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Pharmaceutical Product Quality Research: An Overview for Solid Oral Dosage Forms

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ABSTRACT

Product quality, like safety and efficacy, is a prerequisite for manufacturing approval of all pharmaceutical products. This requirement must not be compromised even after the product has been approved for marketing. Development of in vitro testing methods that are predictive for product *in vivo* performance is the most challenging goal in product quality research. In recent years, our Laboratory has been involved in this area of research for a variety of pharmaceutical products including oral solid dosage forms, metered dose inhalers, suspension products, transdermal patches and topical products including creams, ointments, and suppositories. The author intends to share some of his research experience in addressing product quality issues for the above mentioned dosage forms in a series of review and research articles. As the first in this series, an overview of the quality issue for oral solid dosage forms is presented.

Key words: Product quality, solid oral dosage forms, *in vitro-in vivo* relationship.

INTRODUCTION

The approval of pharmaceutical products marketed in the U.S. is strictly regulated by the Food and Drug Administration. In accordance with the Food, Drug and Cosmetic Act (FD&C Act), all pharmaceutical products require evidence of safety and efficacy for manufacturing approval. Furthermore, manufacturers are required to ensure that the quality of approved products must meet the original New or Abbreviated New Drug Applications (NDA or ANDA) standards throughout the marketing period. Consequently, bioequivalence (BE) evaluations are frequently carried out to ensure product quality during scale-up, change of manufacturing process, manufacturing sites, etc.

Recent advancements in pharmaceutical research have greatly improved our understanding of the relationships of *in vitro* characteristics of pharmaceutical products to their *in vivo* performance. Our Laboratories have been working in this area of research for many years covering a variety of pharmaceutical products, i.e. both immediate release (I.R.) and controlled release

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(C.R.) oral solid dosage forms, metered dose inhalers, suspension products, transdermal patches and topical products including creams, ointments, and suppositories. We strongly believe that with a thorough understanding of the *in vitro* and *in vivo* relationships of these products, we may be able to find a simpler test (under a set of specific *in vitro* test conditions) to ensure product quality and to bypass more complicated and costly BE evaluations.

The objective of this article is to present an overview of our research experience on drug product quality. Since the majority of the drug products on today's market are oral solid dosage forms, it is important to give them first attention in dealing with product quality issues. Other dosage forms mentioned above will be discussed separately in the future.

HISTORIC BACKGROUND

There is no disagreement between the pharmaceutical industry and the regulatory agencies concerning the necessity of quality assurance for drug products due to their direct impact on to human life. However, just how much regulation is necessary and sufficient tends to change from time to time depending on many factors such as available scientific information, available analytical and testing techniques, and economic considerations.

About some thirty years ago, the quality of oral solid dosage forms was considered to be "assured" by random sampling of individual tablet or capsule weight during the manufacturing process. The rationale behind this practice was based on the assumption that the drug ingredients and excipient are mixed homogeneously in the finished product. By controlling the variation of tablet or capsule weight, both the quantity of the active drug ingredient and hence the quality of the product were controlled. This practice was soon deemed to be unacceptable once a specific assay method was available to quantify the active ingredient in the final product. The requirement that the finished product to be assayed for actual drug content became obligatory.

Since Marshall,*et al*[1] presented the first evidence of the possible link between deficiency in drug bioavailability and its poor solubility, pharmaceutical scientists have learned that more emphasis must be given to the amount of drug solubilized in solution to ensure its efficacy. Controlling the amount of active drug ingredient in a dosage form may no longer be sufficient to ensure final product performance. Disintegration, and consequently dissolution of oral solid dosage forms, has emerged as a better and a more appropriate test for product quality.

With the advancement in bioanalytical techniques in recent years, for example, the use of high performance gas and liquid chromatographic separation in combination with highly sensitive detection systems, drug levels in the human body after administration can easily be determined. With the availability of these techniques, BE evaluations have become methods of choice for ensuring product quality. However, making it a routine requirement will undoubtedly increase the economic burden on the industry. To reduce the burden on the industry without compromising the quality of drug products has become the ultimate challenge for pharmaceutical product quality researchers.

ESSENCE OF *IN VITRO/IN VIVO* RELATIONSHIPS

Development of *in vitro* testing method(s) that can reflect the *in vivo* availability of pharmaceutical products has been a primary goal for product quality research. In essence, only with a clearly defined relationship between the biological (*in vivo*) property, and the physicochemical (*in vitro*) property produced by a dosage form, can one consider a simpler *in vitro* test be used as a surrogate for a more complicated *in vivo* evaluation.

