Journal of Pharmacovigilance
ISSN: 2329-6887

Biswas and Halquist, J Pharmacovigil 2016, 4:2
DOI: 10.4172/2329-6887.1000e153

Editorial Open Access

Using Biorelevant *in Vitro* Models Testing to Characterize Release of Non Oral Dosage Forms as another Tool for Safety

Deblina Biswas and Matthew Halquist*

Virginia Commonwealth University, School of Pharmacy, Department of Pharmaceutics, Richmond, VA-23298, USA

***Corresponding author:** Matthew Halquist, Virginia Commonwealth University, School of Pharmacy, Department of Pharmaceutics, Richmond, VA-23298, USA, Tel: 8048272078; E-mail: halquistms@vcu.edu

Received date: April 28, 2016; **Accepted date:** April 28, 2016; **Published date:** April 30, 2016

Introduction

Non-oral dosage forms often comprise of complex dosage forms such as parenterals, implants, drug eluting stents, transdermal patches, liposomes, microspheres and nano-particles as injectable. With the rapid advances in genetic engineering and recombinant DNA technology, the active drug moiety can also be a bio therapeutic (i.e. peptide or protein), which adds an additional layer of complexity to the drug product. *In vitro* dissolution tests/models for oral dosage forms such as tablets and suspensions have long been an indicator of *in vivo* performance of the drug. In commercial manufacturing processes, they act as an evaluative quality control tool. A dissolution test in oral dosage forms ensures minimal inter-batch variability and hence works as a check that the dosage form meets the requisite regulatory and quality standards. These *in vitro* models may also work as a tool for safety (i.e., predict *in vivo* performance and streamline clinical studies). The predictive *in vitro* data from these tests could often help in minimizing steps of clinical trials. In the case of non-oral dosage forms, similar tests that ensure performance verification of the drug are often called "*in vitro* release tests" rather than dissolution tests [1-3]. The rationale being non-oral dosage forms are frequently placed at diverse locations in the body e.g. transdermal patches on skin, drug-eluting stents in coronary arteries [4], suppositories in rectum or urethra, subcutaneous or intramuscular implants (all of which have a different physiological environment). As a result, the action of the drug largely depends on its release from the dosage form. The drug moiety may be carried in complex delivery systems e.g. in a lipid based system such as liposomes, absorbable carrier scaffolds e.g. collagen matrix, injectable biodegradable polymer based matrix which solidifies at the site of action (e.g. ATRIGEL®). In cases like transdermal patches, the release needs to occur through multiple membranes and needs to penetrate through the skin and layers of external barriers before reaching the site of action. In subcutaneous and intramuscular implants the blood flow conditions might affect the time taken by the drug to reach the targeted site. Furthermore, the release mechanism, rate of release, and the time required by the drug to reach the site of action thus varies notably in each unique case. Hence the *in vivo* performance of these complex (non-oral) dosage forms can be characterized more precisely by carefully designed *in vitro* release tests, with design space criteria that are 'biorelevant'. Unlike oral dosage forms where a single standardized USP method or apparatus can be used for dissolution testing of a class of compounds to determine *in vivo* performance (i.e., systemic release). Non-oral dosage forms can release locally with minimal systemic exposure. In such cases the standardized tests may not predict local release. The testing apparatus and method parameters have to be selected or modified accordingly to design a biorelevant reproducible and predictable *in vitro* release test.

Biorelevance in Non-Oral Dosage Forms

Application of biorelevant *in vitro* parameters during *in vitro* release testing of non-oral dosage forms would ensure that the release test data is clinically meaningful and also predictive for detection of changes in the post approval drug product. Incorporation of biorelevance in an *in vitro* release test would involve a) recognition of the 'crucial' *in vivo* parameters that significantly affect release of the drug from the dosage form and b) selection/inclusion of these parameters in the *in vitro* design space to accurately predict the release of the active drug moiety from the dosage form. Biorelevant *in vivo* parameters that are often of significant, influence are criteria pertaining to the physiological positioning of the dosage form and site of action of the drug. These factors are frequently temperature, blood flow rates, tissue barriers, acidity of the microenvironment, osmolarity and pH. These parameters can considerably influence the release of the active moiety from the dosage forms as well as influence their therapeutic effect at the site of action. To make the test more predictable and clinically relevant it is essential to incorporate or simulate at least some or most of these factors into an *in vitro* release test. Inclusion of these parameters in an *in vitro* release test can also determine how a minor change in one of the parameters affects a) the other parameters and b) the overall release of the drug from the dosage form for future formulation changes. For complex non-oral dosage forms, designing of the *in vitro* release test and selection/modification of the appropriate apparatus requires careful research to prevent addition of unrequired layers of intricacy to the design. However, the long-term predictive capabilities of such "*in vitro* release tests" far outweigh the initial inconvenience. Dissolution/release is a test model where a delicate balance needs to be established between the lure of simulation of physiological variables as opposed to making the test simple and more reproducible. Introduction of too many variables with the intention of focusing the test towards biorelevance can also cause the introduction of over complex and non-predictive factors. A very simple biorelevant test maybe rejected on the premise, that it does not provide sufficient discriminatory capability towards crucial process parameters. The paradox thus is, although addition of more biorelevant parameters makes the test clinically meaningful; at the same time addition of complex physiological parameters and their interplay might make the release test less reproducible. It is essential that ultimately the *in vitro* release test is an optimal predictor of the beginning phase (e.g. burst release phase), middle and end phase of the *in vivo* release profile.

