Workshop Report

Workshop III Report: Scaleup of Liquid and Semisolid Disperse Systems


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. Extended release dosage forms represent a more complex situation and in Workshop II 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 quantititative 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

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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 it to 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)