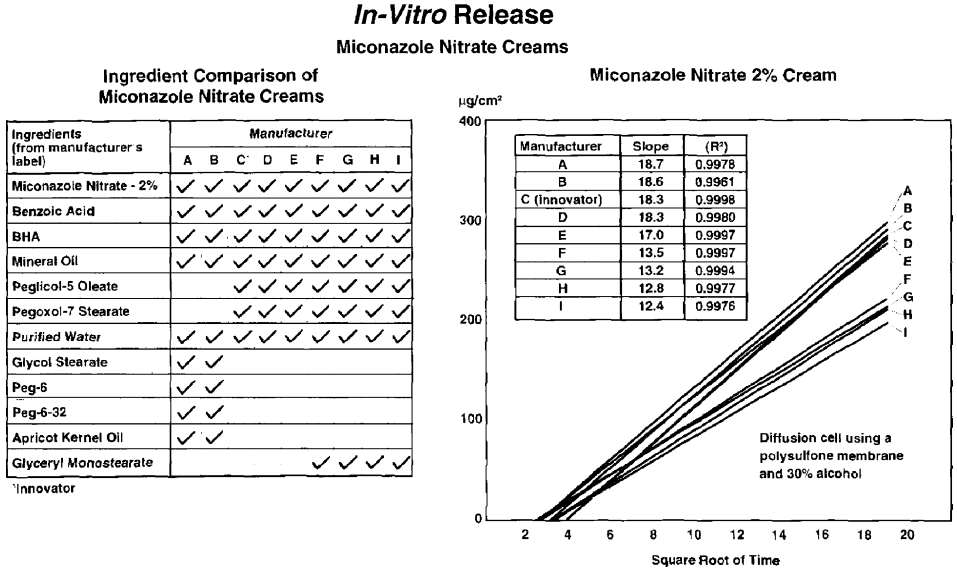


Fig. 1. In vitro release of miconazole cream products.

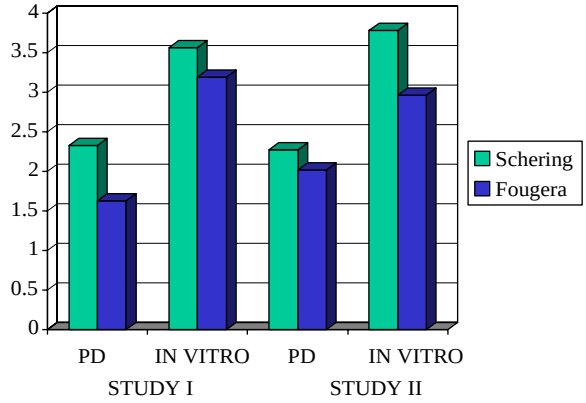
4. In vivo–in vitro relationship

The three consecutive steps involved in topical drug product treatment are (i) drug release from the formulation (ii) drug penetration/diffusion into/through SC and (iii) drug reaching site of action to elucidate pharmacological response. In most of the cases drug penetration through SC is the rate-limiting step. Drug release from the formulation is dependent on the formulation and if the drug is in solution or in suspension form. If the drug is in suspension form, then the drug release is also influenced by the particle size of the active drug substance. Formulation, manufacturing and state of the active substance are generally a proprietary information. However different in vitro properties between different manufacturers of a product suggest that there may be differences in formulation or manufacturing process. These differences may not be significant in terms of its end clinical results. Several examples are described below to show the relationship between in vitro measurement such as in vitro release or a lateral spreading property and in vivo measurement such as PD response or DPK concentration in SC or clinical end point.

