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In the pharmaceutical industry, the Q value is a key parameter in dissolution testing that ensures the quality and performance of solid oral dosage forms like tablets and capsules. But what exactly does it mean?The Q value represents the minimum percentage of the active pharmaceutical ingredient (API) that must dissolve in a specified time to meet regulatory standards. It is crucial for predicting in vivo drug performance and maintaining batch-to-batch consistency.Key Insights:1. Threshold for Compliance:For a product to pass, it must meet the required Q value (e.g., 80%) within the defined time, ensuring effective drug release.2. Testing Stages:Dissolution testing involves three stages (S1, S2, S3), where additional samples are tested if the initial results do not meet the criteria.3. Significance:Ensures consistent drug release.Validates product quality and manufacturing processes.4. Influencing Factors:Variables such as formulation properties, manufacturing conditions, and testing parameters like media composition or agitation speed can impact dissolution results.Why Q+5 in stage 1?The Q + 5% criterion in Stage 1 (S1) of dissolution testing is a regulatory safeguard to ensure consistency and quality of pharmaceutical products. Here's why this additional margin is applied:1. Stringent Quality AssuranceThe Q + 5% requirement ensures that the dissolution performance is robust, leaving little room for variability.It acts as an added buffer to account for minor inconsistencies in manufacturing, testing, or environmental factors.2. Early Detection of Potential FailuresIf a formulation barely meets the Q value during S1, it could signal potential issues with batch quality.The stricter criterion at S1 ensures only high-performing batches proceed without further testing.3. Reduced Need for Additional TestingMeeting Q + 5% minimizes the likelihood of moving to Stage 2 (S2) or Stage 3 (S3), saving time and resources.4. Regulatory ConfidenceRegulatory authorities (e.g., USP, BP, EP) incorporate this requirement to enhance confidence in the reproducibility and reliability of the product's dissolution profile.Practical Implication:For example, if the Q value is 80%, then during Stage 1, each of the 6 tested units must dissolve at least 85% of the API within the specified time.This criterion ensures that only highly consistent products pass at the initial stage, reflecting a robust and well-controlled manufacturing process. Read also: Delayed Release Buffer Stage Overview At the end of the acid stage, the sample must be withdrawn and media added/ adjusted within FIVE minutes. Typically, add 250 mL of 0.20-M tribasic sodium phosphate buffer at 37°C, adjust the pH to 6.8 ± 0.05 while stirring at the specified rate. The dissolution test continues for 45 minutes (or per monograph specifications). Temperature conditions at 37 ± 0.5°C must be maintained throughout the test.. Delayed Release - B1 Samples are taken at the end of the buffer stage, at which point the dosage form should have dissolved. The initial value of Q is calculated as being the total of both the acid and buffer stages. The value of Q is 75% dissolved unless otherwise specified in the individual monograph. The extended release forms should now behave as immediate release forms and so the evaluation of Q is calculated accordingly. Each unit tested must be not less than Q+5% to pass (eg. if Q = 80%, each tablet must not be less than 85% to pass). Delayed Release - B2 If the criteria for buffer stage 1 is not met, then six additional dosage forms are tested. The average of the results from both stages (B1 + B2), a total of 12 dosage forms in all, is calculated and the value must be greater than or equal to Q. No individual unit should have a value less than Q-15%. In our previous example, when Q = 80%, no unit should be less than 65% to pass stage 2. Delayed Release - B3 If the dosage forms do not pass the second stage, then 12 additional units are tested. The average of all 24 units (B1 + B2 + B3) is calculated. The value must not be less than the initial value of Q. In addition, no more than two units can have values of < Q-15% and no tablet can have a value of < Q-25%. If the samples fail at this stage, the entire batch is investigated and possibly rejected. In our previous example where Q = 80%, no two units would be less than 65% and no unit would be less than 55% to pass stage 3. The dissolution specification is expressed in terms of the quantity (Q) of active substance dissolved in a specified time. Using a percent value as a standard allows for easier standardization across all of the monographs and also helps to more easily apply limits based on statistics.As per USP, Q is the amount of dissolved active pharmaceutical ingredient (API).As per EP, Q represents the targeted amount of active substance, which should be dissolved within a certain time and expressed as a percentage of the label claim.How to Calculate Q Value?Let see, USP dissolution acceptance criteria for immediate release dosage form (below figure) -Let's assume that Q = 85% dissolved. Using this, then our acceptance criteria for this table would be:S1 - 6 units tested. Each unit is not less than 90% (Q+5%)S2 - 6 additional units tested. Average of 12 units (Stage 1 plus Stage 2) is equal or greater than 85% (Q), and no unit is less than 70% (Q-15%).S3 - 12 additional units tested. Average of 24 units (Stages 1 + 2 + 3) is equal to or greater than 85% (Q), not more than 2 units are less than 70% (Q-15%), and no unit is less than 60% (Q-25%).Why we need to add 5% or 10% to Q value?We do this because the specifications are all based on n=12. When you start with a smaller sample set with n=6, you need to have tighter criteria since you don't have as much statistical confidence.As you increase the sample set of data, you get closer to being able to use Q since you gain more confidence in your data being an accurate representation of the full lot.As per EP,For most cases in conventional-release dosage forms, when tested under reasonable and justified test conditions, the acceptance criteria at level S1 are that at least 80 per cent of the active substance is released within a specified time, typically 45 min or less. This corresponds to a Q value of 75 per cent, for level S1 the individual value of each of the 6 units tested is not less than Q + 5 per cent, i.e. not