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Workshop Report

Workshop III Report: Scaleup of Liquid and Semisolid Disperse Systems[1]

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BACKGROUND

The American Association of Pharmaceutical Scientists, the Food and Drug Administration and the United States Pharmacopoeia co-sponsored the third in a series of workshops on the scaleup of pharmaceutical dosage forms. The first two workshops dealt with the Scaleup of Immediate Release Oral Solid Dosage Forms (December, 1991) and the Scaleup of Oral Extended Release Dosage Forms (September, 1992). The prior workshops provided further guidance on control of compositional changes, equipment, processing and manufacturing site changes within the context of the FDA's Office of Generic Drugs Guideline #22-90. These workshops, in particular the Extended Release Workshop, focused on *in-vitro/in-vivo* correlations. Dissolution testing as a surrogate for bioavailability/bioequivalence was reviewed for immediate release dosage forms and dissolution requirements were suggested based on the concept of a hierarchical organization of drugs into categories. The categories of high permeability/high solubility, high permeability/low solubility or low permeability/high solubility, and low permeability/low solubility were proposed in the first workshop.[1] Extended release dosage forms represent a more complex situation and in Workshop II[2] there was extensive discussion on the use of dissolution as a surrogate for bioavailability/bioequivalence relative to the current USP categories of "Level A, Level B, or Level C" correlations. Workshop II also presented the concept of using "mapping" studies to determine the range of acceptable *in-vitro* dissolution relative to actual and predicted bioavailability/bioequivalence. The workshop report summarized the iterative nature of the interaction between *in-vitro* dissolution and bioavailability/bioequivalence testing and proposed a decision tree for use in monitoring the scaleup of solid, oral extended release products.

Although liquid and semisolid disperse systems represent a smaller segment of pharmaceutical products than do oral, solid dosage forms, they are an important segment of the pharmaceutical catalog and would greatly benefit from the establishment of additional scientific principles for scaleup. The AAPS/FDA/USP Workshop III on the subject of Scaleup of Liquid and Semisolid Disperse Systems tried to identify the issues involved in the manufacturing scaleup of solutions, emulsions, suspensions, creams, gels, ointments, pastes, and suppositories. Topics of the two and one-half day workshops were organized so as to facilitate development of a physical-chemical data base to support the definitions of major and minor scaleup changes, to explore the feasibility of using *in-vivo* and/or *in-vitro* tests to support the scaleup of non-systemic disperse systems in terms of quality and performance and to delineate key parameters and process changes that affect scaleup of these dosage forms. The goals of the workshop were organized to address and attempt to answer the following key questions:

- What are the critical factors that influence product attributes and performance during the scaleup of liquid and semisolid dosage forms?
- What data exist to support the bioequivalence of a biobatch and/or a production batch following scaleup of liquid and semisolid disperse systems?
- What *in-vitro* and *in-vivo* methodology and/or specifications can be used to support the scaleup of liquid and semisolid formulations?

As with the previous workshops, an essential component of the understanding of scaleup was to define a common lexicon specific to these dosage form types. The lexicon generated by the committee for this specific workshop is included in the attached glossary.

COMPOSITIONAL CHANGES

Workshop Reports I & II proposed a reasonable range of quantitative composition for excipients. Changes within this range were defined as "minor" in scope and, therefore, needed no further justification other than comparison of the dissolution profile. The situation with liquid and semisolid

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

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disperse systems is less well-defined and it is more difficult to define allowable ranges. Typical components of solutions, emulsions, and suspensions include water, oils, buffers, thickeners, emulsifiers/surfactants, preservatives, stabilizers such as antioxidants and chelating agents, co-solvents, flavors, sweeteners, colorants and one or more active ingredients. Typically, the chemical properties of excipients are defined by one or more compendia (USP/NF, BP, JP, EP, etc) or reference documents (Food and Chemical Codex, FDA's GRAS List, etc). However, the physical properties of these materials, which are often critical to their functionality or performance, are often not well defined. Therefore, it is necessary for supplier-to-supplier and inter-lot variability to be defined and evaluated as part of the formulation activity. It is important to note that this issue is an underlying formulation development activity and not necessarily a variable associated with scaleup. Any variability must be defined and, if critical, controlled as part of an understanding of the basic formulation. Excipient variability is not caused by the scaleup of drug product although one might expect that it might be seen more during scaleup when additional lots of material or new suppliers are used.

