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

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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. 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 predicator 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.

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