Pharmaceutical Research, Vol. 16, No. 9, 1999

Workshop Report

Assessment of Value and Applications of In Vitro Testing of Topical Dermatological Drug Products[1,2]

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The FDA recently issued a guidance covering practices of scaleup and post approval changes with semisolids (SUPAC-SS).[17] This guidance outlines the steps that must be taken by a company to maintain certification of its semisolid dermatological products after quantitative changes have been made in their compositions and/or after changes have been made in the sourcing of their key ingredients, in their processing, in their batch sizes, and/or after their site of manufacture has been relocated. A key element within the guidance is a release test to be used to determine if the diffusional release of a drug found in a formulation is the same after changes have been made to the formulation as it was prior to implementing the changes. The AAPS-FDA sponsored workshop was set up to explore this qualifying test. The stated aims of the workshop were: a) to illustrate the methodology and techniques of in vitro release testing, b) to show the sensitivity of in vitro release with respect to manufacturing variables and to variations in components and composition (of specific formulations), c) to recognize in vitro release testing as a useful procedure for SUPAC documentation, d) to highlight and evaluate other applications of in vitro release testing, e) to explore the degree to which in vitro release testing and bioavailability may be related, and f) to evaluate the role of in vitro release testing of topical dosage forms as a tool to improve product quality.

KEY WORDS: SUPAC-SS; topical delivery systems; dermatologicals; release testing; FDA guidances.

BACKGROUND

The FDA has taken steps to reduce the regulatory burden associated with retaining approved statuses of existing products when they undergo change(s) in their content and/or their manufacture (SUPAC guidances). Topical semisolids, most particulaly ointments, creams and gels, present unique challenges in these regards. In SUPAC-SS the diffusional release of a drug from a product is introduced as a means of establishing pre- and post-sameness in product performance. Such testing has obvious parallels to dissolution testing of solid dosage forms.

Because of concern about how release testing might be implemented in regulatory decision making, in 1994 the AAPS established an Ad Hoc Committee on In Vitro Release Testing.[18] This committee reported out its determinations concerning release testing in 1995, concluding that, while the in vitro release

[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), the FDA, or any other organization.

[2] Based on the AAPS/FDA Workshop held in Arlington, Virginia on September 8–10, 1997.

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[17] FDA Guidance for Industry. "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.

[18] Members of the Ad Hoc Committee: Srinivas Tenjarla, then Southern School of Pharmacy, Mercer University, now Southern Research Institute, Chairman; Daniel Bucks, Penederm; Gordon L. Flynn, University of Michigan; William I. Higuchi, University of Utah; Boyd J. Poulsen, Syntex; Joel Sequeira, Schering Plough; Jonas Wang, Johnson & Johnson.

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testing cannot, on first scientific principles, be considered as a test for establishing the bioequivalence of a product relative to an innovator's formulation, such testing does appear to have value: a) in formulation design and optimization, b) for determining the likelihood that changes in composition and/or processing of a formulation might impact its function, and c) for qualifying a new manufacturing method or site. Major residual concerns of the committee included the then existing dearth of systematic investigation of the influences of raw material and processing variables on the release of drugs from semisolids and the absence of convincing evidence that release testing might add positively to lot-to-lot quality. The committee recommended an AAPS task force be constituted to further explore the issue of release testing. This task force, formed in 1996, took stock of the practice and possibilities of release testing, as did an independently formed FDA panel drawn together to work on the SUPAC-SS guidance.[19] The AAPS-FDA workshop on release testing summarized herein was planned by these combined groups.