less than 80 per cent. Typically, a single-point acceptance criterion is sufficient to demonstrate that the majority of the active substance has been released, although in certain circumstances it may be necessary to test at additional time point(s), in order to demonstrate adequate dissolution.Read also: Drug dissolution is a critical attribute of any pharmaceutical product, and it plays a vital role in setting product specifications. The term "Q" is commonly used to express these specifications, and in this article, we will delve into the significance of "Q" and how it is used in designing these specifications.Hello, I'm Bhaskar Napte, the founder of Pharma Growth Hub. In this article, we'll explore the concept of "Q" and its role in pharmaceutical dissolution specifications.To understand "Q," let's refer to official pharmacopoeias. In the United States Pharmacopeia (USP) General Chapter 711, "Q" is defined as the amount of dissolved active ingredient specified in an individual monograph, expressed as a percentage of the labeled content of the dosage unit. In essence, "Q" represents the percentage of the active pharmaceutical ingredient (API) dissolved during the dissolution process.In the context of the European Pharmacopoeia (EP), General chapter 2.9.3, the definition of "Q" remains consistent. It is the specified amount of dissolved active substance expressed as a percentage of the labeled content. This underscores the importance of expressing dissolution in terms of percentages.Dissolution specifications are not typically set at a single step. For immediate-release dosage forms, they may be defined at three different stages (S1, S2, S3), or for modified-release dosage forms, at L1, L2, and L3. Let's examine how "Q" values are calculated using an example.Assuming our "Q" value is set at 85%, here's how acceptance criteria would be determined at each stage:Six units need to be tested.Acceptance criteria: All six units must have dissolution results greater than "Q" + 5%. In this case, that would be 90%. If all units meet this criterion, the product complies with the specification at S1.If one or two units fail at S1, an additional six units are tested.Acceptance criteria: The average of all 12 units (6 from S1 and 6 from S2) should be equal to or greater than "Q" (85%). Individual units can be lower, but none should fall below "Q" - 15%, which in this case is 70%.If any units fail at S2, 12 more units are tested, totaling 24 units (S1 + S2 + S3).Acceptance criteria: The average of all 24 units should be equal to or greater than "Q" (85%). Similar to S2, not more than two units should fall below "Q" - 15%, and none should be less than "Q" - 25%Why the "+5%" at S1 Stage:At the S1 stage, the "+5%" is added to the "Q" value to ensure stringent criteria are met. This adjustment is necessary because, during S1, only six units are tested, providing limited statistical confidence. As we move to S2 and S3 stages with larger sample sizes (12 and 24 units, respectively), we can rely more on the "Q" value itself, as statistical confidence increases.Understanding "Q" in dissolution specifications is crucial for ensuring the quality and effectiveness of pharmaceutical products. The multi-stage approach allows for a comprehensive assessment of dissolution performance, taking into account statistical confidence and ensuring product compliance with established standards.I welcome your thoughts and comments on this important aspect of pharmaceutical quality. Thank you for reading. Senior Executive at SUN PHARMA 5mo What is "Q" and "Q+5%" in Dissolution? Ans: Defining "Q": Q = (Amount of active ingredient dissolved / Labeled amount of active ingredient) × 100 Q-Value Interpretation- 1. Q = 75%: The tablet or capsule meets the dissolution specification if 75% or more of the labeled amount of active ingredient dissolves within the specified time frame. 2. Q 75%: The tablet or capsule fails the dissolution test if less than 75% of the labeled amount of active ingredient dissolves within the specified time frame. To understand "Q," let's refer to official pharmacopoeias. In the United States Pharmacopeia (USP) General Chapter 711, "Q" is defined as the amount of dissolved active ingredient specified in an individual monograph, expressed as a percentage of the labeled content of the dosage unit. In essence, "Q" represents the percentage of the active pharmaceutical ingredient (API) dissolved during the dissolution process. In the context of the European Pharmacopoeia (EP), General chapter 2.9.3, the definition of "Q" remains consistent. It is the specified amount of dissolved active substance expressed as a percentage of the labeled content. This underscores the importance of expressing dissolution in terms of percentages. Calculating "Q" Values: Dissolution specifications are not typically set at a single step. For immediate-release dosage forms, they may be defined at three different stages (S1, S2, S3), or for modified-release dosage forms, at L1, L2, and L3. Let's examine how "Q" values are calculated using an example. Assuming our "Q" value is set at 85%, here's how acceptance criteria would be determined at each stage: 1) S1 Stage: Six units need to be tested. Acceptance criteria: All six units must have dissolution results greater than "Q" + 5%. In this case, that would be 90%. If all units meet this criterion, the product complies with the specification at S1. 2) S2 Stage: If one or two units fail at S1, an additional six units are tested. Acceptance criteria: The average of all 12 units (6 from S1 and 6 from S2) should be equal to or greater than "Q" (85%). Individual units can be lower, but none should fall below "Q" - 15%, which in this case is 70%. 