The potential regulatory applications of *in vitro/in vivo* relationships have been widely explored in recent years[2-5]. The United States Pharmacopeia (USP) has classified them in three

different levels, namely, Level A, a point-to-point correlation; Level B, a statistical moment correlation; and Level C, a single point correlation[6]. Level A is the most desirable correlation since the *in vitro* drug release rate (dissolution) and *in vivo* input rate (absorption) are superimposable or directly proportional. However, Level B and Level C correlations can also be useful in product quality research when Level A correlation can not be achieved.

The guidance for Scale-Up and Post Approval Changes for Immediate Release solid dosage forms (SUPAC-IR)[7] developed recently by the Food and Drug Administration (FDA) represents a milestone in employing in vitro information for assessing the impact of change in manufacturing on *in vivo* performance. The eventual extension of the guidance in employing *in vitro* data for *in vivo* evaluation to extended-release solid oral dosage forms will constitute another milestone. Future product quality research for pharmaceuticals other than oral solid dosage forms will probably follow the same concept in employing *in vitro* and *in vivo* relationships.

IN VITRO DISSOLUTION TESTS

Apparatus

Dissolution testing, performed under selected test conditions, has long been considered as the most valuable *in vitro* method to predict *in vivo* performance for many oral solid dosage forms. At the present time, there are four compendial dissolution systems adopted by the USP for solid oral dosage forms: namely, Basket, Paddle, Reciprocating Cylinder (Bio-Dis) and Flow-Through Cell systems[8]. While the Basket and Paddle are simple apparati that have been used widely for over twenty years for most I.R. oral solid dosage forms, the Bio-Dis and Flow-Through apparati are good complements for C.R. oral dosage forms.

In selecting the appropriate apparatus for an *in vitro* test, our experience has been not to limit our choices to the compendial systems. Some unconventional systems, such as the Rotating Dialysis Cell[9] and Index Release[10] apparati have been proved to be successful in establishing *in vitro* and *in vivo* relationships for some C.R. formulations. Of course, all systems used must be carefully evaluated for their suitability in dealing with the individual formulation. There is no simple way of finding the appropriate apparatus for each formulation. Understanding the mechanism of the drug release and the characteristics of a formulation is perhaps the best approach to finding a successful *in vitro* test for product quality research.

Medium

Physiological relevant buffer solutions are the media of choice for all I.R. and C.R. oral solid dosage forms. These buffer solutions cover a wide range of pH values from pH 1.2 (gastric fluid) to as high as pH 8.0 (large intestine). The once preferred choice, water, may not be appropriate due to lack of buffering capacity. The test performed with this medium may not be relevant to the *in vivo* situation especially for drug compounds which exist as sodium salts. These drugs are generally highly soluble in water and give solutions with a high pH value. At gastric acidity, the low pH of the solution neutralizes the base soluble salts, and consequently the drug compounds may be precipitated out. To fully characterize the drug release from oral solid dosage forms that simulate *in vivo* conditions, multi-media dissolution profiles seem to be the best choice.

Dissolution media containing alcoholic or other organic solvents are occasionally used when drug products are sparingly soluble in an aqueous medium. However, such media are not physiologically relevant and not likely to generate good data for *in vivo* interpretation. The alternate methods generally involve the inclusion of surface acting agents (surfactant) in the aqueous medium. Among a wide variety of cationic, anionic and neutral species, such as sodium lauryl sulfate (SLS) and polysorbate (Tween) are the most commonly used surfactant

in compendial methods. In pursuing the best methods for product quality research, many other surfactant such as sodium dioctylsulfosuccinate, cetylpyridinium, and octoxynol (Triton X-100), as well as others have been looked at in our laboratory.

Inclusion of enzymes in the dissolution medium, though not routinely used, is quite acceptable due to their natural occurrence in the gastrointestinal (G.I.) tract. Recent studies of pellicle formation due to crosslinking in gelatin capsule shells suggest that addition of enzymes (pepsin or pancreatin) in dissolution media may be beneficial[11]. The discriminative effect of the test method when enzyme is added is not likely different from the media without enzyme.

Conditions

With physiological relevance in mind, all dissolution tests for oral solid dosage forms were carried out at 37°C with very few exceptions. On the contrary, the speed of aggitation or rate of medium flow can be varied widely for individual products. In fact, the easiest way to obtain various drug release profiles is by varying the aggitation speed or medium flow.

