Dissolution Media Change for Delayed-Release Dosage Forms: Tips and Tricks

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Overview of Media Change for Delayed-Release Dosage Forms

Solid oral dosage forms are designed to release drug at a predictable rate to allow the drug to be absorbed into the blood stream and be bio-available to render a therapeutic effect. The term modified-release is applied to products that are designed to control the rate of release of a drug substance over a course of time, and/or location within the GI tract, to accomplish a therapeutic effect. Modified-release forms are further subdivided based upon the desired therapeutic effect and include:

- Extended-release – These products typically release at least two times the rate compared to a conventional immediate-release product. Subcategories of extended-release dosage forms include controlled-release, sustained-release and long-acting drug products.
- Delayed-release – These drug products release drug substance at a time other than immediately after administration. Release occurs incrementally or after exposure to acidic media to ensure that the drug did not release in the gastric region but in an area of the intestinal region. Common examples of these drugs include enteric-coated aspirin and other NSAID products because of the gastric irritation they may otherwise cause.
- Targeted-release – These dosage forms release drug at or near the intended physiologic site of action. An example of targeted-release would be mesalazine for treating inflammatory bowel disease. This drug is highly permeable so its release must be controlled to only release locally at the disease site.
- Orally disintegrating tablets (ODT) – These forms disintegrate and dissolve rapidly in the saliva after oral administration. The release of the drug is dispersed in saliva and swallowed with little or no water.

The United States Pharmacopeia (USP) defines delayed release tablets as enteric-coated to prevent an appreciable release of the medication until the tablet has passed through the stomach to prevent the drug from being destroyed or inactivated by gastric juices or where it may irritate the gastric mucosa. For differentiation, an extended-release product if formulated in such a manner to make the contained medicament available over an extended period following ingestion. Delayed-release formulations are enteric coated while extended-release formulations are not enteric-coated and therefore, they are not similar or interchangeable.

According to Remmington's Pharmaceutical Sciences, most delayed release dosage forms are enteric-coated tablets although some enteric-coated pellets or granules have been encapsulated as well. Since the drug-containing portion of an enteric-coated product will not be released until the dosage form passes into the intestinal tract, gastric-emptying time will be critical when rapid onset of action is desired.

Tips for Dissolution Testing of Enteric Coated Products by Media Addition and Media Exchange

The Media Addition Method: USP <711> Dissolution, Delayed-Release Dosage Forms, Method A

Media addition is performed for several reasons. Primarily, we associate media addition as the more popular of the two options for evaluating enteric coated products, which are designed to be resistant to dissolving in the gastric environment. These delayed-release products require methods allowing for pH change to take place from a typical gastric pH between 1.2 and 2.0, to a buffered media capable of dissolving the coating and allowing the product to disintegrate and dissolve for several reasons:

- To protect the gastric lining from an API that may be irritating (e.g., aspirin)
- To protect the API from the acidic gastric fluids, which may degrade the API
- To allow a site-specific drug to release the API at a specific pH associated with a section of the intestinal tract where the API may dissolve and provide a local effect in the intestinal wall

Regardless of the reason, the USP <711> Dissolution chapter outlines the two primary methods for evaluating dissolution of delayed-release products: Method A, which is a media addition method and Method B, which is a media exchange method. Both options have advantages and disadvantages and for this discussion we will focus on both methods.

The media addition technique (Method A) is perhaps the easier of the two methods because the dose is introduced as typically required for immediate release products, a sample is pulled at the end of the gastric period, buffered media is added, pH is checked, and the run continues until the remaining timepoints are pulled. There are two sets of acceptance criteria that are applied; one for the acid stage and one for the buffer stage. The acid stage is supposed to demonstrate a limited release of the drug in the gastric region. The buffer stage should demonstrate that enough drug is released in buffered media, representing the targeted area of the intestinal tract, and is available in enough quantity to provide the intended therapeutic effect according the acceptance criteria for each stage.