SCIENTIFIC RATIONALE, METHODOLOGY AND EXPERIMENTAL DEMONSTRATIONS

Scientific Rationale

Release testing can, in principle, reveal a lot about the physical attributes (solubility, microscopic viscosity, emulsion state, particle size, etc.) of a semisolid dosage form. In the release test a thick layer of a semisolid is placed in contact with a reservoir and diffusion of drug out of the semisolid and into the medium of the reservoir is followed. In most instances, diffusive communication between the delivery system and the reservoir is through a membrane to keep the product and the receptor medium physicochemically distinct. Membranes are chosen to offer the least possible diffusional resistance. The system's configuration is such that, after a short lag period, release conforms to kinetics expected for diffusion of a chemical out of a 'semi-infinite medium' and into a 'sink'. Regardless of whether the releasing system is a solution or a suspension, the momentary release rate tracks the depth of penetration of the forming gradient within the semisolid application. Beginning at the moment when the receding boundary layer's diffusional resistance assumes dominance of the kinetics of release, the amount of drug released, M, becomes proportional to the square root of time, with the momentary rate of release, dM/dt, becoming proportional to the reciprocal of the square root of time. These quantitative dependencies of release were set out decades ago for solution and suspension systems (1,2,3).

The kinetic and thermodynamic processes underlying the release of drugs from ointments, creams and gels differ in fundamental ways from the processes which determine the partitioning and uptake of the drugs from clinical applications of the same dosage forms. Every attempt is made in the release test to keep the composition of the formulation intact over the releasing period. Thick applications are applied to the test membrane and the diffusion cell system is capped to prevent volatile substances from evaporating. When used clinically, the same formulations are spread thinly (≈20 μm) and are more often than not applied in the open. Substances like ethanol and water, when present, evaporate away quickly. Even substances like propylene glycol evaporate appreciably over a 24 hour period. Consequently, the compositions of applications of creams and gels and some ointments are subject to continual change over the therapeutic delivery period. A membrane is chosen for the release test which offers as little added resistance to transport as possible. In the clinic the systems are applied to an acknowledged high resistance membrane, the stratum corneum of human skin. The stratum corneum, when intact, invariably controls the delivery rate.

[19] The FDA Task Force members: Vinod P. Shah, FDA Chairman, Michael Corbo, Wilson T. DeCamp, Jerome S. Elkins, Terry G. Feldman, Gordon L. Flynn, David DeMagistris, Deborah R. Miran, Prakash V. Parab, David M. Pearce, Donald Schuirmann, Frank Pelsor, Paul Schwartz, Avaraham Yacobi.

Release from Solution Systems

In the absence of a surface resistance of consequence, the release of drugs through a planar surface of semisolid having all of its drug in solution is expected to conform closely to the following equation (1):

$$M = h \cdot C_0 \cdot \left(1 - \frac{8}{\pi^2} \cdot \sum_{m=0}^{\infty} \frac{\exp\left(-\frac{D(2m+1)^2 \cdot \pi^2 \cdot t}{4 \cdot h^2}\right)}{(2m+1)^2}\right) \tag{1}$$

where:

M = amount of drug released into the sink per cm^2
h = total thickness of the semisolid matrix
C_0 = concentration of the drug in the releasing matrix, making $h \cdot C_0$ the amount of drug in the semisolid slab per cm^2 of the slab
D = diffusion coefficient of the drug through the matrix
t = time

The first 30% of release from a solution follows the following far simpler mathematical dependency (2):

$$M = 2 \cdot C_0 \sqrt{\frac{D \cdot t}{\pi}} \tag{2}$$

It can be seen that the amount released is directly proportional to the initial uniform concentration in the matrix, C_0. It is also proportional to the $\sqrt{t}$. The addition of a surface resistance, as would be encountered in a hydrodynamic (unstirred) boundary layer or with the interposition of an actual membrane, only delays the onset of this dependency.