4.1. In vitro release and PD and/or DPK measurements

1. In two successive double blind PD measurement studies of betamethasone valerate creams, a clear difference in response was observed between two brands. In vitro release studies also showed different release rate of the two brands, and rank orderly correlated with PD response, Fig. 2 [9].
2. Two betamethasone dipropionate 0.05% cream products, Diprolene and Diprosone are in two potency category, category 1 and 3, respectively. Category 1 is higher potency than category 3. In vitro release rate using vertical diffusion cell system, polysulfone support membrane and 30% alcohol as a receptor medium reflected release rates that can be rank orderly correlated to the designated potency of the dosage form. Diprolene cream showed faster release rate and is in higher potency category compared to Diprosone cream that showed slower release rate and is in lower potency category [4].
3. Two hydrocortisone 2.5% cream preparations showed different steady state stratum corneum concentrations (DPK) and PD response. These observations were also rank orderly correlated with the in vitro release rate, Fig. 3 [10].

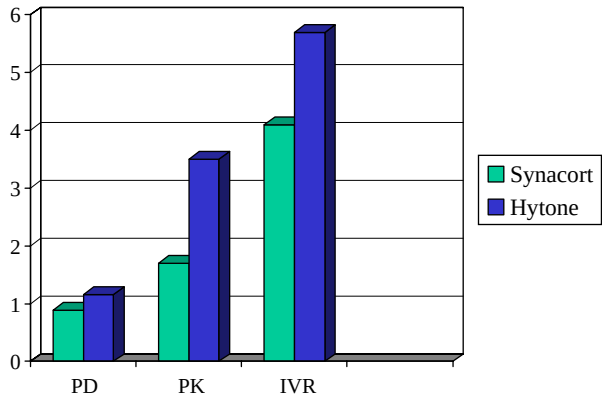
Correlation between pharmacodynamic (PD) response and in vitro release rate in 60% ethanol: water for betamethasone valerate creams



VP Shah, J Elkins and JP Skelly; J Pharm Sci: 81:104-106, 1992

Fig. 2. Pharmacodynamic and in vitro release of betamethasone valerate crems. PD, pharmacodynamics, visual blanching score (scale: 0–3); in vitro release, in vitro drug release, mcg/cm^2 in 6 h.

Correlation between pharmacodynamic (Pd), pharmacokinetic (PK) and in vitro release characteristics of two hydrocortisone creams



D Caron, C Queille-Roussel, VP Shah and H Schaefer J Am Acad Dermetol 23:458-462, 1990

Fig. 3. Pharmacodynamic, dermatopharmacokinetic and in vitro drug release rate of Synacort and Hytone hydrocortisone creams. PD, pharmacodynamics, visual blanching score (scale: 0–3); PK, steady state drug concentration in stratum corneum, ng/cm^2; in vitro release, in vitro drug release, mcg/cm^2 × 10 in 6 h.

4.2. Physical (rheological) properties and DPK

A three way crossover DPK study was carried out using tretinoin 0.25% gel formulations from Ortho, Bertek and a generic product from Spear Pharmaceuticals by Pershing et.al. [2]. FDA approved all three products for the treatment of acne vulgaris based on clinical trials. Bertek product was clinically not equivalent to Ortho reference product, but was found to have less side effects compared to Ortho product

Table 1
Tretinoin + isotretinoin concentrations in stratum corneum

Parameter	Ortho product A	Bertek product B	Generic product C	Ratio Ortho/ Bertek
C_{max} (ng/cm^2)	168.0	114.3	174.6	1.47
AUC 0–t (ng h/cm^2)	741.2	377.1	773.4	1.97

Data from Lynn Pershing study (Ref. [2]).

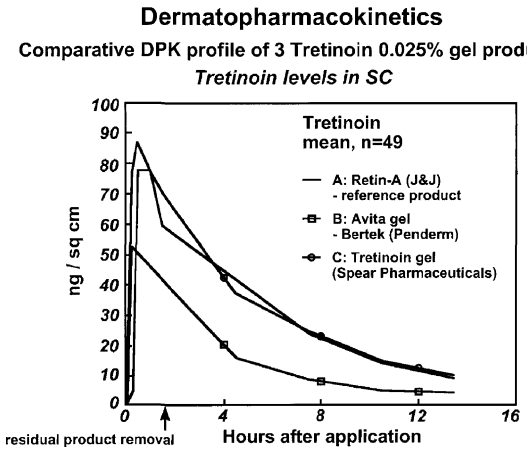


Fig. 4. DPK profile of Ortho, Bertek and a Generic tretinoin 0.025% gels (Pershing's data), Ref. [2].