3) S3 Stage: If any units fail at S2, 12 more units are tested, totaling 24 units (S1 + S2 + S3). Acceptance criteria: The average of all 24 units should be equal to or greater than "Q" (85%). Similar to S2, not more than two units should fall below "Q" - 15%, and none should be less than "Q" - 25% Why the "+5%" at S1 Stage: At the S1 stage, the "+5%" is added to the "Q" value to ensure stringent criteria are met. This adjustment is necessary becausye, during S1, only six units are tested, providing limited statistical confidence. As we move to S2 and S3 stages with larger sample sizes (12 and 24 units, respectively), we can rely more on the "Q" value itself, as statistical confidence increases. See more comments To view or add a comment, sign in (originally posted by Ken Boda, Dissolution Product Specialist on LinkedIn) One question I frequently get is about Q in the USP. What is Q? How to I determine Q? How do I interpret the acceptance tables? USP defines Q as the quantity or the "amount of dissolved Active Pharmaceutical Ingredient (API) specified in an individual monograph, expressed as a percentage of the labeled content of the dosage unit...". When we look at a Q value, we are looking at what percent has dissolved at that time for that product. Using a percent value as a standard allows for easier standardization across all the monographs in the USP and also helps to more easily apply limits based on statistics. Having the tables defined in USP and instead of the individual monographs also helps to greatly reduce the size of each monograph as well! The Acceptance Tables are broken down into several categories, depending on what type of dosage form is being tested. You will find tables for Immediate-Release Dosage Forms, Immediate-Release Dosage Forms Pooled Sample, Extended-Release Dosage Forms, and Delayed-Release Dosage Forms. Acceptance criteria in the USP are based upon 12 samples, otherwise seen as n=12. In the acceptance tables, this is Stage 2. In stage 2, you will see that your average release is equal to Q. Stage 1 is essentially a shortcut based on statistics where you can pass the test with only 6 samples, or n=6, using a tighter set of acceptance criteria. If n=12 doesn't pass, then you move to stage 3, where you have a total of 24 samples or n=24. In Stage 3, you have a larger sample size, so the statistics allow for a wider range of acceptance. The Immediate-Release acceptance table is as follows: Let's assume that Q = 85% dissolved. Using this, then our acceptance criteria for this table would be: S1 - 6 units tested. Each unit is not less than 90% (Q+5%) S2 - 6 additional units tested. Average of 12 units (Stage 1 plus Stage 2) is equal or greater than 85% (Q), and no unit is less than 70% (Q-15%). S3 - 12 additional units tested. Average of 24 units (Stages 1 + 2 + 3) is equal to or greater than 85% (Q), not more than 2 units are less than 70% (Q-15%), and no unit is less than 60% (Q-25%). Some things to note here. You see that the specifications loosen as the sample size increases - this is due to increased confidence in statistics. You are also allowed limited outliers which can be well below Q in Stages 2 and 3. For Immediate Release with Pooled Sampling, the table looks quite a bit different. Here, you are taking a Pooled Sample - basically 1 sample which is a mixture of the n=6 to n=12 of that stage. Since you're only testing 1 sample per stage, you are testing fewer samples and the statistical requirements therefore are much tighter. Using the same Q = 85%, your acceptance criteria would be: S1 - 95% S2 - 90% S3 - 85% For Extended Release Products, you are now dealing with acceptance ranges. You must meet the table for each specification point in the dissolution monograph. It isn't uncommon to have 3 individual specifications, each which must be met in the following table: Let's assume for this table, that we are choosing a later timepoint and our acceptance criteria range is 70-80%. Our acceptable limits in the table would then be: L1 - 70-80% L2 - Average of 70-80%. No individual dose is outside of 60-90%. L3 - Average of 70-80%. Only 2 units can be outside of 60-90%. No units can be outside of of 50-100%. If we have 3 timepoints, you would need to confirm that each of these 3 timepoints meets this acceptance table. Delayed-Release Products have a separate acceptance table to allow for an acidic challenge and buffer stage. In the acidic challenge, you ideally want to see nothing dissolved indicating that the dose is fully protected from the stomach acid. Please note that this table is not compendial in the Japanese Pharmacopeia. In the delayed-release tables, you have one for the Acid Phase (A) and another for the Buffer Phase (B). The Acid Phase is pretty self-explanatory. In the Buffer Stage, you see something very similar to the Immediate-Release table above. If we assume Q = 85% again for the Buffer Stage, our passing values would be: B1 - Each unit is not less than 90% B2 - Average of 12 units is equal than or greater to 85%, and no unit is less than 70%. B3 - Average of 24 units is equal or greater to 85%, not more than 2 units are less than 70%, and no unit is less than 60%. I hope this walkthrough of Q in USP is helpful. For further clarification, feel free to contact Agilent's dissolution experts at dissolution.hotline@agilent.com. DE46758677 In the pharmaceutical industry, ensuring the consistent quality and performance of solid oral dosage forms like tablets and capsules is paramount. Among the many parameters assessed during quality control, the Q value in dissolution testing stands out as a critical benchmark. But what exactly does the Q value signify, and why is it so important?This article delves into the intricacies of the Q value, its role in dissolution testing, and the rationale behind associated regulatory standards like the Q+5% criterion.The Q value represents the minimum percentage of the active pharmaceutical ingredient (API) that must dissolve in a specified time frame to meet regulatory standards. It acts as a measure of how effectively a drug releases its active ingredients in simulated conditions, which closely mimic the human gastrointestinal tract.Meeting the Q value ensures that the drug will perform consistently in vivo, delivering the intended therapeutic effect. It also reflects batch-to-batch consistency, which is critical for patient safety and regulatory compliance.For a pharmaceutical product to pass dissolution testing, it must meet the required Q value (e.g., 80%) within the stipulated time. This guarantees that the drug releases an adequate amount of the API to achieve the desired therapeutic outcome.ALSO READ: Types of Dissolution Test ApparatusDissolution testing is a rigorous, multi-stage process involving three stages:Stage 1 (S1): Initial testing of 6 dosage units. All must meet the stringent Q + 5% requirement.Stage 2 (S2): Additional 6 units are tested if S1 criteria are not met, ensuring the average dissolution meets Q standards.Stage 3 (S3): If variability persists, 12 more units are tested to evaluate compliance.The tiered approach provides