Key points to consider during the Delayed-Release (Method A) media addition test:

- Dosage Introduction: The dose must be introduced into nonrotating media for the paddle method. This is a special consideration if a staggered start is used to allow an analyst enough time to pull and filter samples and to add media within the ±2% time tolerance. It is important to maintain the requirements for dose introduction as described in the <711> Dissolution chapter. Typically paddle methods are used for most enteric coated methods because the enteric coating for some products may be damaged by the rotating basket method due to contact abrasion with the screen surface.
- Time: Because the dose never leaves the media, the (dissolution) clock never stops, and all test times and actions must conform to the ±2% time tolerance. For manual testing, this may best be accomplished by staggering the start to allow the analyst enough time to perform the italicized steps above. The ±2% rule applies not only to pulling a sample but filtering it also. In other words, you don't have a sample until it is filtered, and this is true for all timepoints. For automated methods of analysis, the sample may be automatically collected and filtered but

remember the volume correction for the remaining timepoints if the sample volume is not replaced.

- Media: Only preheated media is added. Typical media addition methods begin with around 750 mL of gastric media. After the gastric sample is pulled, buffered media preheated to 37.0 ± 0.5°C is added to each vessel. Typical buffer stage media consists of the addition of 250 mL of preheated 0.20 M tribasic sodium phosphate buffer. The analyst will have to ensure that the media is added, the pH is checked, and adjusted to a pH of 6.8 ± 0.05 units if necessary; all within 5 minutes of the gastric timepoint. Remember, the clock never stops. The method should also be developed and validated to ensure the proper pH is obtained after the buffered media is added. Media adjustment may be accomplished with 2 N hydrochloric acid or 2N sodium hydroxide. Temperature of the buffered media must also be recorded to ensure that the test conditions were maintained.

Attention to these steps and details will ensure that the delayed-release testing for enteric coated products is performed as intended with the USP <711> Dissolution chapter for the Method A, media addition method.

- The Media Exchange Method: USP <711> Dissolution, Delayed-Release Dosage Forms, Method B
- Dosage Introduction: The media exchange method works best for single entity dosage forms, in other words, capsules containing enteric coated pellets are best tested by the media addition method because all the pellets or particles may be difficult to transfer to remove from the acid stage media for placement in the buffer stage media. First, the dose must be introduced into nonrotating media acid stage media for the paddle method. The time starts as the tablet settles to the bottom of the vessel. The sample is usually placed in 1000 mL of 0.1 N hydrochloric acid for the acid stage media and allowed to run for 2 hours according to USP. Methods exist with USP monographs utilizing 900 mL and shorter acid stage run times of 30–60 minutes. A simultaneous start is usually convenient for the media exchange test because at the end of the acid stage, there are several options for continuing the test in the buffer stage under the “Time” section below. At the end of the acid phase the analyst will need to pull and filter samples within the ±2%-time tolerance. It is important to maintain the requirements for dose introduction as described in the <711> Dissolution chapter. Typically, the paddle methods are most commonly used for media exchange as well because the enteric coating for some products may be damaged by the rotating basket method due to contact abrasion with the screen surface.
- Time and media exchange methods: In this case, the clock is suspended or paused after pulling the samples, which allows raising the drive unit to access the vessels. The two primary methods that have the shortest turnover time are replacing media in the original vessel or removing the drug and dropping into another apparatus set up with the buffer stage media.
    - Removing the sample: Immediately after the sample is withdrawn from the acid stage immediately raise the drive unit, suspend the timer and remove each vessel containing the enteric product. The dose is best removed by pouring the media through six small stainless steel “tea strainers” that will capture each of the doses; remember to identify the strainers to avoid sample mix up.
    - Replacing the dose in the original vessel: After removing the sample, immediately pour the preheated 37.0°C buffer stage media into the original empty vessel and replace the

