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Roundtable Conference Report: "The Importance of Hydrodynamics in Dissolution Testing"

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OVERVIEW

The Roundtable Conference sponsored by VanKel Technology Group entitled "The Importance of Hydrodynamics in Dissolution Testing" was held at the 1997 (November) American Association of Pharmaceutical Scientists (AAPS) Meeting in Boston. The purpose of the roundtable was as follows: 1) debate the importance of hydrodynamics in USP dissolution methods due to the recent introduction of PEAK vessels as a proposed alternative to the vessels currently used in the USP Apparatus 2; 2) discuss the concerns and potential impact of PEAK vessels on dissolution testing; present and share experiences and case studies. The session panel consisted of Professor Arnold H. Beckett, Professor Emeritus University of London, Generex Inc. Canada, Dr. Ian Borst, Ontario Ministry of Health, Ontario, Canada, Tinh T. Quach, Apotex Inc. Canada., Vivian A. Gray, United States Pharmacopeia, Dr. Saeed A. Qureshi, Health Protection Branch, Health and Welfare Canada, and Dr. Jennifer B. Dressman, J.W. Goethe University, Frankfurt, Germany. Dr. Charles Collins, Duquesne University, Pittsburgh, PA., USA., served as moderator. The meeting was well attended and there was a lengthy question and answer period with very active participation from the audience. The speakers presented as follows:

Hydrodynamics of USP 1, USP 2, and USP 3.

Professor A. H. Beckett

Since the mid - 70's there has been criticism about the hydrodynamic movement of media relative to the dosage form in USP 1 and 2 in which regions of the bulk media move at different rates causing poor mixing which becomes specially obvious with sparingly soluble drug formulations in USP vessels. These inadequate flow characteristics are shown in USP 1 when particles containing the drug leave the basket and float to the surface if they are of low density or settle on the base of the vessel, if they are denser, where they do not move in the medium. Moreover, there are other disadvantages such as the tendency for gummy substances clogging the basket screen and the system being extremely sensitive to dissolved gases in the dissolution fluid. These effects have significant impact on the observed (dissolution rate) solid dosage forms during the dissolution test. USP Apparatus 2 (paddle) overcomes many disadvantages of the basket. The modern designed instruments virtually eliminate the mechanical and physical problems previously reported, e.g. centering, vibration etc. However, the "coning" phenomena on USP 2 is commonly observed due to system hydrodynamics especially when the instrument is operated at 50 rpm and the products contain a sparingly soluble drug in a high percentage of insoluble excipients and also for certain slow release formulations. The formation of the cone significantly reduces the dissolution rate and produces a wide variation in results, which affects the uniformity of data and therefore meaningful product specifications. This poorly stirred cone region exists even if particulate matter is not present to make it visible. Thus if tablets are placed at the base of the vessel, the dissolution results can be different than if placed to the side of this base. Dissolved gases in dissolution fluids, the size and shape of sinkers and fixed sampling probes can perturb this non-visible cone and thus lead to erratic results. Due to the design and reciprocating pump action of the USP 3, dissolution rates are not affected by changes in the geometry or the presence of dissolved gases. Studies (1) using calibrator tablets were shown that small changes in the geometry of the system and deaeration or non-deaeration has negligible effect on the dissolution rates for USP 3 because the absence or presence of bubbles does not alter the movement of the dosage form and the hydrodynamics of the system sufficiently to affect the dissolution rates. Dissolution from a product into the moving dissolution medium is desired in dissolution testing, rather than having other uncontrolled rate processes slow down erratically the process of dissolution.

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Review of Literature on Cone Effect in USP 2

Tinh Quach

This speaker provided some recent references on the influence of "cone formation" on the USP 2 dissolution test. The first reference was from a 1995 AAPS Poster that demonstrated the effect of an observable "cone formation" on the dissolution profile. The "cone formation" artificially depressed the dissolution profiles and led to dissolution failure of the product which had been proven to be bioequivalent. The second reference from an internal communication highlighted the inappropriate testing condition at 50 rpm which caused low erratic dissolution results; however, complete and consistent dissolution results are achieved under similar testing conditions except at a faster paddle speed of 75 rpm. The next example was from the work of the FDA laboratories involving the new proposed 10 mg prednisone NCDA #2 calibrator tablets. During the dissolution the tablet pow-

der formed into a distinct cone underneath the paddle and was extremely sensitive to dissolved gases in the medium and somewhat sensitive to other physical changes except vibration. The "cone" and other parameters have a significant effect on the outcome of dissolution test results. The next two examples were from papers presented at the 1995 Drug Information Association (DIA) conference in Toronto, where it was noted that a wide variation in test results can be found by merely placing the tablet in different positions in a regular vessel (center and off-center), and significant shifts in dissolution profiles can also be observed when the rpm speed is dropped from 50 to 45. The "cone effect" was further verified in a recent collaborative study with the VanKel Technology Group by comparing the dissolution of calibrators in USP and PEAK vessels for USP 2 (1).