multiple opportunities for testing, ensuring reliable results while minimizing unnecessary wastage of resources.The Q value plays a pivotal role in pharmaceutical quality control by:Ensuring Consistent Drug Release: It validates that each dosage form releases the API predictably and consistently over time.Maintaining Product Quality: By meeting dissolution standards, manufacturers ensure high-quality products.Validating Manufacturing Processes: It reflects the effectiveness of manufacturing processes, from formulation to production.Several variables can affect the dissolution process, including:Formulation Properties: Characteristics like particle size, solubility, and excipients can impact dissolution rates.Manufacturing Conditions: Factors such as compression force during tablet formation or coating integrity influence how a drug dissolves.Testing Parameters: Testing conditions, including media composition, pH, and agitation speed, play a crucial role in achieving accurate results.In Stage 1 (S1) of dissolution testing, the regulatory requirement of Q + 5% is applied to ensure additional rigor. For instance, if the Q value is 80%, each of the 6 units tested must dissolve at least 85% of the API within the specified time. But why is this additional margin necessary?The Q + 5% criterion enhances quality assurance by:If a formulation barely meets the Q value during Stage 1, it could indicate potential issues with batch quality. The stricter criterion ensures that only high-performing batches pass without the need for further testing.By meeting the Q + 5% requirement in S1, manufacturers can minimize the likelihood of proceeding to S2 or S3, saving valuable time and resources.Regulatory agencies such as the USP, BP, and EP incorporate the Q + 5% requirement to bolster confidence in the reproducibility and reliability of a product's dissolution profile.A key question often arises: Why is the tolerance for Q set at 5% and not a stricter (3%) or broader (10%) range? The 5% tolerance is a carefully chosen compromise between ensuring quality and accommodating minor variability.The 5% tolerance originated from guidelines established by the United States Pharmacopeia (USP) and the FDA. Initially, the tolerance was set at 10%, but as manufacturing technologies and analytical methods improved, it was reduced to 5% to ensure greater product consistency. Accounting for Manufacturing Variability: A 5% tolerance allows for minor differences in manufacturing processes while maintaining product integrity.Analytical Variability: Analytical methods like HPLC or UV spectroscopy, which measure dissolution, have inherent variability. The 5% margin accommodates this.Clinical Relevance: Small variations within a 5% range are considered clinically insignificant, meaning they do not affect the drug's efficacy or safety.Increased False Failures: A 3% tolerance could result in more products failing due to minor and clinically irrelevant variations.Reduced Efficiency: Tighter tolerances would increase rework, retesting, and manufacturing waste.Reduced Product Quality: A wider tolerance could compromise product consistency, affecting drug efficacy and safety.Regulatory Non-Compliance: A 10% margin might not meet regulatory standards, leading to potential compliance issues.Understanding and adhering to the Q value and its associated tolerances have real-world implications:For Manufacturers: Meeting the Q + 5% criterion reflects robust manufacturing and quality assurance practices, reducing the risk of product recalls or regulatory action.For Regulators: The Q value offers a standardized metric to assess drug performance, ensuring patient safety and therapeutic effectiveness.For Patients: Consistent dissolution profiles guarantee reliable drug delivery and efficacy, enhancing trust in pharmaceutical products.The Q value in dissolution testing is a cornerstone of pharmaceutical quality control, ensuring that drugs perform predictably and consistently. By adhering to stringent standards like the Q + 5% criterion, manufacturers can maintain high product quality, regulatory compliance, and patient trust.Understanding the rationale behind the 5% tolerance further underscores the delicate balance between precision and practicality in the pharmaceutical industry. Ultimately, the Q value serves as a vital link between scientific rigor, manufacturing excellence, and therapeutic reliability. Created by ZHATKIN Yurii, last modified by MONTARD Laurence on Sep 15, 2021 Answer:Q represents the targeted amount of active substance, expressed as a percentage of the label claim, which should be dissolved within a certain time. The 'Q value' should be seen as a "reference value" to which the dissolution results are compared. Such a comparison applies both to conventional-release dosage forms and the buffer stage of the dissolution test of gastro-resistant dosage forms.For more information on dissolution testing, refer to general chapter 5.17.1. Recommendations on dissolution testing. Dissolution testing plays a crucial role in the pharmaceutical industry. It helps determine the rate at which a drug substance dissolves in a chosen solvent or medium. The results of dissolution testing provide valuable insights into the drug's release characteristics, bioavailability, and effectiveness. A parameter used to evaluate dissolution data is the q value. So, what is meant by q value in dissolution? **The q value in dissolution refers to the amount of drug substance dissolved at a specific time during a dissolution test. It is a numeric value that indicates the percentage of drug dissolved within a specified time interval.** The q value is a fundamental parameter used to assess drug release from solid oral dosage forms, such as tablets and capsules. It allows pharmaceutical researchers and manufacturers to monitor and compare the dissolution behavior of different formulations, evaluate batch-to-batch consistency, and ensure product quality and performance. FAQs on q value in dissolution: 1. How is the q value determined in dissolution testing? The q value is determined by measuring the concentration of the drug substance in the dissolution medium at a specific time, usually using validated analytical techniques. 