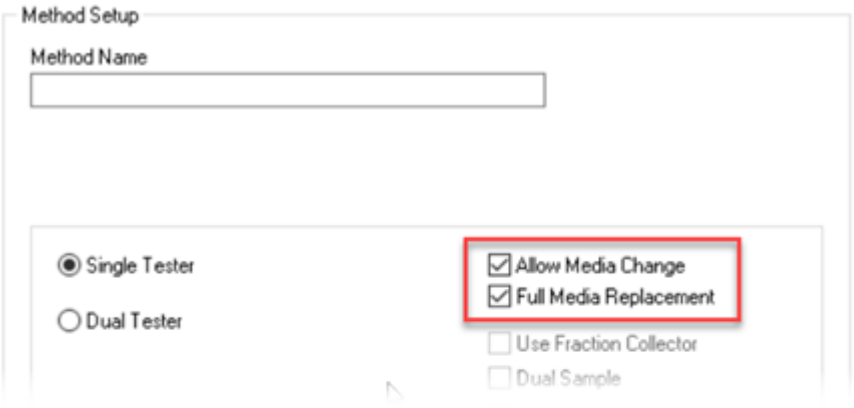
vessel in its original position and repeat with the other five vessels as quickly as possible. Upon placing the last vessel, immediately lower the drive unit back into position and introduce the dose into the preheated nonrotating media as stated earlier and restart the timer for the remainder of the test in the buffer stage.

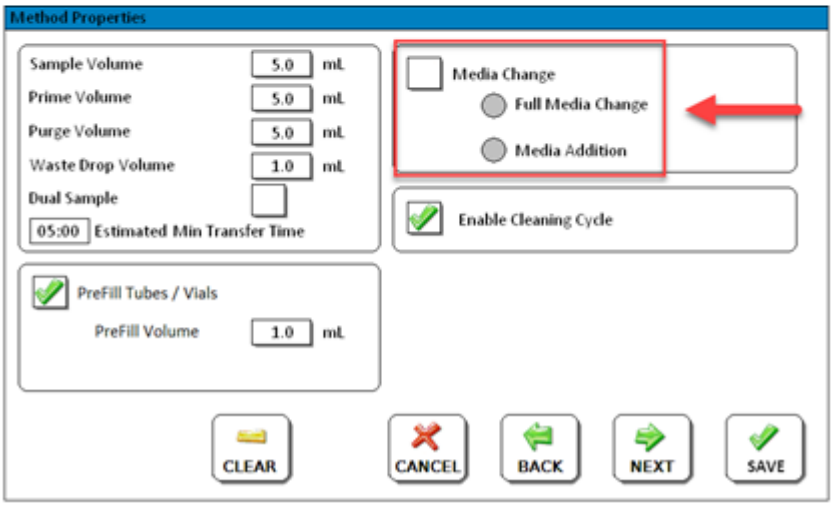
- Replacing the dose in another apparatus: This is probably the fastest turnover for media exchange however it may be difficult to perform with automated sampling equipment because you will need to execute two methods for analysis. While the acid stage test is running, another apparatus may be set up containing the buffer media and preheated to 37°C. After sampling and capturing the dosage form as described above, introduce the dose into the pre-heated non-rotating media start the paddle rotation and restart the timer for the remainder of the test in the buffer stage.

- Media: Only preheated media is added. Typical media exchange methods begin with 1000 mL of the acid stage media. After the acid stage sample is always placed in buffered media preheated to 37.0 ± 0.5°C. The analyst will have to ensure that once the media is added, the pH is checked and adjusted if necessary. The method should also be developed and validated to ensure the proper pH is obtained after the buffered media is exchanged. Temperature of the buffered media must also be recorded to ensure that the test conditions were maintained.

Attention to these steps and details will ensure that the delayed-release testing for enteric coated products is performed as intended with the USP <711> Dissolution chapter for the Method A, media addition method or Method B, media exchange method.
Agilent's Dissolution systems can account for the differences in how the Media Addition or Exchange is performed. The firmware or software of the instrumentation routinely requires the user to clarify which process or method will be utilized. By indicating whether a media addition (Method A) or full media change (Method B) will occur, the system knows how to handle the overall timing of the program – depending on whether the dosage form was temporarily removed from the media.

Agilent's Cary WinUV Dissolution software (mentioned earlier) and 850-DS Sampling Station firmware (following) require the user to specify the type of media change. This allows the instrumentation to properly document the timing





References: Remmington's Pharmaceutical Sciences; Mack Publishing, Easton, PA 18042

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