When the rotating dialysis cell is employed in product quality research, the characteristics of the membranes used is another factor to consider. Generally, a hydrophilic membrane with less than 1 μm pore size is used for oral solid dosage forms[9].

Calibrations

As with all other analytical instrumentation and testing equipment, assessment of the critical test variables is essential to determine the suitability of the test method. Calibration of the dissolution apparatus is an absolute prerequisite to ensure the validity of the method. In the case of the most commonly used basket and paddle apparati, the use of USP calibrators according to the system suitability tests is usually adequate. For other types of apparatus where standard calibrators were not available, in-house calibration methods had to be established.

A good overall assessment of apparatus specifications and conditions begins with a good calibration method. It is difficult to establish a single calibrator to control all tests that reflects formulation characteristics. Therefore, in product quality research, apparatus-specific calibrators were established for each individual apparatus to satisfy the demands of each individual formulation. The calibrator(s) were usually rugged and suitable for use between different brands and laboratories, as well as sensitive enough to reveal system failures.

Dissolution Profiles

In product quality research, complete dissolution profiles under various media and conditions are essential for *in vivo* interpretation. One frequently used technique is a topographical expression of time versus pH values and per cent drug released to form a three dimensional plot[12,13]. This information is particularly useful for C.R. solid dosage forms and for I.R. products that exhibit slow release characteristics. The rationale is presumably that the absorption of drug may occur throughout the whole G.I. system for these types of products.

OTHER *IN VITRO* TESTS

For those oral solid dosage forms that do not have to be absorbed systemically to produce a therapeutical effect, the above described *in vitro* dissolution testing is not suitable for product quality assurance. In such cases, we need to understand the mechanism of action before devising an appropriate alternate method. One recent example investigated by our laboratory involves a bile acid sequestering antilipemic agent, cholestyramine resin. It is administered orally as a dietary therapy to reduce elevated serum total and low-density lipoprotein cholesterol levels in patients with primary hypercholesterolemia.

In humans, cholesterol is oxidized to bile acids and converted into conjugated salts in the liver. These bile salts are secreted into the gas-

trointestinal lumen to assist digestion of fats and then reabsorbed. Cholestyramine, an anion exchange resin, interferes with the reabsorption process of the bile salts by forming nonabsorbable complexes that trigger a compensatory increase in the oxidation of systemic cholesterol to bile acids. Knowing its mechanism of action, an *in vitro* test that evaluates the capacity and kinetic of binding of the bile salts onto resins was established[14]. Product quality assurance for the resin products could then be established by a simple *in vitro* test.

VALIDATION

There are basically two aspects of validation in pharmaceutical product quality research. First, the *in vitro* tests developed must be validated to ensure that the test methods are reproducible: the precision aspect for test quality. Secondly, the tests must be validated to ensure that the results generated are in good agreement with the *in vivo* performance: the accuracy aspect for predictability. The precision aspect involves the development of a rugged procedure and is generally easy to attain. The accuracy aspect requires the establishment of *in vivo* and *in vitro* relationships, and is frequently a more difficult task. Nevertheless, the importance of the *in vivo/in vitro* correlation for product quality research has been widely recognized by pharmaceutical scientists and regulatory agencies all over the world. Publications and workshops dealing with *in vivo* and *in vitro* relationships[15-17] have been greatly increased in recent years. All these developments have greatly improved our success in product quality research.

FUTURE PROSPECTS

In addition to safety and efficacy requirements, product quality is another important elements for premarketing approval of pharmaceutical products. Unlike the safety and efficacy elements, product quality assurance is required not only for premarket approval, it is absolutely necessary for post-approval manufacturing as well. To develop a meaningful *in vitro* test which has the ability to predict the expected *in vivo* performance is always a driving force for all future research on pharmaceutical product quality. The payoff for its success is tremendous on both economic and regulatory fronts. With advancement of new testing technologies, increasing knowledge of how to evaluate *in vitro/in vivo* relationship, and recognition for its urgent need for lessening regulatory burdens, the prospect for future research remains exciting and challenging.

DISCLAIMER:

The views expressed in this presentation represent the personal views of this author. They do not represent the views of the Food and Drug Administration, and have no official endorsement by the Agency.