Comparison of USP and PEAK Vessels Dissolution for Apparatus 2 using Calibrators.

Dr. Ian Borst

The PEAK vessels were introduced to improve the hydrodynamics for USP 2 by eliminating the poorly stirred region or "coning," observed at speeds of 50 rpm and 75 rpm, under the paddle in USP vessels. The PEAK vessel has a cone of accurate dimensions molded into the base of the vessel; this glass cone effectively displaces the unstirred cone, forcing the material into the region of appropriate hydrodynamics, where all the surfaces of the product are constantly and uniformly exposed to the moving medium.

Our studies have shown that with Prednisone NCDA#2 10 mg tablets approximately a two fold increase in dissolution occurs with PEAK vessels and paddle speeds of 50 rpm in contrast to USP vessels using the standard media used for these calibrators. Changes in rotation speed of 50, 75 and 100 rpm had negligible affect on dissolution rate using PEAK vessels, but gave substantial increasing dissolution using the USP vessels. Similar comparative dissolution data was found for USP Salicylic Acid 300 mg tablets in regard to changes in rotational speed.

Also dissolution studies were conducted to compare the dissolution rate for the calibrators: USP Prednisone 50 mg, USP Salicylic Acid 300 mg and Prednisone NCDA#2 10 mg tablets in deaerated and non-deaerated media. The dissolution results were found to be very similar whether employing deaerated or non-deaerated media in PEAK vessels but not in USP vessels, where in the latter more variability was observed.

Comparison of dissolution rate using USP 2 with USP and PEAK vessels versus USP 3 for USP Salicylic Acid 300 mg and chlorpheniramine 16 mg tablets indicated that the USP 2 using PEAK vessels give comparable dissolution to those using USP 3. In contrast the USP 2 gives lower results.

A recent collaborative study with 5 laboratories has shown for USP salicylic acid that total variance (within and between labs) is lower using USP 2 with PEAK vessels than it is in the USP vessels.

It must be emphasized that the PEAK vessel is not the "concave-bottom" (see USP XV111 1970, p 934) of the earlier USP vessel which was not designed for dissolution testing, since the flasks had been in use for general chemical purposes. The latter flasks were ultimately rejected because of hydrodynamic concerns and problems with manufacturing reproducibility. It is important to realize the simplicity in design and principle of the PEAK vessel is highly effective in solving many reported dissolution problems experienced by many workers in the field using the USP 1 & 2 methods.

To summarize the important application for PEAK vessels:

- Higher dissolution rates at same rotation speeds as USP,
- Changes and improves the hydrodynamics with elimination of the poorly stirred cone region under the paddle which develops using sparingly soluble drug and excipients, and slow release formulations,
- Eliminates or reduces the need for deaeration of dissolution media,
- Gives better reproducibility as evidenced by collaborative study,
- Gives dissolution results at 50 rpm comparable to those obtained using USP apparatus 3 at 10 to 20 dpm,
- Reduces the time and effort in running USP system suitability tests.

Report on the USP Dissolution and Bioavailability Subcommittee Activity Regarding the Peak Vessel.

Vivian Gray

The Subcommittee is not opposed to the use of the peak vessel but they would like to see more data from different manufacturers before adding it to Dissolution <711>. If this vessel was added to <711> it would not take the place of any apparatuses that are now official. More than likely the first appearance of the peak vessel in USP would be in an informational general chapter that would discuss new general dissolution testing apparatuses. The USP laboratory has explored the use of the peak vessel using calibrator tablets, for some vitamin preparations, and in the multi-unit pooled initiative.

It is unlikely that the peak vessel would be used instead of the Apparatus 2 round bottomed vessel for established products, as this would introduce an entirely different hydrodynamic situation for the product — with no link to the history or stability of the product. The anticipated use of the peak vessel would be where an in-vivo and in-vitro correlation may be obtained. At this time, the peak vessel would be used when the other apparatuses were found, through testing, not suitable for such correlations. Some analysts have suggested that a higher paddle speed in the official Apparatus 2, 75 or 100 rpm may produce the same effect as the peak vessel. A higher speed may eliminate the coning for some products.

