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IMPACT OF THE CHOICE OF EXCIPIENTS (PREFORMULATION/FORMULATION) ON THE DISCRIMINATING POWER OF A DISSOLUTION METHOD

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ABSTRACT

The dissolution test is a test that is mandatory for any molecular entity formulated under a solid dosage form such as hard/ soft gelatin capsules or tablets. Performing a dissolution test is not, per se, a challenge since dissolution apparatus type one (1) or two (2) have been well designed for this purpose. Numerous dissolution methods exist for generic and innovator drugs. These methods are developed daily. During the 80's and the beginning of the 90's, drug substances were classified highly soluble and permeable (BCS1); Formulation and dissolution method developments were not as challenging as they are nowadays. However, over the past 20 years, since molecules have become more and more hydrophobics, not soluble (BCS 2, 4) and permeable (BCS2) or not (BCS4), the formulation development became increasingly important to make these drug substances more soluble or at least to show a "workable" solubility rate for dissolution method development. It is one thing to generate solubility profile for a drug substance, but it is completely different for a drug product (formulated product) to get the same profile. The best scenario would be that the formulation is not held responsible for any differences in the drug substance's profile. The authors of this short communication, an analytical chemist, and a formulator show more than 40 years of experience in drug development and have been through these challenges with different kinds of drug substances. They will try to expose, based on their experiences, expertise and proven track records that formulation development combined with dissolution method development should be considered artistry, as getting a discriminatory dissolution method is not as easy as it seems.

INTRODUCTION

Dissolution of a drug substance has always been key for any molecular entity to be absorbed, irrespective of the way it will permeate the absorption window. Indeed, the active pharmaceutical ingredients must be under molecular state (and not under a particulate matter) to diffuse through passive or active transport mechanisms. Before the 90's, new molecular entities could be considered as BCS class 1 molecules, most of them being highly soluble and highly permeable.[1] Furthermore, a lot of phase I clinical studies used to be performed through the IV route. One of the reasons for this was to reach 100% bioavailability, irrespective of the physical state of the volunteers/patients, the pheno and genotyping and to ensure formulation could not be held responsible for any biopharmaceutical challenge, such as weak dissolution and absorption in the gut. It is already known in the literature.[2] that BCS 1 molecules, being soluble and permeable, when formulated under immediate release/oral dosage form, are not impacted by their formulation composition. It increases the fact that the pharmacokinetic (PK) profiles generated from these same BCS 1 entities, formulated under liquid or solid oral dosage forms, should not be impacted by their compositions. Therefore, their respective dissolution profiles (i.e. the same BCS1 molecular entity) formulated differently in composition and under different solid dosage forms, should demonstrate similar dissolution profiles, with f2 value above 50,[3] as well as bioequivalence.

Nonetheless, in the quest for nanomolar efficiency, a paradigm shift was observed during the 90's, and almost 50% of the new active pharmaceutical ingredients became less and less soluble and permeable, leading to be classified as BCS 4.[4] The synthesis of poorly water-soluble drugs is still ongoing.[5,6] leading to numerous BCS 2 (poorly soluble, highly permeable, and BCS4 (poorly soluble and permeable) molecules. It became obvious that "druggability" went down, showing that contrarily to BCS 1 molecules, formulation became as important, not only from a stability standpoint, but also from a bioavailability perspective. In parallel, it also became increasingly important to characterize the new molecular entities (NMEs), not only from a wet chemistry perspective (assay, impurities, solvents …) but also from a solid-state characteristics (polymorphism, solvatomorphism, pseudopolymorphism) and physical

stability point of view.

More precisely, this preformulation step was able to provide information, determine the stability behavior of a drug substance alone, and versus different excipients over time and under different conditions of temperature and humidity. Solid-state characteristics such as polymorphism became very important and helpful to monitor the stability of all the APIs. Polymorphism is the ability for a molecule to exist under different crystal structures.[7] Each of these structures may show different solubility rates and stability over time. Thus, from a theoretical standpoint, an amorphous structure shows a higher solubility rate but tends to recrystallize over time. This indicates an overall stability change since solubility rate will decrease and so should the bioavailability. Based on the above, most of the drugs were developed with crystalline structure since, from a thermodynamical angle, this solid state will remain the same over time, irrespective of temperature and humidity conditions. To enhance the solubility rate, drug substances became micronized to increase their specific surface area. Nowadays and as described above, some drug substances being so hydrophobic and with high logP, we select amorphous structures under high supervision to (as much as possible) maintain the stability, reliability, and drug product performance over the whole shelf life. In the same line and continuity, excipients and formulation development became more and more important to generate stable, reliable, and bioavailable drug products. Roller compaction became very attractive for APIs showing poor flowing properties and avoiding water/liquid for granulation for hydrate sensitive API. Some excipients exist under different grades to satisfy the targeted formulation development process.