The workshop recognized that the relative composition of inactive excipients may need to be adjusted during the scaleup process in order to optimize the formulation. These adjustments may result from the need to compensate for manufacturing losses associated with scaleup and, in these circumstances, are made to assure that the product continues to fall within pre-established specifications and ranges. It was acknowledged that for any excipient that was not associated with control of drug release from the dosage form or known to affect drug permeation, formula adjustments would be considered "minor". Changes to any excipient which would impact on drug release or permeability from the dosage form would be "major" and would require substantial documentation. Because of the general lack of *in-vitro/in-vivo* correlations of topical drug products, such changes may require a multi-tiered approach for their justification including evaluation of *in-vitro* release of drug and drug permeability; the use of diffusion cell measurements (e.g. Franz cell), or predictive surrogate biological models, pharmacodynamic models (e.g. vasoconstrictor assays for corticosteroids); and pharmacokinetic methodology (e.g. skin stripping) as alternates to clinical evaluation or as an adjunct to a modified (reduced) clinical program.

It was the consensus of the committee that pharmaceutical formulators and analytical chemists should develop meaningful analytical tests for the components used in semisolid, suspension and emulsion dosage forms. This may be more important with these dosage forms due to the fact that many components are natural products with varying degrees of purity, or polymers with varying molecular weights. Some excipients are known to show variability as a result of differences in manufacturing history, especially differences in processing temperature. The development of innovative analytical methodology, used together with physical observations can prevent unwanted changes in final product characteristics such as polymorphism or phase changes. The primary attributes of excipients and/or active ingredients that the committee thought should be monitored are polymorphism, particle size, melting point or range, phase transition points and molecular weight or molecular weight distribution (polymeric excipients) in addition to the traditional measurements of purity and potency.

SCALEUP EQUIPMENT AND PROCESS

The primary finished product attribute to control during the scaleup of a liquid or semisolid disperse system, manufactured in identical, similar, or different equipment is the degree of "sameness" of the finished dosage form to previous lots. Four criteria are used to evaluate sameness: 1) adherence to raw material controls and specifications; 2) adherence to in-process controls; 3) adherence to finished product specifications; and 4) bioequivalence to previous lots. It is generally agreed that the methodology to assess the biological equivalence of dosage forms during process development and scale-up is less precise and less predictive than that used for oral delivery systems. The importance of control (criteria 1, 2 and 3 above) for liquid and semisolid disperse systems must be emphasized.

The section on compositional changes addresses the issue of raw material controls as applied to both excipients and active drug substances. It also addresses some of the final product methodologies and tests to be used in conjunction with other in-process and finished product specifications. This applies to situations of different manufacturing equipment, or a different manufacturing site with or without different equipment, and different processing procedures. The primary in-process and finished product specifications and controls that are evaluated could typically be selected from the following list based on the dosage form type and the specific formula and manufacturing process.

SOLUTIONS

In-Process Controls

- agitation (rate, intensity, and duration)
- heat gain/loss (rate and overall time)
- order of addition
- filtration

Finished Product Specifications and Controls

- chemical potency
- purity
- pH
- clarity
- preservative efficacy
- viscosity
- specific gravity
- stability
- weight loss

EMULSIONS/SUSPENSIONS

In-process Controls

- agitation (rate, intensity, and duration)
- temperature of phases
- heat gain/loss (rate and overall time)

order of addition
particle size reduction (conditions and effectiveness)
emulsification conditions (time, rate and temperature)

Finished Product Specifications

chemical potency
purity
content uniformity
preservative effectiveness
pH
particle size (suspensions)
particle size distribution (suspensions)
morphology (suspensions)
rheology
settling rate (suspensions)
resuspendibility (suspensions)
specific gravity
emulsion physical stability (droplet size, syneresis)
in-vitro release profile
stability

GELS

These dosages forms are thickened solutions or suspensions. Appropriate controls and specifications such as viscosity, specific gravity and *in-vitro* release listed for Emulsions/Suspensions should be evaluated.

