60.4 METHODS TO ASSESS THE BE OF TOPICAL DOSAGE FORMS FOR LOCAL ACTION

When a topical drug product is applied to the skin, the API must be released from the vehicle before it is available for penetration into the stratum corneum and lower layers of the skin (15).

A topical formulation is a complex system, and the kinetics and dynamics of release of the APIs from its vehicle have been the topic of investigation in many research papers (16–20).

BE of topical dosage forms may be demonstrated by comparing the test and reference products using appropriate pharmacokinetic (PK), pharmacodynamic (PD), clinical, or in some instances in vitro tests to obtain a biowaiver (21–33).

Currently, relatively few surrogate approaches to assess the BE of topical dosage forms for local action have been explored apart from the VCA (2) for use to assess the BE of topical corticosteroid products. Most regulatory authorities insist on clinical endpoint studies in patients to confirm BE.

Table 60.2 depicts various options (excluding VCA publications) where descriptions of some methodologies and related data to assess BE have been published:

60.5 BIOWAIVERS

A generic product may be suitable for a biowaiver if its Q1/Q2/Q3 equivalence can be established against the RLD.

In vitro release testing (IVRT) entails measurement of the drug released from the vehicle into a receptor medium, separated by an inert membrane (50) and used to quantify the amount of API released from semisolid dosage forms and to determine its release rate (15). The FDA's SUPAC-SS guidance (51) recognizes IVRT for semisolid dosage forms as a test for product "sameness" following minor formulation, process, and/or manufacturing site related changes to an approved topical dosage form. IVRT has been established as a compendial method by the USP (52) for performance testing of semisolid dosage forms. In addition, IVRT is used to support formulation development, to compare a generic product with innovator formulations, and to determine release data from various formulations used in clinical trials (53). It has been proven to be useful to detect differences in Q1 and Q2 properties between similar products and also the microstructure and arrangement of matter between formulations (Q3) (54). In 2003, the experts from FIP/AAPS pointed out that there was an absence of a standard test protocol that can be applied to all formulations (55). It was suggested that the data obtained from IVRT investigations can be employed as quality indicators and for the screening of the compositions prior to in vivo testing. However, it was noted that in spite of the very fast development of this field, anatomical and physiological factors are not represented in these investigations (56). Until recently, among the numerous publications involving the application of IVRT, comprehensive validation of IVRT systems and methods have been conspicuously absent from the literature. Although various efforts (17, 57, 58) have been made by several researchers to develop a standardized method to measure in vitro drug release from a product using diffusion cells, a comprehensive validation that would be generally applicable to all topical dermatological dosage forms has only recently been published (59).

TABLE 60.2
Options for BE Assessment of Topical Dosage Forms Not Intended to be Absorbed

METHOD	REFERENCES
Dermatopharmacokinetic methods also known as tape stripping (TS)	(34–42)
Dermal microdialysis (DM)	(43–47)
Open-flow microperfusion (dOFM)	(26, 48, 49)
In vitro methods (IVRT) – for "biowaiver" purposes only	See "Biowaivers" section