As an example, calcium phosphate exists under anhydrous, dihydrate and trihydrate forms.[8] This flexibility is very helpful depending on the physico-chemical characteristics of the API, and to determine the formulation process that will be developed. But it must be kept in mind that the formulator should focus on both formulation and analytical development, which is not necessarily the case, being focused only on development of a robust, reliable, and reproducible formulation.

Otherwise, he may have generated the best formulation from a manufacturing standpoint, but analytical development and especially dissolution test, may become very challenging to develop. This last point will be explained further in the following section.

The development of a dissolution method can be a very tedious and challenging process. The first step is to test the Active Pharmaceutical Ingredient (API) in various dissolution media ranging from pH 1.2 to 7.2. Sink conditions are defined as 3X the concentration of the projected highest dose of the drug product. This represents a challenge since in most cases, little is known about the highest dose strength in early formulation and product development. Frequently, sink conditions studies are performed with a target of 10X the highest strength concentration.

Once the dissolution medium has been selected the first formulations of the drug product are available, dissolution method development can begin. For immediate release formulations, it is preferable to use USP Apparatus I (Baskets) or II (Paddles). Based on the formulation, tablets can be tested with either Apparatus I or II. As for capsule formulations, App II is recommended since the capsules have a propensity to float or get trapped in air bubbles with the App I Baskets apparatus.

It is suggested to test tablets with a paddle rotating speed of 50 rpm. Aliquots should be acquired every 10 minutes to determine if a profile can be obtained. On a side note, the Fiber Optics technology provides a lot more flexibility to dissolution method development since measurements can be acquired as quickly as every 5 seconds.

Early on, it is better to quantify dissolution samples using straight UV spectrophotometry. Dissolution profiles should be acquired at different paddle speeds, namely 75 and 100 rpm, and visual observations should made and recorded by the dissolution chemists. Phenomena such as tablet stickiness (tablets sticking to the side of dissolution vessels), coning, formation of air bubbles around tablets are critical for a dissolution method to be significant and discriminatory.

Once a dissolution method has been developed, some preliminary validation work should be performed to help chemists and formulators in the event atypical results are found. Those results should be thoroughly investigated.

Over the years, one of the current the authors, chemical analyst by training, has worked with many fine formulators. Historically, there is a lack of communication between analytical chemists and formulators, and that will be discussed next in a real case study. Working with compound X which was highly soluble, sink condition studies for the API had determined that 10X sink conditions were achieved in acidic media, namely 0.1N and 0.01N Hydrochloric Acid (HCl). Being the conventional choice as per industry and USP practices, 0.1N HCl was selected as the dissolution medium. A nice dissolution profile was observed for the drug product.

Working along with formulators, altered/aberrant tablets were manufactured in laboratory to determine the discriminating power of dissolution method. Altered tablets were tested using Apparatus 2 at 50 and 75 rpm. Results showed that there were no significant differences in dissolution profiles. Because of concerns from internal regulatory authorities about the lack of discriminating power of the dissolution method, it was suggested to

change the dissolution medium from 0.1N to 0.01N HCl.

Additionally, there was pressure from regulatory agencies to use 0.01N HCl as a medium because it was more representative of the stomach‟s pH in „fed‟ state.

Dissolution profiles were performed in 0.01N HCl and a better profile was obtained. Analytical chemists were somewhat concerned because sink condition studies had determined that the solubility of the API was about the same in the two media. Stability samples were re-tested using 0.01N HCl as the medium. Sampling points were taken at 5, 10, 15, 20 and 30 minutes. Altered tablets were also re-tested in 0.01N HCl and there were no statistical differences (f2 factor) between profiles of the established formulation and altered tablets.

As the company was getting ready for manufacturing of engineering batches, the realization became obvious that with 4 dose strengths in various packages and stability conditions; automation of the dissolution test would be needed to support the stability testing from a laboratory capacity perspective. Experiments were performed using the Zymark Multidose Workstation™,[9] and dissolution conditions were same as the ‘manual’ method.

Surprisingly, results were quite different from the manual method of sampling as a 10% bias was observed at the 10-minute mark. Chemists spent time in the laboratory performing manual and automated dissolution tests. Experiments indicated that manual and automated methods were not equivalent. Early in drug development, 0.1N HCl had been selected as the dissolution medium of choice. Automated dissolution testing was performed on one lot for each 4 dose strengths with 0.1N HCl as medium and the outcome matched results obtained with the manual method and the f2 factor calculation was used as comparison. The results had showed that results were comparable and acceptable in 0.1N HCl.