CREAMS/OINTMENTS

Creams are thickened emulsions and ointments are thickened, generally, non-aqueous solutions or suspensions. Therefore, the controls/specifications listed in the table for Emulsions/Suspensions such as viscosity, specific gravity *in-vitro* release and temperature history should be monitored. Additionally, control of the temperature history of creams and ointments may be important to understanding the impact of these on release characteristics.

SUPPOSITORIES

Suppositories may either be formulated with non-aqueous bases (fats, fatty esters, hydrogenated oils, etc.) or with aqueous-soluble bases (glycols and other high molecular weight alcohols). Drugs may be dissolved or suspended in the base and the controls/specifications used to evaluate these should be based on whether the drugs are suspended or dissolved. The temperature history of suppositories should be monitored based on scale and processing equipment. The impact of this history on polymorphic transition, solubilization of active ingredient, phase transition, changes in melting or congealing behavior and drug release should be monitored for the finished dosage form.

The key to effective control of the scaleup and processing of these dosage forms, as with all other dosage forms, is based on appropriate process validation with the key measures of conformity being in-process and final product controls and specifications, comparative accelerated stability, and *in-vitro* release testing or use of other surrogate methods of final dosage form performance.

APPROACHES TO *IN-VITRO* AND *IN-VIVO* TESTING

The formulator is advised that it may be possible to select one or more of the following techniques to evaluate and control liquid and semisolid disperse systems. Although these techniques may not be true measures of the bioavailability or *in-vivo* performance of a dosage form, they can be used in conjunction with other techniques to further assure the performance reproducibility and control of the finished product. When used with analytical and physical techniques on dosage forms scaled-up by appropriate validated processes, they are valuable tools to aid formulation scientists in the development and evaluation of finished product. However, they may not be applicable to every topical formulation.

• ABSORPTION MODELS

For topically applied drugs intended to provide systemic effect, a number of tests may be used to determine the kinetics of penetration. The primary approach is to measure systemic plasma concentrations of the drug directly, using sensitive and specific analytical methods. A second approach, often employed where assay sensitivity is insufficient, involves the measurement of percutaneous absorption of radiolabeled drug *in-vivo* (animal or man). A deficiency of the latter approach may be the failure to confirm an identical manufacturing history for the test product and the intended commercial product. The test product is almost always made at smaller, lab bench scale or involves adding a labelled drug to the test product. Therefore, the test batch has a unique formulation history which could affect the release performance of the product.

• *IN-VITRO* DRUG RELEASE MEASUREMENT

Techniques for the measurement of release of active drug substances from topical drug products have been outlined by a number of authors.[3,4,5,6] The USP issued a stimulus to the revision process in the March/April, 1993 Pharmacopeial Forum which describes the method for *in-vitro* release measurement of topical dosage forms.[7] Other authors have applied *in-vitro* release effectively to the quality control of antifungal creams.[8] Whenever *in-vitro* release methodology is applied, all the data collected should be utilized in the evaluation of the release performance[9]. This test is appropriate for monitoring product reproducibility during scale-up or transfer to another manufacturing site. While these methods may be considered for evaluation of process and formulation parameters, the relevance for comparison of different formulations across manufacturers is much more questionable.

• MODIFIED STOUGHTEN-MCKENZIE VASOCONSTRICTOR ASSAY[10]

This procedure quantitates skin penetration using the pharmacological effect (i.e., skin blanching) induced by topically applied corticosteroids. The technique can be used for liquid, gel, cream and ointment formulations of

this important class of drugs but does not apply to any other drug classes.

