



In vitro release testing for semisolid formulations



In vitro release method development and validation for employment as a rational tool in the dermatological product development and quality control procedure

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Introduction

Dissolution testing in the pharmaceutical industry has been employed as fundamental tool in the formulation design and quality control of finished products. Although initially employed for solid oral dosage forms it has recently widened its concept and application for semisolid dosage forms. In this special dosage forms the test is usually referred and named as in vitro release testing (IVRT), since the drug in dissolved state in the vehicle has to diffuse and be released by the vehicle, becoming available to penetrate into skin. For quality control purposes, the method can be employed as performance test that should be designed to demonstrate the dosage forms were manufactured according to specifications

and all critical manufacturing steps assuring batch-to-batch sameness. Secondly, in research and development the focus of release testing is shifted to other purpose. The vehicle composition and design strongly influence the product performance and how rapid the drug will be then released into the skin. Therefore the test can provide some predictive estimates in respect to the in vivo performance of a drug product.

The FDA Guidance on Scale up and Post Approval Changes for Semisolid (SUPAC-SS) represents the current scientific opinion from FDA on the topic and it is intended to lower the regulatory barriers placed on the industry while assuring the effectiveness of the product.

Considering the regulatory perspective the in vitro release testing can be a cost and time-saving alternative to bioequivalence studies for assessing product sameness after postapproval changes. In response to this current demand, Across Barriers GmbH has established the service offering the development and validation of in vitro release tests intended to be employed either to initial screening of experimental formulations in the product development phase or to assess batch-to-batch sameness and the correspondence of products postapproval changes according to SUPAC-SS.

Release testing for quality control

Present quality control tests for topical dermatological preparations include identification, assay, homogeneity, rheological properties, specific gravity and particle size determination. These tests provide little information about the drug release properties of the product or the effect of processing and manufacturing variables on the performance of the finished dosage forms. Since the in vitro release rate can reflect the combined effect of several physical and chemical parameters, it represents an essential tool in quality control to assess product "sameness" under certain scale-up and postapproval changes for semisolid products. The physical characteristics from semisolid products widely vary from each other and no single test procedure would be suitable for all semisolid dosage forms. It is therefore clear the need of developing a method for each formulation product.

Release testing in formulation screening

Besides the applications for quality control purpose, in vitro release testing also plays an important role during the drug product development. The use of animal skin (e.g. rat or porcine skin) next to ex vivo human skin is widely employed as an approach to assess dermatological formulations performance. Since a wide range of experimental formulations is necessary in the early screening phase of a drug product, it therefore will require the use and/or sacrifice of many animals. In vitro release testing is a cost-effective alternative to narrow the selection of test products candidates to the subsequent biopharmaceutical characterization phase, representing a rational strategy in the screening phase. The figure below illustrates the mechanism of drug release.

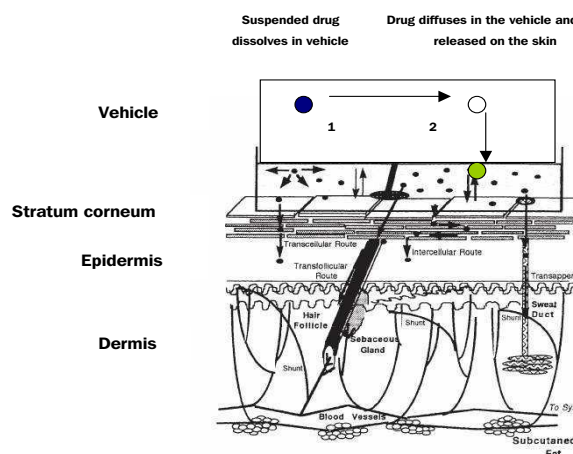


Figure 1: Representative figure of the drug release from semisolid formulations. The suspended drug dissolves in the vehicle and diffuses through it until be released on the skin. experiments are important to characterize the vehicle performance in terms of drug solubility, diffusion and release (steps 1 and 2).

Employment of diffusion cells

Among the methods described for release testing the employment of Franz cell system fitted with a synthetic membrane is widely described and accepted. The formulation is applied in the donor compartment. The drug diffuses through the synthetic membrane being released into the acceptor medium. The selected membrane should provide an inert holding surface for the test formulation, but not a barrier, so that the drug release would reflect the vehicle properties and not the membrane rate-limiting properties. It is important to confirm that there is no interaction, physical or chemical, between the membrane and the formulation. The nature of the membrane have be also considered in the method development phase in order to select the less resistant to drug diffusion and enhance sensitiveness of the method. The medium to be employed in the release studies should provide a "diffusional sink" for the active ingredient released from the semisolid formulation and if the method is employed for SUPAC-SS purpose, it should be also able to distinguish postapproval formulations which undergone level 2 and level 3 changes. The most important factor for the selection of receiving medium is the solubility of the active ingredient in the medium. Another important factor is that it should not be no more than 30% of the total amount of the dose applied released into the medium at the end of the experiment in order to avoid receptor back diffusion into donor compartment.