USP 1 & 2 Variability in NCDA 10 mg Prednisone, USP Calibrators & Glyburide Tablets

Dr. S. A. Qureshi

Results were presented from a recently completed international collaborative study to assess the variability in drug dissolution testing. The study was conducted under the auspices of QLMCS section of the FIP with the participation of 28 laboratories including many from Pharmacopeial and national agencies such as USP and FDA. Following a common protocol, the participating laboratories analyzed the same lots of USP prednisone and salicylic acid calibrators, and US FDA prednisone (NCDA #2 tablets), and a marketed 5 mg glibenclamide (glyburide) tablet product. The experiments were conducted using paddle and basket methods 50 (calibrators) and 75 (glibenclamide) rpm. During the presentation and follow-up discussion, Dr. Qureshi stated that the results from the study using USP calibrator tablets with regard to the variability were as expected and comparable to the results of the PhRMA studies conducted to develop Dissolution Apparatus Suitability Ranges. The variability in the results, with paddle method, using FDA calibrator, was higher than the results with USP prednisone calibrator tablets (CV 18 vs 9%). For the glibenclamide tablets, a CV of 14-37% was observed, depending upon time and the type of apparatus employed. In concluding remarks, it was stated that due to the high observed variability in dissolution testing, it appears that in many cases the impact of formulation or manufacturing changes on the drug release characteristics would be difficult to detect, particularly with multipoint profiles. In addition, responding to a question, Dr. Qureshi stated that, based on the results from the current study, it also appears that failure to meet the USP Dissolution Apparatus Suitability Test does not truly mean that the apparatus is "out of compliance". The reason for not meeting the Suitability Criterion, appears to be due to unrealistically tight Suitability Ranges, as these ranges are developed excluding extreme values from PhARMA collaborative studies without investigation (i.e. statistical order). The full details of the study and the results have been submitted for publication.

Comparison of In-Vitro Dissolution of FK366 Using Various Methodologies With In-vivo Performance.

Prof. Dr. J. B. Dressman

The data is presented on behalf of Fujisawa Pharmaceutical Co., Japan. Dissolution of the reference capsule formulation and a test tablet formulation of a poorly water-soluble compound, FK366, was studied at 50, 75 and 100 rpm paddle using normal dissolution vessels, and also at 50 rpm paddle using PEAK vessels. The capsules dissolved more quickly than the tablets. The greatest difference was observed at 50 rpm, whereas at 100 rpm the dissolution rates were similar, with 75 rpm being intermediate. Dissolution rates with the PEAK vessels at 50 rpm were similar to the results at 75 rpm using normal dissolution vessels. Bioequivalence studies in 12 healthy subjects indicated that the two products were absorbed at similar rates and to the same extent. It was concluded that 50 rpm paddle was unsuitable for predicting in-vivo performance of FK366 products, whereas 100 rpm paddle in this case predicted the in-vivo performance well. The PEAK vessels were also able to partly avoid the over-discrimination observed at 50 rpm with the normal vessels. Dr. Dressman suggested that, because of the differences between products in terms of the forces necessary for disintegration of the dosage form, that any hydrodynamic condition that is reasonable in terms of the range of contraction patterns in the GI tract and which results in good in-vitro / in-vivo correlation should be accepted for the dissolution test.

ROUNDTABLE SUMMARY

The consensus of the meeting was that the dissolution rate should reflect the release of the drug from the formulation and not be influenced by inappropriate hydrodynamics which can result in misleading and variable data. USP 2 employing appropriate rotational speeds with USP vessels can predict in-vivo performance, but the system may possess significant variability as evidenced by collaborative studies on calibrators. PEAK vessels have been demonstrated to possess less variability or more reproducibility than when using USP vessels as well as eliminate the coning effect experienced in some formulations at the traditional rotation speed of 50 rpm for USP 2, and provides greater opportunities to establish meaningful in-vitro / in-vivo relationships.

Note: The views expressed in this report may not necessarily reflect the opinions of all the panelists and their affiliated organizations and VanKel Industries, Inc.

REFERENCES

(1) Beckett, A.H., Quach, T.T. & Kurs, G., *Dissolution Technologies*, 1996, Vol. 3, Issue 2, Page 7.