2. Why is the q value important in dissolution testing? The q value provides quantitative data on drug release rates, helping researchers understand the formulation's dissolution behavior and predict its performance in the body. 3. What is the significance of q value in pharmaceutical quality control? The q value enables continuous monitoring of batch-to-batch consistency and identifies any potential variations or noncompliance with dissolution specifications. 4. Can the q value alone determine the effectiveness of a drug formulation? No, the q value is just one of several parameters used to evaluate drug release. Other factors like dissolution profile shape, similarity factors, and dissolution efficiency are also considered for comprehensive assessment. 5. How is the q value used to evaluate generic drug products? When seeking regulatory approvals, generic drug manufacturers must demonstrate that their product's dissolution profile and q value are similar to that of the reference (brand) product. 6. Are there any guidelines or regulatory requirements regarding q value in dissolution testing? Yes, regulatory authorities such as the United States Pharmacopeia (USP) and the European Pharmacopoeia (Ph. Eur.) provide guidelines on dissolution testing, including the determination and acceptance criteria for the q value. 7. Can the q value be used to compare drug formulations from different manufacturers? Yes, the q value is a standardized parameter that allows comparison between different drug formulations to assess equivalency or similarity. 8. Is the q value the same for all drugs? No, the q value varies for different drug substances and dosage forms. Each drug has its own dissolution behavior, which depends on factors such as solubility, formulation composition, and manufacturing process. 9. Can the q value be used to predict drug bioavailability? While the q value provides some insights into drug release, it does not directly predict bioavailability. Other factors, such as drug absorption and metabolism, also influence bioavailability. 10. Can the q value be influenced by experimental conditions or dissolution apparatus? Yes, the q value can be influenced by factors like agitation rate, temperature, and choice of dissolution medium. These parameters must be carefully controlled to ensure accurate and reproducible results. 11. Are there any limitations to using the q value in dissolution testing? Yes, the q value only provides a snapshot of drug release at a specific time point. It may not capture the complete dissolution behavior, especially for drug products with complex release profiles. 12. Is the q value an internationally recognized parameter in dissolution testing? Yes, the q value is widely accepted and used globally as a parameter in dissolution testing for assessing product quality, equivalence, and performance. It helps ensure the safety and efficacy of pharmaceutical products. Dive into the world of luxury with this video! Your friends have asked us these questions - Check out the answers! 711 DISSOLUTION This general chapter is harmonized with the corresponding texts of the European Pharmacopoeia and/or the Japanese Pharmacopoeia. The texts of these pharmacopeias are therefore interchangeable, and the methods of the European Pharmacopoeia or the Japanese Pharmacopoeia may be used for demonstration of compliance instead of the present general chapter. These pharmacopeias have undertaken not to make any unilateral change to this harmonized chapter. Portions of the present general chapter text that are national USP text, and therefore not part of the harmonized text, are marked with symbols () to specify this fact. This test is provided to determine compliance with the dissolution requirements where stated in the individual monograph for dosage forms administered orally. In this general chapter, a dosage unit is defined as 1 tablet or 1 capsule or the amount specified. Of the types of apparatus described herein, use the one specified in the individual monograph. Where the label states that an article is enteric-coated, and where a dissolution or disintegration test that does not specifically state that it is to be applied to delayed-release articles is included in the individual monograph, the procedure and interpretation given for Delayed-Release Dosage Forms is applied unless otherwise specified in the individual monograph. For hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the Dissolution specification, repeat the test as follows. Where water or a medium with a pH of less than 6.8 is specified as the Medium in the individual monograph, the same Medium specified may be used with the addition of purified pepsin that results in an activity of 750,000 Units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP Units of protease activity per 1000 mL. USP Reference Standards 11— USP Chlorpheniramine Maleate Extended-Release Tablets RS (Drug Release Calibrator, Single Unit). USP Prednisone Tablets RS (Dissolution Calibrator, Disintegrating). USP Salicylic Acid Tablets RS. (Dissolution Calibrator, Nondisintegrating). Apparatus 1 (Basket Apparatus) The assembly consists of the following: a vessel, which may be covered, made of glass or other inert, transparent material1 ; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size or heated by a suitable device such as a heating jacket. The water bath or heating device permits holding the temperature inside the vessel at 37 ± 0.5 during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. An apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom and with one of the following dimensions and capacities: for a nominal capacity of 1 L, the height is 160 mm to 210 mm and its inside diameter is 98 mm to 106 mm; for a nominal capacity of 2 L, the height is 280 mm to 300 mm and its inside diameter is 98 mm to 106 mm; and for a nominal capacity of 4 L, the height is 280 mm to 300 mm and its inside diameter is 145 mm to 155 mm. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.2 The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble that could affect the results. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the specified rate given in the individual monograph, within ±4%. Shaft and basket components of the stirring element are fabricated of stainless steel, type 316, or other inert material, to the specifications shown in Figure 1. A basket having a gold coating of about 0.0001 inch (2.5 µm) thick may be used. A dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the bottom of the basket is maintained at 25 ± 2 mm during the test. Fig. 1. Basket Stirring Element Apparatus 2 (Paddle Apparatus) Use the assembly from Apparatus 1, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm from the vertical axis of the vessel at any point and rotates smoothly without significant wobble that could affect the results. The vertical center line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in Figure 2. The distance of 25 ± 2 mm between the bottom of the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. A suitable two-part detachable design may be used provided the assembly remains firmly engaged during the test. The paddle blade and shaft may be coated with a suitable coating so as to make them inert. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float. An alternative sinker device is shown in Figure 2a. Other validated sinker devices may be used. Fig. 2. Paddle Stirring Element Fig. 2a. Alternative sinker. All dimensions are expressed in mm. Apparatus 3 (Reciprocating Cylinder) NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; inert fittings (stainless steel type 316 or other suitable material), and screens that are made of suitable nonsorbing and nonreactive material and that are designed to fit the tops and bottoms of the reciprocating cylinders; and a motor and drive assembly to reciprocate the cylinders vertically inside the vessels and, if desired, index the reciprocating cylinders horizontally to a different row of vessels. The vessels are partially immersed in a suitable water bath of any convenient size that permits holding the temperature at 37 ± 0.5 during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smooth, vertically reciprocating cylinder. A device is used that allows the reciprocation rate to be selected and maintained at the specified dip rate given in the individual monograph within ±5%. An apparatus that permits observation of the specimens and reciprocating cylinders is preferable. The vessels are provided with an evaporation cap that remains in place for the duration of the test. The components conform to the dimensions shown in Figure 3 unless otherwise specified in the individual monograph. Fig. 3. Apparatus 3 (reciprocating cylinder) Apparatus 4 (Flow-Through Cell) The assembly consists of a reservoir and a pump for the Dissolution Medium; a flow-through cell; and a water bath that maintains the Dissolution Medium at 37 ± 0.5. Use the specified cell size as given in the individual monograph. The pump forces the Dissolution Medium upwards through the flow-through cell. The pump has a delivery range between 240 and 960 mL per hour, with standard flow rates of 4, 8, and 16 mL per minute. It must deliver a constant flow (±5% of the nominal flow rate); the flow profile is sinusoidal with a pulsation of 120 ± 10 pulses per minute. The flow-through cell (see Figures 4 and 5), of transparent and inert material, is mounted vertically with a filter system (specified in the individual monograph) that prevents escape of undissolved particles from the top of the cell; standard cell diameters are 12 and 22.6 mm; the bottom cone is usually filled with small glass beads of about 1-mm diameter with one bead of about 5 mm positioned at the apex to protect the fluid entry tube; and a tablet holder (see Figures 4 and 5) is available for positioning of special dosage forms, for example, inlay tablets. The cell is immersed in a water bath, and the temperature is maintained at 37 ± 0.5. Fig. 4. Large cell for tablets and capsules (top) Tablet holder for the large cell (bottom) (All measurements are expressed in mm unless noted otherwise.) Fig. 5. Small cell for tablets and capsules (top) Tablet holder for the small cell (bottom) (All measurements are expressed in mm unless noted otherwise.) The apparatus uses a clamp mechanism and two O-rings to assemble the cell. The pump is separated from the dissolution unit in order to shield the latter against any vibrations originating from the pump. The position of the pump should not be on a level higher than the reservoir flasks. Tube connections are as short as possible. Use suitably inert tubing, such as polytef, with about 1.6-mm inner diameter and chemically inert flanged-end connections. The determination of suitability of a test assembly to perform dissolution testing must include conformance to the dimensions and tolerances of the apparatus as given above. In addition, critical test parameters that have to be monitored periodically during use include volume and temperature of the Dissolution Medium, rotation speed (Apparatus 1 and Apparatus 2), dip rate (Apparatus 3), and flow rate of medium (Apparatus 4). Determine the acceptable performance of the dissolution test assembly periodically. The suitability for the individual apparatus is demonstrated by the Apparatus Suitability Test. Apparatus Suitability Test, Apparatus 1 and 2— Individually test 1 tablet of the USP Dissolution Calibrator, Disintegrating Type and 1 tablet of USP Dissolution Calibrator, Nondisintegrating Type, according to the operating conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the certificate for that calibrator in the apparatus tested. Apparatus Suitability Test, Apparatus 3— Individually test 1 tablet of the USP Drug Release Tablets (Single Unit) according to the operating conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the certificate. Apparatus Suitability Test, Apparatus 4— [To come.] Apparatus 1 and Apparatus 2 Immediate-Release Dosage Forms Place the stated volume of the Dissolution Medium (±1%) in the vessel of the specified apparatus given in the individual monograph, assemble the apparatus, equilibrate the Dissolution Medium to 37 ± 0.5, and remove the thermometer. Place 1 dosage unit in the apparatus, taking care to exclude air bubbles from the surface of the dosage unit, and immediately operate the apparatus at the specified rate given in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the Dissolution Medium and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. [NOTE—Where multiple sampling times are specified, replace the aliquots withdrawn for analysis with equal volumes of fresh Dissolution Medium at 37 or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.] Perform the analysis as directed in the individual monograph using a suitable assay method.3 Repeat the test with additional dosage form units. If automated equipment is used for sampling or the apparatus is otherwise modified, verification