Table 2
Tretinoin + isotretinoin concentration in stratum corneum

Parameter	Ortho product A	Bertek product B	Ratio Ortho/ Bertek
C_{max} (ng/cm^2)	59.0	74.25	0.80
AUC 0–t (ng h/cm^2)	955.0	1031.75	0.93

Data from Tom Franz study (Ref. [11]).

and was superior to placebo. The generic product was clinically equivalent to the reference product. Table 1 and Fig. 4 summarizes the DPK data for the three products. DPK results indicated that the generic product was BE to the reference Ortho product. Bertek product was not bioequivalent to reference Ortho product. The DPK levels for Bertek product was lower than that of the reference Ortho product. These results were in agreement with clinical end point observations. Franz and co-workers carried out another DPK study using only two products, Ortho and Bertek product [11]. The results shown in Table 2 and Fig. 5, also conclude that DPK results from Ortho product and Bertek product were significantly different and not bioequivalent.

Even though the two studies came to the same final conclusions that Ortho product and Bertek product are not bioequivalent, the order of DPK profiles of the two products were reversed in the two studies (Figs. 4 and 5). Pershing's study showed that Ortho product had higher DPK concentration time profile than Bertek product. On the other hand, Franz's study showed the opposite, Bertek product had higher DPK concentration profile than Ortho product. This is a disturbing factor and it challenges the DPK methodology for its general application as a viable regulatory method for BE of topical dermatological drug products. A close evaluation of the two procedures used in Pershing study and Franz study revealed interesting findings and possible explanation of the anomaly of the observed results.

The methodology used by Pershing involved application of 5 μl gel sample to 1.13 cm^2 (1.12 cm in diameter) of skin surface area, and used 1.3 cm diameter D-Squame adhesive discs for SC removal from the center of drug application area [2]. The methodology employed by Franz involved application of 20 μl of gel to 2×2 cm of skin surface area, and used 2.5×5 to 5.5 cm Transpore adhesive tape for removal of SC [11]. This is represented graphically in Fig. 6. Pershing's method discarded first two SC tape strips as unabsorbed drug and analyzed tape discs 3–12 for DPK determination. On the other hand, Franz's method also discarded first two tape strips as unabsorbed drug but measured drug content in tape strips