Aliquots are removed from the receptor phase and monitored within 6 hours, yielding a release curve. The slope of the curve represents the release rate. Across Barriers GmbH offers complete release method development employing Franz-cell systems considering all important parameters regarding membrane and medium selection.

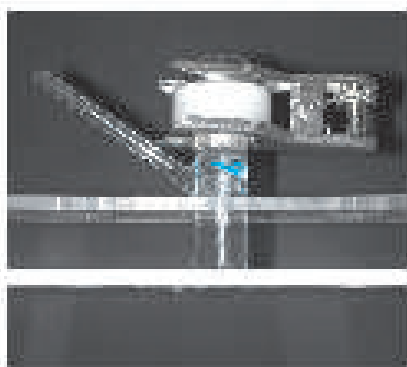


Figure 2: Representative figure from a Franz diffusion cell setup. The test formulation is applied in the donor compartment, the drug is released from the formulation and diffuses through the inert membrane into the acceptor medium. The samples are removed along 6 hours.

In vitro release method development

The in vitro release method development with the employment of Franz cells comprises the appropriate membrane and receiving medium selection and the investigation of the method sensitiveness after parameters selection. Membrane candidates should be investigated in terms of resistance to drug diffusion. Receptor medium should assure adequate drug solubility and stability. In case the method will be applied for confirming product sameness after SUPAC-SS level 2 and level 3 postapproval changes, it should provide suitable sensitiveness to distinguish prechanged from postchanged formulation. Test formulations are assayed in parallel to reference formulation. For the method development modified formulation is required to simulate change in the components or composition, the manufacturing (process and equipment), the scale-up/scale-down of manufacture, and/or the site of manufacture of a semisolid formulation during the postapproval period as described in the FDA Guidance. The figure 3 illustrates a experimental run according to SUPAC-SS Guidance, where reference product is compared to test product.

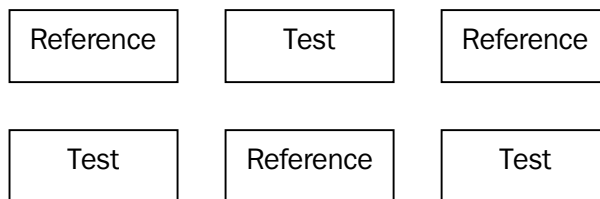


Figure 3: The typical in vitro release testing apparatus has six cells. For each run of the apparatus, the two products being compared should be assigned to the six cells as follows: where "Test" represents the Postchange Lot (Test product) and "Reference" represents the Prechange Lot (Reference product). This approach of including both products in each run of the in vitro apparatus will help ensure an unbiased comparison in the event of a systematic difference between runs.

In vitro release method validation

After selection of suitable membrane and acceptor medium, the method has to be validated with regard its repeatability, reproducibility and robustness. Franz cell-to-Franz cell variability can be employed to assess method repeatability whereas the method reproducibility can be assessed performing experiments in different days (inter-day and inter week precision) and with different employees. For robustness, the critical parameters have to be selected to be investigated. A robust method has to keep the reproducibility and repeatability against small changes in the experiment conditions, as change in the pH, temperature and stirring rate.

Analytics

Before initiating an in vitro release experiment, an analytical method for analyzing and detecting the active ingredient has to be developed and validated. The effort expended on validating the analytical method will depend on the questions to be addressed in the study and the how the data is to be used. In addition to the classical LC-UV/PDA/MS detection methods, a scintillation counter is available for detecting radioactively labeled substances or markers. If the customer has already an analytical method for release experiments or a method employed for another purpose, Across Barriers GmbH is flexible to offer an analytical method adaptation reducing the time spent in the analytical method development. Across Barriers GmbH offers a wide range of analytical services and qualified analytical team

Results

The following figures show selected representative results from Across Barriers GmbH. They offer an overview of the areas in which the technology can be applied.

Quality control and SUPAC-SS test

In vitro release testing is an essential tool for monitoring batch-to-batch sameness. This section presents the employment of a validated IVRT method for quality control of triamcinolone acetonide o/w creams 0.1%. The graphic below shows the release profile of one commercial formulation from two different approved batches. Since they have passed the classical quality control tests (drug content, pH, viscosity and others) their release rate have not shown significant difference (Mann-Whitney-U statistical test was employed according to SUPAC-SS Guidance).