Release from Suspension Systems

Providing that the particle size of a suspended drug is sufficiently small to obviate particle dissolution as a rate-influencing factor, under the circumstance when the total amount of drug present greatly exceeds its solubility, drug release through the planar surface of a suspension matrix and then through a modest external resistance conforms to (3):

$$h_M{}^2 + \frac{2D_M \cdot h_{aq} \cdot h_M \cdot K}{D_{aq}} = \frac{2D_M \cdot C_s \cdot t}{Q} \tag{3}$$

where:

h_M = thickness of the expanding drug free boundary layer in the matrix
h_{aq} = thickness of the interposed membrane (or hydrodynamic boundary layer)
D_M = diffusion coefficient of the drug in the semisolid matrix
D_{aq} = diffusion coefficient of the drug in the interposed membrane (or hydrodynamic layer)
Q = total amount of drug, in solution and suspended, in the matrix
K = semisolid matrix to membrane (hydrodynamic boundary layer) partition coefficient
C_s = solubility of the drug in the releasing matrix
t = time

As time passes, the particle cleared zone of thickness h_M grows such that:

$$h_M^2 >> \frac{2D_M \cdot h_{aq} \cdot h_M \cdot K}{D_{aq}} \quad (4)$$

and, from this point in time on the amount released follows:

$$M = \sqrt{2 \cdot Q \cdot D_M \cdot C_s \cdot t} \quad (5)$$

A plot of M versus $\sqrt{t}$ should be linear with a slope of $\sqrt{2 \cdot Q \cdot D_M \cdot C_s}$. Equation 4 reveals that the time of transition into $\sqrt{t}$-dependency is partition coefficient dependent. The more *relatively* soluble the drug is in the releasing matrix (the larger the partition coefficient as defined above), the longer it takes for the $\sqrt{t}$-dependency to obtain. This seems to explain why some data published recently appear linear with time. These principles of release and the associated equations have been given substantial experimental demonstration over the years (4–29).

The release process is driven by the concentration differential expressed across the boundary formed in the releasing matrix. The momentary rate of release depends on the thickness of this layer and the layer's microscopic fluidity, the latter the principal determinant of a drug's diffusion coefficient through the semisolid medium. In cases where a fraction of the drug, small or large, is present as suspended matter, the solubility of the drug sets the steepness of the operative concentration gradient across the receding boundary. When the drug is completely dissolved, the bulk phase concentration determines the gradient's steepness. The gradient ebbs and thus release slows as time passes.

Methodology

Typically, 200 mg or more of an ointment, cream or gel is spread over a suitable membrane and the membrane with its application is placed application side up in a Franz (vertical) diffusion cell (typically of 15 mm diameter orifice). Sampling is usually performed with volume replacement with fresh receptor medium through a sampling side-arm. In the most common commercial diffusion cell configuration, the contents of the receiver compartment are stirred with a magnetic stirrer modified to assure that effective convective mixing extends to the membrane's undersurface. Six cells tend to be run simultaneously. A releasing surface temperature of about 32°C is maintained throughout a run.

To achieve a sink condition, the receptor medium must have a high capacity to dissolve or carry away the drug in question. This is accomplished by keeping the thermodynamic activity of the drug in the receiver medium at a tiny fraction of that initially found in the semisolid (as close to zero as achievable) or by using flow-through technique. It is desirable to minimize the receptor medium's capacity to elute ingredients from the semisolid matrix other than the drug. A receptor medium is chosen which is compatible with the membrane and formulation.

It is possible at times to study the release of drugs from ointments into aqueous media in the absence of a separating membrane. The release rates of the drugs, betamethasone dipropionate, fluocinonide and clobetasol propionate, from ointments were equivalent with and without interposed membranes, establishing that the membranes used is studying release can and usually do function solely as supportive structures (32). Creams and gels invariably contain phases and adjuvant components which are watery, water miscible or water soluble. A membrane must be placed between them and the receptor to maintain their physical integrities. Membranes are selected for use which: a) are commercially available (the practical way to assure reproducible membrane properties over time), b) have little capacity to bind the drug, c) have little tendency to interact with the releasing medium, and d) offer the least possible diffusional resistance. The inertness and low diffusional resistance of polysulfone membranes have favored their use in the FDA's labs. Other membranes have also been employed successfully.