REFERENCES

1. Marshall, E., Cutting, W. and Emerson, K. 1938. The Toxicity of Sulfanilamide. J. Am. Med. Assoc. 110:252-255.
2. Skelly, J.P., Amidon, G.L., Barr, W.H., *et al.* 1990. *In vitro* and *in vivo* Testing and Correlations for Oral Controlled/Modified Release Dosage Forms. Pharm. Res. 7:975-982.
3. Cardot, J.M. and Beyssac, E. 1993. *In vitro/in vivo* Correlations: Scientific Implications and Standardization. Eu. J. Drug Metab. Pharmacok. 18(l):113-120.
4. Skelly, J.P. and Shiu, G.K. 1993. *In vitro/in vivo* Correlations in Biopharmaceutics: Scientific and Regulatory Implications. Eu. J. Drug Metab. Pharmcok. 18(l):121-129.
5. Amidon, G.L., Lennernas, H., Shah, V.P. and Crison, J.R. 1995. A Theoretical Basis for a Biopharmaceutics Drug Classification: The Correlation of *in vitro* Drug Product Dissolution and *in vivo* Bioavailability. Pharm. Res. 12(3):413-420.
6. USP Pharmacopeial Forum (July-August,

1991). *In-vitro* and *in-vivo* Evaluation of Dosage Forms. pp. 2222-2234. United States Pharmacopeial Convention, Inc. Rockville, MD., U.S.A.

7. Federal Register, Food and Drug Administration 1995. Immediate Release Solid Oral Dosage Forms; Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; *in vitro* Dissolution Testing; *in vivo* Bioequivalence Documentation; Guidance; Notice, pp. 61638-61643.
8. USPXXIII/NF 18. 1995. Chapter 724. Drug Release. pp. 1793-1794. The United States Pharmacopeia Convention, Rockville, MD., U.S.A.
9. El-Arini, S.K., Shiu, G.K. and Skelly, J.P. 1990. Theophylline Controlled Release Preparations and Fatty Food: An *in vitro* Study Using the Rotating Dialysis Cell Method. Pharm. Res. 7(11):1134-1140.
10. Civiale, C., Ritschel, W.A., Shiu, G.K., Aiache, J.M. and Beyssac, E. 1991. *In vivo-in vitro* Correlation of Salibutamol Release from a Controlled Release Osmotic Pump Delivery System. Meth. Find. Exp. Clin. Pharmacol. 13(7):491-498.
11. Shiu, G.K., Worsley, W.N., Asafu-Adjaye, E. and Lesko, L.J. 1994. Dissolution Study of Gelatin Capsule Drug Products. Pharm. Res. 11 (10): S11.
12. Skelly, J.P., Yamamoto, L.A., Shah, V.P., *et al.* 1986. Topographical Dissolution Characterization for Controlled Release Products: New Technique. Drug Dev. Ind. Pharm. 12: 1159-1175.
13. Skelly, J.P., Yau, M.K., Elkins, J.S., *et al.* 1986. *In vitro* Topographical Characterization as a Predictor of *in vivo* Controlled Release Quinidine Gluconate Bioavailability. Drug Dev. Ind. Pharm. 12: 1177-1201.
14. Interim Guidance: Cholestyramine Powder *in vitro* Bioequivalence, 1994. Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855.
15. Blume, H.H., McGilveray, I.J. and Midha, K.K. 1995. Report of Consensus, Pre-Conference Satellite on *in vivo/in vitro* Correlation of Bio-international 94. Eu. J. Pharm. Sci. 3:113-124.
16. Drug Information Association Workshop on *in vitro* Dissolution of Immediate-Release Dosage Forms. Development, *in vivo* Relevance and Quality Control Issues. June 6-7, 1995. Toronto, Canada.
17. American Association of Pharmaceutical Scientists/USP Workshop on Dissolution Calibration and Testing. September 28-29, 1995. Arlington, Virginia.

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藥品品質研究：口服固體劑型概論

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摘　要

藥品品質諸如安全性與有效性，是所有藥品核准製造之首要達到的基準。這基準甚至在藥品已被核准上市後也不能有所妥協。體外試驗方法的開發以預測藥品在體內的性能，是藥品品質研究的最具挑戰性目標。近年來本實驗室已參與多種藥品包括口服固體劑型、定劑量吸入劑、懸液、經皮吸收貼片及外用乳膏、軟膏、栓劑之研究。本文作者擬將上述劑型之研究經驗提出一系列綜論和研究議題供共同探討。本文首先介紹口服固體劑型之品質概論。

關鍵詞：藥品品質，口服固體劑型，體外－體內關聯性。