Standardized methods offered by the USP are frequently used for dissolution testing of immediate and controlled release formulations. Currently, seven apparatuses are available; however, these apparatuses have not been standardized for parenterals such as implants, microspheres. These standardized tests though appropriate for oral

immediate release (IR) products, might not meet the specific needs of a biorelevant/biomimetic predictive model for these complex dosage forms. In such cases it is beneficial to the researcher to ascertain the applicability of the USP model before applying it to the release tests. Modifications to the standardized USP apparatuses or non-compendial methods might be required to make the *in vitro* release tests more predictive. If after initial release testing with standard USP apparatuses (e.g. paddle apparatus or flow through cell) it is determined that a non-oral dosage form requires a modified or special apparatus to meet the clinically meaningful specifications, the modified apparatus and the method requires to be validated extensively. Any such validated apparatus or release tests also essentially needs to be 'discriminatory' between formulations [3,5]. It is critical to choose the most predictive apparatus for release testing of these complex non-oral dosage forms.

Conclusion

Biorelevant 'real time release tests' are of particular significance during pre-clinical, post approval (marketing and manufacturing) stages of a drug [2]. These tests can be used for: a) monitoring and predicting the outcome during minor formulation changes in the process, b) as a quality control test for detection of inter batch variability in the end product [2,3] and c) can function as a discriminatory dissolution/release model between different formulation variants. The primary expectation from a well-developed and validated biorelevant test method would be the ability to predict in terms of release or dissolution, how any intrinsic variation in any of the process variables of commercial manufacturing conditions would affect changes in the *in vivo* release profile of the drug. At the same time the principal impetus behind developing such tests are also to: 1) minimize time 2) cost 3) streamline clinical trials and 4) to make the final drug product safer by predicting their performance in advance. Over the past few decades, applying biorelevance in release and dissolution testing has proven to be a powerful tool towards providing *In Vitro-In Vivo* Relationships/Correlation (IVIVR/IVIVC). Such predictive relationships obtained from IVIVR/IVIVC can be effectively translated to clinically meaningful specifications and contribute towards relevant information pertaining to the performance of the drug. However, often times since such complex dosage forms might be available in only one kind of formulation (e.g. in cases of some protein based implants: available only as a formulation that is released from scaffolds). In such cases, reaching a Level A correlation or meeting the levels of correlation as for an immediate release dosage form might be difficult. Due to the a) complexity in physiological positioning (e.g. drug eluting stents) and b) unique release profiles (e.g. local release instead of systemic release) of non-oral dosage forms, there is lack of information regarding the consistency of the design space and variables for *in vitro* release models. This has prompted the FDA to exercise caution in establishing guidelines for the dissolution/release testing of such dosage forms. There is sufficient evidence of a significant need for further research and development towards improved adaptable *in vitro* model systems, which can be predictive of *in vivo* formulation release of complex non-oral dosage forms.

References

1. Burgess DJ, Hussain AS, Ingallinera TS, Chen ML (2002) Assuring quality and performance of sustained and controlled release parenterals: Workshop report. AAPS pharmSci 4:13-23.
2. Brown CK, Friedel HD, Barker AR, Buhse LF, Keitel S, et al. (2011) FIP/AAPS joint workshop report: dissolution/*in vitro* release testing of Novel/Special dosage forms. AAPS Pharm SciTech 12: 782-94.
3. Siewert M, Dressman J, Brown CK, Shah VP, Aiache JM, et al. (2003) FIP/AAPS guidelines to dissolution/*in vitro* release testing of novel/special dosage forms. AAPS Pharm SciTech 4: 43-52.
4. Seidlitz A, Nagel S, Semmling B, Grabow N, Sternberg K, et al. (2011) Biorelevant dissolution testing of drug-eluting stents: Experiences with a modified flow-through cell setup. Dissolution Technologies 18: 26-34.
5. Bhardwaj U, Burgess DJ. A novel USP apparatus 4 based release testing method for dispersed systems. Int J Pharm 388: 287-294.