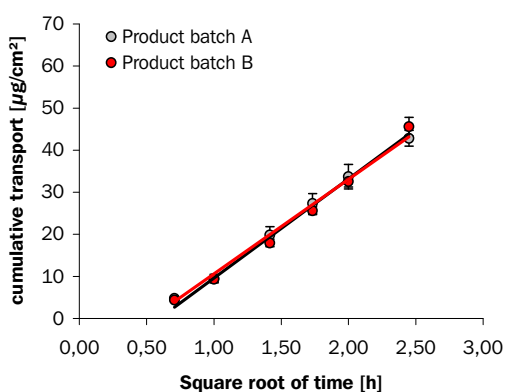


Figure 4: Release profile of triamcinolone acetonide cream 0.1% from 2 different batches. Data represent mean values \pm SD of 6 different diffusion cells for each test product.

A third batch from the same product was submitted to opened-container storage during 30 days at 40° C in order to force critical modifications in the vehicle, which might strongly affect the product performance. The figure 5 shows the release profile of the modified or stressed product (test formulation) compared to the reference product. The storage at 40°C has probably provoked modifications in the physicochemical properties of the vehicle, particularly regarding its water content, which has consequently reflected in the release rate. Our validated IVRT method has demonstrated capacity of discriminating critical alterations when, proving

its usefulness to assess product sameness after critical changes.

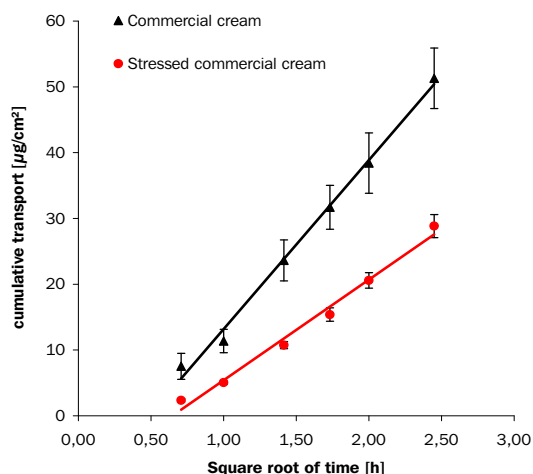


Figure 5: Release profile of triamcinolone acetonide cream 0.1% reference product and test product (stressed formulation). Data represent mean values \pm SD (n = 6).

Formulation optimization and development

Experimental formulations can be compared to each other or cross compared with marketed formulations in terms of release performance in the development and/or optimization phase giving a sign of what would be the performance in vivo. The figure 6 illustrates the cross comparison between innovator prednicarbate product 0.25% and test formulations prepared at the same strength with different experimental vehicles.

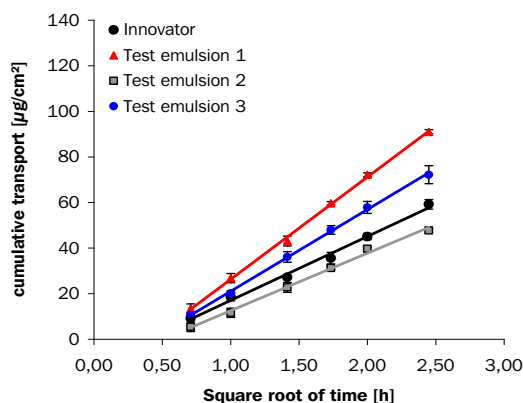


Figure 6: Release profile of prednicarbate test products 0.25% cross-compared with innovator. Data represent mean values \pm SD (n=3).

The results clearly demonstrate that the test emulsion 1 and test emulsion 3 have presented higher release rate in comparison to reference product. This demonstrates the usefulness of the validated IVRT method in the screening phase of a product development.

Service of Across Barriers GmbH: when to apply a validated in vitro release method?

Applications for quality control purpose:

- Did your formulation undergo postapproval change and now you need approval from regulatory affairs?
- Do you plan to change excipients from your formulation and elucidate the impact of this change in its release performance?
- Do you plan to change the manufacturing site and assess the sameness between the batches produced in site 1 compared to site 2?
- Did you change the equipments or manufacturing procedure from your product and now you would like to assess the correspondence between the formulations manufactured with method and/or equipment 1 and method and/or equipment 2?
- Would you like to implement an additional quality control procedure, which gives more information regarding vehicle performance than classical quality control methods?

Applications for formulation screening:

- Would you like to have predictive estimates in respect to the in vivo performance of a drug product before proceeding to biopharmaceutical characterization?
- Would you like to have a cost-saving formulation screening, reducing the number of candidates for the next development phases?
- Are you developing a new dermatological drug product and would like to compare it in terms of release performance with commercial formulations?

- Are you developing a generic product and would like to compare it in terms of release rate with innovator formulation?
- Would you like to investigate the effect of aging in the release performance of your test formulation?
- Would you like to optimize or redesign the vehicle from your drug product and characterize it in terms of release performance?

Using Across Barriers GmbH in vitro release testing you minimize time and costs in your product development phase.

Conclusion

The employment of Across Barriers GmbH IVRT methods will increase significantly the chances of success in the pharmaceutical development of semisolid dosage forms and will fit the requirements of your schedule.

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