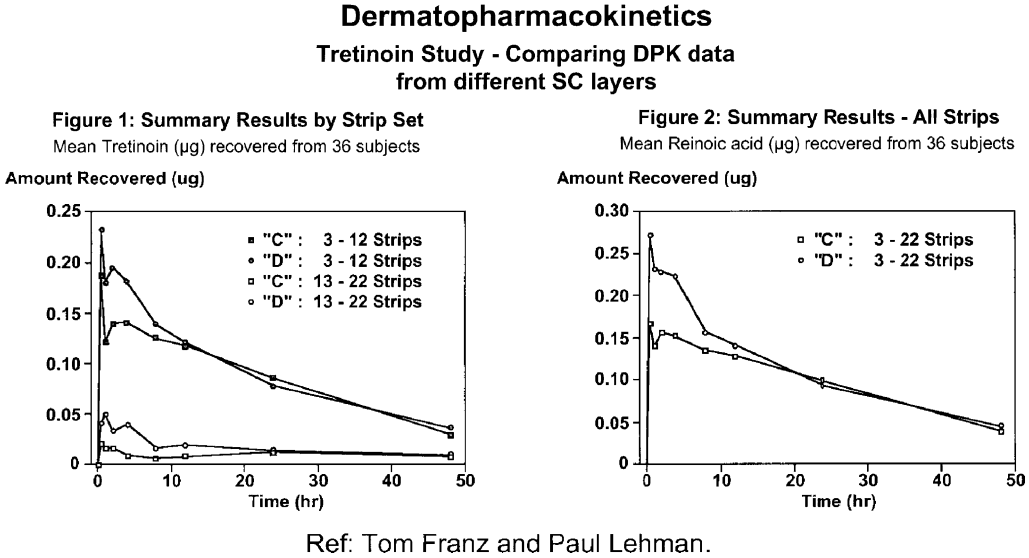
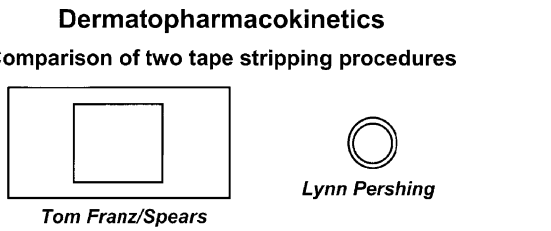
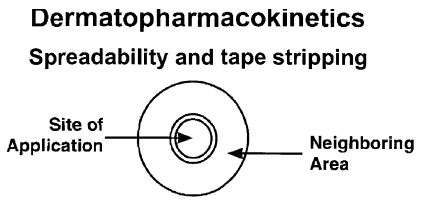


Fig. 5. DPK profile of Ortho (C) and Bertek (D) tretinoin 0.025% gels (Franz's data), Ref. [11].



Area of Application:	2 x 2 cm	1.12 cm diameter
Amount applied	20 ul	5 ul
Area tape stripped	2.5 x 5 - 5.5 cm	1.3 cm diameter
Tape used	Transpore (3M)	D-Square (Cuderm)

Fig. 6. Drug application area and drug removal (tape-stripping) area: comparison between Pershing and Franz procedure.



Drug Concentration in Neighboring Area

Time	Retin - A	Avita
0.5 hours	2.33	5.33
2.0 hours	1.64	22.01

Fig. 7. Drug concentration in stratum corneum concentration at the site of application and neighboring area for two products, Retin A (Ortho) and Avita (Bertek).

from 3 to 12 and 13 to 22 for DPK. However, DPK measurements from 3 to 12, 13 to 22 and 3 to 22 resulted in the same conclusions. The rheological properties of the two formulations, Ortho and Bertek reveal that Ortho product has a firmer consistency and stays at the site of application whereas Bertek product is more fluid in nature and tends to spread laterally in the neighboring region. This physical property of the dosage form was easily observed by placing the spots of the gel products on the filter paper. Ortho product remained at the site, whereas Bertek product underwent lateral spreading. The generic product from Spear Pharmaceuticals behaved similar to Ortho product.

The lateral spreading phenomena of topical dermatological drug product was also observed during DPK studies with 0.5% clobetasol cream and emollient cream [12]. In this case, the cream product showed much higher SC drug concentration than emollient cream at the site of application, and the emollient cream showed significantly higher SC drug concentration in the neighboring region than the cream product. This has been attributed to lateral spreading properties of the emollient cream [8,12].

Preliminary experiment with tretinoin gel products indicated that the drug concentration in SC with Bertek product in the neighboring region was 13 times higher than with Ortho product (Fig. 7 with data). These results help explain the anomaly observed in the two DPK study results by Pershing and Franz. Pershing's protocol removed SC only from the site of application for analysis whereas Franz's protocol removed SC from much larger area than the site of drug application, which included neighboring area. Since Bertek product spreads laterally, the drug is distributed in lateral SC area, thus resulting in higher estimation of SC concentration. The results from these two studies emphasize that (i) the spreading phenomena should be carefully evaluated in designing study protocol and (ii) drug application area and SC stripping area should be standardized for use of DPK methodology. In the case of tretinoin and clobetasol, the DPK results could be correlated to the physical properties of the formulation.