Composition of the formulation was reviewed with the formulator, and it was decided to further investigate the solubility of each excipient. Literature searches were conducted and revealed that solubility of the main excipient was 10X less in 0.01N HCl than in 0.1N. Additional tests were performed, and it became clear that the phenomenon of coning was observed with 0.01N HCl as the dissolution medium. When using the automated method, insertion of the probe (which had a wider diameter than the probe used for manual sampling) at the 5-minute sampling point, led to disruption of the ‘cone’. Hence, this explained the difference or bias observed between the manual and automated methods.[10]

Collaboration with the manufacturer led to design of new sampling probes which mimicked the size of probes used for the manual method. Equivalent profiles were obtained with new probes and the method was successfully validated.

Many years later, the current analytical chemist author still believes that the dissolution method developed and validated generated a profile that was truly ‘artificial’. It was more dependent on solubility of the main excipient than the API itself. A few questions arise; should the particle size or particle size distribution of the main excipient have been investigated? If investigated, should dissolution profiles have been performed with formulations having the main excipient with different particle size or particle size distribution?

Afterall, if particle size is important for the API, why not the excipients? Could the drug load of the API been investigated in the formulation development process to determine if it had an impact on dissolution? Could other alternate excipients have been evaluated? All these questions remain unanswered.

Furthermore, this raises the importance of a good collaboration and communication between the analytical chemists, solid state scientists, formulators, quality/compliance, and internal regulatory affairs during drug development. One cannot sit behind a desk and determine which parameters should be used in a dissolution method with the sole purpose of ‘generating a profile’. Practical work along with observations of the dosage behavior which form in the dissolution vessel is of essence. The analytical chemist author’s opinion is that a thorough evaluation of each excipient should be considered when developing the formulation of a solid dosage form.

The analytical chemist author has been involved with many technology transfers throughout his career, transferring this method to a manufacturing and testing site would have represented an enormous challenge. The initial transfer to the automated method revealed this trial and several publications discuss the impact of sampling probe size which can alter the hydrodynamics in the dissolution vessel.[10] In this case study, sink conditions were achieved with the API but problems arose when formulated with excipients.

Although stability data showed that the formulation was stable with description, assay, degradation products, water content, disintegration results all meeting tight acceptance criteria; dissolution results exhibited high variability depending on which laboratory performed the test. As a former colleague and mentor said many years ago: ‘Dissolution is not a science, it is an art’.

In this communication, authors tried to illustrate that formulation and analytical development are closely connected and should not be dissociated. Somehow chemical analysts and formulators should share the same language event though they have been trained differently. Furthermore, analytical development should not be considered as a support to formulation development but as important as formulation development in the whole pharmaceutical development

step. Finally, when a protype drug product will jump in early phase I/IIa clinical development, if something unanticipated happens, it will then be possible to say that neither formulation nor analytical development could be held responsible for these unexpected results.

REFERENCES

1. https://database.ich.org/sites/default/files/M9_Guideline_Step4_2019_1116.pdf.
2. https://www.fda.gov/files/drugs/published/Dissolution-Testing-and-Acceptance-Criteria- for-Immediate-Release-Solid-Oral-Dosage-Form-Drug-Products-Containing-High-Solubility-Drug-Substances-Guidance-for-Industry.pdf.
3. https://www.pharmacy.umaryland.edu/media/SOP/wwwpharmacyumarylandedu/centers/cersievents/dissolution-similarity/zhen-zhang-slides.pdf.
4. Mehul Menta, FDA: BCS workshop, 2002.
5. Boyd B.J et al. Successful oral delivery of poorly water-soluble drugs both depends on the intraluminal behavior of drugs and of appropriate advanced drug delivery systems. Eur. J. Pharm. Sci., 2019; 137: 104967.
6. Savjani K.T., Gajjar A.K., Savjani J.K. Drug Solubility: Importance and Enhancement Techniques. ISRN Pharm, 2012; 1–10.
7. Chistyakov, D. and Sergeev, G. The Polymorphism of Drugs: New Approaches to the Synthesis of Nanostructured Polymorphs. Pharmaceutics, 2020; 12: 34-42.
8. Handbook of pharmaceutical excipients, 6th edition.
9. Zymark and MultiDose are registered trademarks of Zymark Corporation.
10. Automated sampling of in vitro dissolution medium: effect of sampling probes on dissolution rate of prednisone tablets. T S Savage, C E Wells.