As with all other tests done on pharmaceutical products, the release test must be validated. To an extent, the type of physical system, ointment, cream or gel, dictates the operational parameters of the test. The most common testing configuration has already been described.[20] A rugged, linear and specific assay for the samples is required. The drug must be adequately stable in the collection medium. Sink conditions have to be assured. Where weak electrolytes are involved, pH has to be adjusted appropriately and maintained. A support membrane (polysulfone, polypropylene, cellulose, polyamide, polyacrylate, polyvinyl, etc.) is chosen and tested for its system compatibility and also to assure it minimally impacts the $\sqrt{t}$-lag time. Assembly of the diffusion cell is standardized. If cell closures made of a rubber or plastic are used, their abilities to sorb the drug in question have to be checked. The amount and the mechanism of application of formula needs standardization. Occlusion is ordinarily favored to assure the formula's physical properties remain intact. Sampling times and the total elapsed experimental time must be determined and standardized in preliminary experiments. In this regard, six hours is the usual test duration in FDA labs. The experimental period can be different than the FDA's depending on the physicochemical properties of system, receptor, and membrane. The $\sqrt{t}$-lag time should be a small fraction (less than 10%) of the total elapsed time of an experiment. Other factors to be taken into account and possibly varied in course of validating an in vitro release procedure

[20] The inverse of this design, a vertical cell configuration with the product or an application thereof covered first by a membrane and then overlayered with the collecting medium is also a workable configuration.

include: a) the system's total drug concentration; b) concentrations of system's excipients (especially structure forming ingredients); c) the nature of mixing (high versus low shear) and time used in mixing during manufacturing operations; d) the temperature history of manufacturing; and e) the order of adding ingredients to form the system. With suspensions, the crystalline form of the drug, the drug's particle size, the drug's particle size distribution, and the quality of the drug's dispersion in the semisolid should be looked into.[21]

When proper care is taken in the manufacture of semisolid systems and then in testing them with respect to their abilities to release the drugs they contain, M versus $\sqrt{t}$ release profiles have proven highly linear and very reproducible. Work from several laboratories on suspension systems containing incrementally varied total drug concentrations have corroborated that the amount released and the momentary release rate are each proportional to the $\sqrt{Q}$. Since the slope of the standard M versus $\sqrt{t}$ plot takes a value of $\sqrt{2 \cdot Q \cdot D_M \cdot C_s}$, independent measurement of either C_s or D_M provides a means of determining the companion variable.

Based on work from several laboratories, the particle size of a dispersed drug impacts release. The $\sqrt{t}$-release rate invariably increases incrementally with decreasing particle size (increased surface area). The same seems to be true with respect to emulsion droplet size of droplets formed in an o/w cream (vanishing cream) (30). Apparently smaller droplets can be cleared of their drug contents more rapidly than larger ones, just as, at a given total drug content, smaller drug particles with greater overall surface area dissolve more rapidly than do larger ones. The amount of the micellar phase formed in preparing an emulsion base (vanishing cream) has an effect on release, with release being faster with increased surfactant in the system (30). However, when the waxy composition of a vanishing cream was varied, the $\sqrt{t}$-release rate was little changed (30).

SCALE-UP AND POST-APPROVAL CHANGES FOR SEMISOLID PREPARATIONS (SUPAC-SS)

Guidances on scale-up and post-approval changes (SUPAC) are intended to lower the regulatory burden placed on the industry while assuring the continued safety and the effectiveness of drug products. The guidances are dosage form specific but each defines three levels of formulation change, essentially minor, moderate and major, for a given type of dosage form and indicates and/or recommends: a) chemistry, manufacturing and control tests to support each level of change, b) in vitro release tests and/or in vivo bioequivalence tests to support each level of change, and c) filing documentation needed to support each level of change. Each guidance allows certain changes in the categories of a) components and composition, b) manufacturing site, c) manufacturing process and equipment, and d) scale of manufacturing. Depending on the defined level of change, reporting requirements escalate from notation in the Annual Report to a submission of a Changes Being Effected Supplement to submission of a Prior Approval Supplement. Prior to the issuance of the guidances, time-consuming Prior Approval Supplements were usually required.