5. Conclusions

It is feasible to have an in vitro–in vivo correlation for topically applied drug products, but it is not essential. The IV–IVC for topically applied drug products poses a major challenge, is more difficult compared to orally administer solid dosage forms.

References

[1] V.P. Shah, G.L. Flynn, A. Yacobi, H.I. Maibach, C. Bon, N.M. Fleischer, T.J. Franz, S.A. Kaplan, J. Kawamoto, L.J. Lesko, J.-P. Marty, L.K. Pershing, H. Schaefer, J.A. Sequeira, S.P. Shrivatsava, J. Wilkin, R.L. Williams, AAPS/FDA workshop report: bioequivalence of topical dermatological dosage forms—methods of evaluation of bioequivalence, Pharm. Res. 15 (1998) 167–171.

[2] L.K. Pershing, J.L. Nelson, J.L. Corelett, S.P. Shrivastava, D.B. Hare, V.P. Shah, Assessment of dermatopharmacokinetic approach in the bioequivalence determination of topical tretinoin gel products, J. Am. Acad. Dermatol. 48 (2003) 740–751.

[3] Guidance: topical dermatologic corticosteroids: in vivo bioequivalence, Office of Generic Drugs, Center for Drug Evaluations and Research, FDA, June 1995.

[4] V.P. Shah, J.S. Elkins, R.L. Williams, Evaluation of the test system used for in vitro release of drugs for topical dermatological drug products, Pharm. Dev. Technol. 4 (1999) 377–385.

[5] R. Pillai, V. Shah, L. Abriola, P. Caetano, G.L. Flynn, Release of hydrocortisone from a cream matrix: dependency of release on suspension concentration and measurement of solubility and diffusivity, Pharm. Dev. Technol. 6 (2001) 373–384.

[6] G.L. Flynn, V.P. Shah, S.N. Tenjarala, M. Corbo, D. DeMagistris, T.G. Feldman, T.J. Franz, D.R. Miran, D.M. Pearce, J.A. Sequeira, J. Swarbrick, J.C.T. Wang, A. Yacobi, J.L. Zatz, Workshop report: assessment of value and applications of in vitro testing of topical dermatological drug products, Pharm. Res. 16 (1999) 1325–1330.

[7] CDER, FDAGuidance: SUPAC-SS Nonsterile semisolid dosage forms, Scale-up and postapproval changes: chemistry, manufacturing, and controls; in vitro release testing and in vivo bioequivalence documentation, May 1997.
[8] H.J. Weigmann, J. Lademann, S. Schanzer, U. Lindemann, R. von Pelchrzim, H. Schaefer, W. Sterry, V. Shah, Correlation of the local distribution of topically applied substances inside the stratum corneum determined by tape-stripping to differences in bioavailability, Skin Pharmacol. Appl. Skin Physiol. 14 (Suppl. 1) (2001) 98–102.
[9] V.P. Shah, J. Elkins, J.P. Skelly, Relationship between in vivo skin blanching and in vitro release for betamethasone valerate creams, J Pharm. Sci. 81 (1992) 104–106.
[10] D. Caron, C. Queille-Roussel, V.P. Shah, H. Schaefer, Correlation between drug penetration and blanching effect of topically applied hydrocortisone cream in human beings, J. Am. Acad. Dermatol. 23 (1990) 454–462.
[11] FDA Advisory committee for Pharmaceutical Science, Transcript of discussion, November 2001.
[12] H.J. Weigmann, J. Lademann, R. von Pelchrizm, W. Sterry, T. Hagemeister, R. Molzahn, M. Schaefer, M. Lindsxheid, H. Schaefer, V.P. Shah, Bioavailability of clobetasol propionate—quantification of drug concentrations in the stratum corneum by dermatopharmacokinetics using tape stripping, Skin Pharmacol. Appl. Skin Physiol. 12 (1999) 46–53.