- SKIN STRIPPING

Skin stripping removes successive layers of stratum corneum for analysis of drug content and can help determine the impact of both formulation and process changes on the degree of drug penetration. There is insufficient data to confirm the value of this method for bioavailability testing but the technique has been investigated and appears to have specific application to antifungals, corticosteroids and an antiviral product[11].

Much more extensive reviews on these methods have been published elsewhere.[12,13] Readers are advised to review these approaches and evaluate them for application during stages of formulation development. If a history is obtained during product development this information should prove useful in showing the degree of sameness during scaleup.

Finally, it is suggested that any organization involved in the scaleup of liquid and semisolid disperse systems obtain regulatory input from the FDA (both Center and District levels) to assure that the proposed specifications and test methods for control of the components and finished dosage forms are adequate and acceptable to the reviewing scientists.

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GLOSSARY OF TERMS
SCALE-UP WORKSHOP ON LIQUID AND SEMISOLID DISPERSE SYSTEMS

1. **Creams**
   Semisolid emulsions with a creamy white opaque appearance that contain suspensions or solutions of drug substances for external applications.
2. **Drug Release**
   The disassociation of a drug from its formulation thereby permitting the drug to be distributed into the skin or be absorbed into the body where it may exert its pharmacological effect.
3. **Emulsification**
   A process in which two immiscible phases are mixed to generate a stable mixture.
4. **Emulsifying agent**
   Any agent that substantially delays the time required for emulsion droplets to coalesce.
5. **External phase**
   The external phase or the continuous phase of an emulsion is represented by that portion of the emulsion that surrounds the internal phase.
6. **Gels**
   A semisolid system in which the liquid phase is constrained within a three dimensional cross-linked matrix. The drug substance may be solubilized or suspended within the liquid phase.
7. **Internal phase**
   The internal phase or the dispersed phase of an emulsion comprises the droplets that are found in the emulsion.
8. **Liposome**
   An artificial vesicle of one or more concentric bilayers composed of one or more synthetic or naturally occurring lipids.
9. **Liquid crystal**
   An organic liquid whose physical properties resemble that of a crystal (high degree of order) while still permitting some freedom of movement and shape change.
10. **Micro-emulsion**
    An oil/water or water/oil emulsion producing a transparent product that has a droplet size less than 0.15μ and does not have the tendency to coalesce.
11. **Oil-in-water emulsion**
    An emulsion in which oil droplets (internal phase or dispersed phase) are dispersed in an aqueous phase (external phase or continuous phase).
12. **Ointments**
    Semisolid preparations that soften but not melt when applied topically and function as protective or emollient vehicles.

13. **Pastes**
    An ointment-like preparation which contains a high proportion of insoluble solids.
14. **Pilot batch**
    The manufacture of a product, under small-scale conditions, using similar equipment and process as intended for commercial production.
15. **Preservative**
    An agent that prevents or inhibits microbial growth in a formulation to which it has been added.
16. **Sedimentation rate**
    The rate at which sediment (non-soluble material) settles out of a suspension.
17. **Solutions**
    Liquid preparations that contain one or more soluble drugs. Solutions may also contain other ingredients which help to stabilize or solubilize the active drug substance.
18. **Suppositories**
    A dosage form consisting of a dissolved or dispersed active ingredient in a solid, which melts or dissolves upon administration via the rectal, vaginal or urethral route.
19. **Suspending agent**
    An excipient added to a suspension to decrease the rate of sedimentation of the active ingredients.
20. **Suspensions**
    Preparations of finely divided, undissolved drug(s) dispersed in a liquid phase.
21. **Syrups**
    Concentrated solutions of sugar in water that may or may not contain flavoring agents or drugs, which possess taste masking properties for bitter and saline drugs.
22. **Unit Process**
    A specific operation (i.e., weighing, mixing, etc.) within the overall process product manufacture.
23. **Viscosity**
    The resistance of a system to flow under an applied stress.
24. **Water-in-oil emulsion**
    An emulsion in which water droplets (internal phase or dispersed phase) are dispersed in an oil phase (external phase or continuous phase).