Relevant Level 1 changes under SUPAC-SS are:

I. Components and Composition
   A. ≤5% change in the amount of any or, collectively, all excipients
   B. a change in supplier of a non-structure forming ingredient or a change in supplier of a structure-forming excipient which is a single chemical entity (purity ≥ 95%)

II. Manufacturing Equipment and Process
   A. introduction of alternative equipment of the same design and operating principles within approved application ranges
   B. change in the order of addition of components

III. Batch Size
   A. up to a ten-fold scale-up (or scale-down) of the batch size

IV. Manufacturing Site:
   A. move of production to different area within the approved manufacturing facility.

In the instance of a Level 1 change, a company need only perform already obligatory NDA (ANDA) application and compendial drug product tests on its product. Final documentation of such changes is made in the annual report. Importantly, multiple Level 1 changes are treated no differently than a singular Level 1 change. The first production batch following a Level 1 change must be placed on long-term stability.

The tie-in between release testing and SUPAC-SS is first realized for Level 2 changes. Level 2 changes under SUPAC-SS are:

I. Components and Composition
   A. >5% but ≤ 10% change in the amount of any one or, collectively, all excipients
   B. a change in supplier of a structure-forming excipient which is not a single chemical entity

II. Manufacturing Equipment and Process
   A. introduction of new processing equipment operating by principles different than the equipment originally qualified or operating outside of approved operating ranges (e.g., high shear to low shear or vice versa)
   B. change in the process of combining product phases

III. Batch Size
   A. greater than a ten-fold scale-up (or scale-down) of the batch size

IV. Manufacturing Site:
   A. move of production to different building on the same manufacturing campus (no in vitro release test required).

[21] After standardizing the cell features and procedural features and showing that results are reproduced, the basic formula may be manipulated with respect to its total drug content, its manner of processing, the drug's particle size, and the contents and sources of other ingredient to establish the test's ability to discriminate between the 'reference formula' and formulas made with such deliberate content and processing variations. In these regards, release is particularly and dependably altered by changing the total concentration of drug in the formulation. Product content uniformity can be put to test by taking samples from different locations within the lot. It is thought unlikely that a 'cook-book' test might cover all testing needs. Rather, the general method has to be adjusted to accommodate individual drugs within their specific formulations.

Level 2 Changes Require a Changes Being Effected Supplement

Release testing data which show that the release of the drug from its formulation has not been altered (within specified statistical bounds) are a required part of the information to be presented in the supplement.

Level 3 Changes Require a Prior Approval Supplement

Level 3 component and composition changes require submission of bioequivalence data but the move to a new production site can be qualified with a Changes Being Effected Supplement and supportive release data.

Statistical considerations in in vitro release are illustrated by the in vitro release comparison test described in the SUPAC-SS Guidance. Desirable features of such testing procedures include a simple experimental design, a reasoned data set, and a straightforward, well-understood statistical analysis procedure and decision rule. Testing must take into account the nature of the generated data and the sources of variation that affect the study. Experience suggests that release test outliers may occur, so a nonparametric statistical analysis procedure has been decided upon. Testing is typically done six cells at a time and the possibility of a run-to-run component of variability is considered. Thus both post-change (test) and pre-change (reference) lot material are to be included in each run. A two-stage testing procedure was adopted such that lots with similar in vitro release rates and typical cell-to-cell variability would have a high probability of passing the test at the first stage, but similar lots with unusually high cell-to-cell variability that might not pass the test at the first stage would have a second chance to pass. The proposed statistical procedure is based on a well-known nonparametric confidence interval method (the Wilcoxon Rank Sum test or Mann-Whitney test) applied to the logarithms of the estimated in vitro release rates.