that the modified apparatus will produce results equivalent to those obtained with the standard apparatus described in this general chapter is necessary. Dissolution Medium— A suitable dissolution medium is used. Use the solvent specified in the individual monograph. The volume specified refers to measurements made between 20 and 25. If the Dissolution Medium is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the specified pH given in the individual monograph. [NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. If dissolved gases influence the dissolution results, dissolved gases should be removed prior to testing.4] Time— Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. Specimens are to be withdrawn only at the stated times within a tolerance of ±2%. Extended-Release Dosage Forms Proceed as directed for Immediate-Release Dosage Forms. Dissolution Medium— Proceed as directed for Immediate-Release Dosage Forms. Time— The test-time points, generally three, are expressed in hours. Delayed-Release Dosage Forms NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA Use Method A or Method B and the apparatus specified in the individual monograph. All test times stated are to be observed within a tolerance of ±2%, unless otherwise specified. Method A— Procedure (unless otherwise directed in the individual monograph)— ACID STAGE— Place 750 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the specified rate given in the monograph. After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under Buffer Stage. Perform an analysis of the aliquot using a suitable assay method. The procedure is specified in the individual monograph. BUFFER STAGE— [NOTE—Complete the operations of adding the buffer and adjusting the pH within 5 minutes.] With the apparatus operating at the rate specified in the monograph, add to the fluid in the vessel 250 mL of 0.20 M tribasic sodium phosphate that has been equilibrated to 37 ± 0.5. Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 minutes, or for the specified time given in the individual monograph. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method. The procedure is specified in the individual monograph. The test may be concluded in a shorter time period than that specified for the Buffer Stage if the requirement for the minimum amount dissolved is met at an earlier time. Method B— Procedure (unless otherwise directed in the individual monograph)— ACID STAGE— Place 1000 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the rate specified in the monograph. After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under Buffer Stage. Perform an analysis of the aliquot using a suitable assay method. The procedure is specified in the individual monograph. BUFFER STAGE— [NOTE—For this stage of the procedure, use buffer that previously has been equilibrated to a temperature of 37 ± 0.5.] Drain the acid from the vessel, and add to the vessel 1000 mL of pH 6.8 phosphate buffer, prepared by mixing 0.1 N hydrochloric acid with 0.20 M tribasic sodium phosphate (3:1) and adjusting, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. [NOTE—This may also be accomplished by removing from the apparatus the vessel containing the acid and replacing it with another vessel containing the buffer and transferring the dosage unit to the vessel containing the buffer.] Continue to operate the apparatus for 45 minutes, or for the specified time given in the individual monograph. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method. The procedure is specified in the individual monograph. The test may be concluded in a shorter time period than that specified for the Buffer Stage if the requirement for minimum amount dissolved is met at an earlier time. Apparatus 3 (Reciprocating Cylinder) NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA Immediate-Release Dosage Forms Place the stated volume of the Dissolution Medium in each vessel of the apparatus, assemble the apparatus, equilibrate the Dissolution Medium to 37 ± 0.5, and remove the thermometer. Place 1 dosage-form unit in each of the six reciprocating cylinders, taking care to exclude air bubbles from the surface of each dosage unit, and immediately operate the apparatus as specified in the individual monograph. During the upward and downward stroke, the reciprocating cylinder moves through a total distance of 9.9 to 10.1 cm. Within the time interval specified, or at each of the times stated, raise the reciprocating cylinders and withdraw a portion of the solution under test from a zone midway between the surface of the Dissolution Medium and the bottom of each vessel. Perform the analysis as directed in the individual monograph. If necessary, repeat the test with additional dosage-form units. Dissolution Medium —Proceed as directed for Immediate-Release Dosage Forms under Apparatus 1 and Apparatus 2. Time —Proceed as directed for Immediate-Release Dosage Forms under Apparatus 1 and Apparatus 2. Extended-Release Dosage Forms Proceed as directed for Immediate-Release Dosage Forms under Apparatus 3. —Proceed as directed for Extended-Release Dosage Forms under Apparatus 1 and Apparatus 2. Time —Proceed as directed for Extended-Release Dosage Forms under Apparatus 1 and Apparatus 2. Delayed-Release Dosage Forms Proceed as described for Delayed-Release Dosage Forms, Method B under Apparatus 1 and Apparatus 2 using one row of vessels for the acid stage media and the following row of vessels for the buffer stage media and using the volume of medium specified (usually 300 mL). Time —Proceed as directed for Immediate-Release Dosage Forms under Apparatus 1 and Apparatus 2. Apparatus 4 (Flow-Through Cell) Immediate-Release Dosage Forms Place the glass beads into the cell specified in the monograph. Place 1 dosage unit on top of the beads or, if specified in the monograph, on a wire carrier. Assemble the filter head, and fix the parts together by means of a suitable clamping device. Introduce by the pump the Dissolution Medium warmed to 37 ± 0.5 through the bottom of the cell to obtain the flow rate specified in the individual monograph and measured with an accuracy of 5%. Collect the eluate by fractions at each of the times stated. Perform the analysis as directed in the individual monograph. Repeat the test with additional dosage-form units. Dissolution Medium —Proceed as directed for Immediate-Release Dosage Forms under Apparatus 1 and Apparatus 