ON THE PROS AND CONS OF IN VITRO RELEASE

In a panel discussion session of the workshop[22] the PhRMA view that SUPAC-SS places an "undue reliance on in vitro release testing to characterize performance characteristics of finished topical dosage forms" was expressed. PhRMA's position was that "based on available scientific evidence and uncertainties that have been raised, the May 1997 SUPAC-SS Guidance for industry needs to be modified to remove ambiguous and inconsistent provisions regarding the acceptance and utility of the in vitro release test." PhRMA concluded that quality assessment approaches existing prior to SUPAC-SS were adequate for assessing the impact of processing and/or composition changes of semisolid dosage forms. In sharp contrast, the FDA view was that in vitro release is based on sound scientific principles and can be used to assure product sameness between pre-change and post-change dosage forms. The FDA took the position that SUPAC-SS actually offers flexibility with regard to use of the in vitro release test. The Agency went on record as being open to alternative approaches as long as information is provided supporting inapplicability of the release test for SUPAC-SS purposes. Those considering alternative procedures and statistical analyses were advised to discuss these with the Agency before implementing them.

Some representatives from the industry and academe strongly supported SUPAC-SS and the use of in vitro release as a product qualifying tool under the SUPAC-SS Guidance. There was general agreement that the test is not a bioequivalence measure, however. The point was made that the test is not overly discriminating and thus suited to SUPAC-SS uses. For instance, substantial changes in the amounts of certain structural ingredients of a standard vanishing cream did not materially alter hydrocortisone's release from the system (30). Additionally, the FDA has shown that different lots of the same formulation tend to release their drugs at the same rate (31,32). Consequently, failure of a dosage form to meet the in vitro release requirement following a Level 2 or 3 change represents a serious departure from expected behavior. Such failure does not necessarily signal that the formulation is clinically unsatisfactory, but it is a call to look further into the situation to identify the reason for the discrepant behavior. An overall impression was that SUPAC-SS represents an appreciable improvement over previously existing FDA formulation requalification requirements despite the fact that in vitro release testing imposes a new burden. The test is receiving attention in Europe given USA-European harmonization efforts.

SUMMARY AND CONCLUSIONS

The release test is reproducible. Established receding boundary theory undergirds the test. The theoretical principles associated with release from suspension systems are particularly well demonstrated. Release data are clearly valued in formulation development in several industrial laboratories. Release rates have proven sensitive to the state of solubilization of a drug, to the drug's particle size, to the method and rigor of drug distribution, and to other factors of system composition and processing.

The following consensuses concerning release testing of semisolids were reached at the workshop:

I. In vitro release testing is based on sound scientific principles. Experience with the test demonstrates that the procedure is rugged and reproducible and that the $\sqrt{t}$-release rate is a distinguishing property of the formulation in question;

II. The in vitro release test can serve as a research tool in the course of developing formulations,

III. The use of in vitro release to demonstrate product sameness for the purposes of SUPAC-SS is acceptable,

IV. The release test is neither a surrogate test for bioavailability nor for bioequivalence and should be used only as supportive evidence in such evaluations,

V. The in vitro release test should not be used for comparing fundamentally different formulations (e.g., ointments vs: creams),

VI. In vitro release is generally formulation dependent and therefore should not be used to compare similar formulations of different manufacturers. The meaningful use of the release test is for showing that the fundamental properties of a formulation of given content and manufacturing method have essentially

[22] Panel composition: Gordon L. Flynn, Vinod P. Shah, James E. Tingstad, Thomas White, Avaraham Yacobi.

been maintained following a SUPAC-SS-defined Level 2 change,

VII. Changes made in a specific manufacturing process and/or in a specific formulation's composition may affect the release rate. Such changes suggest, but are not proof, that the formulation's drug delivery attributes may have been altered,

VIII. The release rate may provide evidence of product sameness, or lack thereof, of different batches of a given semisolid product. Whether the test is sufficiently discriminating for it to function as the sole measure or even a principal measure of batch-to-batch reproducibility of a given product is a matter of controversy,

IX. While the theoretical principles associated with release testing of semisolid suspensions (drugs in suspension) are well established, more work is needed to reach the same level of understanding when a drug is completely in solution,

X. No universal release testing procedure nor universal test conditions exist. Rather, the release test must be tailored to a formulation. Suitable test conditions can usually be developed,

XI. A change in in vitro release rate may be indicative of a change in the clinical performance of the dosage form in question.

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