2. Time —Proceed as directed for Immediate-Release Dosage Forms under Apparatus 1 and Apparatus 2. Extended-Release Dosage Forms Proceed as directed for Immediate-Release Dosage Forms under Apparatus 4. Dissolution Medium —Proceed as directed for Immediate-Release Dosage Forms under Apparatus 4. Time —Proceed as directed for Immediate-Release Dosage Forms under Apparatus 4. Delayed-Release Dosage Forms Proceed as directed for Delayed-Release Dosage Forms under Apparatus 1 and Apparatus 2, using the specified media. Time —Proceed as directed for Delayed-Release Dosage Forms under Apparatus 1 and Apparatus 2. Immediate-Release Dosage Forms Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to Acceptance Table 1. Continue testing through the three stages unless the results conform at either S1 or S2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph,expressed as a percentage of the labeled content of the dosage unit; the 5%, 15%, and 25% values in Acceptance Table 1 are percentages of the labeled content so that these values and Q are in the same terms. Stage Number Tested Acceptance Criteria S1 6 Each unit is not less than Q + 5%. S2 6 Average of 12 units (S1 + S2) is equal to or greater than Q, and no unit is less than Q 15%. S3 12 Average of 24 units (S1 + S2 + S3) is equal to or greater than Q, not more than 2 units are less than Q 15%, and no unit is less than Q 25%. Extended-Release Dosage Forms Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to Acceptance Table 2. Continue testing through the three levels unless the results conform at either L1 or L2. Limits on the amounts of active ingredient dissolved are expressed in terms of the percentage of labeled content. The limits embrace each value of Qi, the amount dissolved at each specified fractional dosing interval. Where more than one range is specified in the individual monograph, the acceptance criteria apply individually to each range. Level Number Tested Criteria L1 6 No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time. L2 6 The average value of the 12 units (L1 + L2) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time. L3 12 The average value of the 24 units (L1 + L2 + L3) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final test time. Delayed-Release Dosage Forms NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA. Acid Stage— Unless otherwise specified in the individual monograph, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to Acceptance Table 3. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level. Level Number Tested Criteria A1 6 No individual value exceeds 10% dissolved. A2 6 Average of the 12 units (A1 + A2) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved. A3 12 Average of the 24 units (A1 + A2 + A3) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved. Buffer Stage— Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to Acceptance Table 4. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of Q in Acceptance Table 4 is 75% dissolved unless otherwise specified in the individual monograph. The quantity, Q,specified in the individual monograph is the total amount of active ingredient dissolved in both the Acid and Buffer Stages, expressed as a percentage of the labeled content. The 5%, 15%, and 25% values in Acceptance Table 4 are percentages of the labeled content so that these values and Q are in the same terms. Level Number Tested Criteria B1 6 Each unit is not less than Q + 5%. B2 6 Average of 12 units (B1 + B2) is equal to or greater than Q, and no unit is less than Q – 15%. B3 12 Average of 24 units (B1 + B2 + B3) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%. 1 The materials should not sorb, react, or interfere with the specimen being tested. 2 If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens. 3 Test specimens are filtered immediately upon sampling unless filtration is demonstrated to be unnecessary. Use an inert filter that does not cause adsorption of the active ingredient or contain extractable substances that would interfere with the analysis. 4 One method of deaeration is as follows: Heat the medium, while stirring gently, to about 41, immediately filter under vacuum using a filter having a porosity of 0.45 µm or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated deaeration techniques for removal of dissolved gases may be used. Immediate-Release Dosage FormsUnless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to Acceptance Table 1. Continue testing through the three stages unless the results conform at either S1 or S2. The quantity (Q) is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content of the dosage unit; the 5%, 15%, and 25% values in Acceptance Table 1 are percentages of the labeled content so that these values and Q are in the same terms.Immediate-Release Dosage Forms Pooled SampleUnless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either S1 or S2. The quantity (Q) is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.Extended-Release Dosage FormsUnless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to Acceptance Table 2. Continue testing through the three levels unless the results conform at either L1 or L2. Limits on the amounts of active ingredient dissolved are expressed in terms of the percentage of labeled content. The limits embrace each value of Qi, the amount dissolved at each specified fractional dosing interval. Where more than one range is specified in the individual monograph, the acceptance criteria apply individually to each range.Delayed-Release Dosage FormsAcid stage: Unless otherwise specified in the individual monograph, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to Acceptance Table 3. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.Buffer stage: Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to Acceptance Table 4. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of Q in Acceptance Table 4 is 75% dissolved unless otherwise specified in the individual monograph. The quantity (Q) specified in the individual monograph is the total amount of active ingredient dissolved in both the Acid Stage and the Buffer Stage, expressed as a percentage of the labeled content. The 5%, 15%, and 25% values in Acceptance Table 4 are percentages of the labeled content so that these values and Q are in the same terms.Reference: USP 〈711〉 DISSOLUTIONRead also: Dissolution Test Interpretation as per BPPooled Sampling in Dissolution