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BASIC OF COMPUNDING: POTENCY AND STABILITY TESTING FOR LIQUID ORAL PREPARATION

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ABSTRACT

Pediatric patients often require specialized medications that are not commercially available in suitable formulations or dosages. In such cases, hospital pharmacies play a crucial role in compounding customized medications to meet the unique needs of pediatric patients. Compounded medications for pediatric patients should undergo appropriate quality control measures, including stability testing, to ensure safety and efficacy.

Compounding potency and stability testing are crucial aspects of quality control for oral preparations by determining the quality and effectiveness of oral preparations in pharmacy compounding. Potency testing ensures that the active ingredients in the formulation are present in the desired concentration and maintain their efficacy throughout the product's shelf life. Stability testing, on the other hand, determines the shelf life of the preparation by assessing its physical, chemical, and microbiological stability under various storage conditions.

Potency Testing: Potency testing for liquid oral preparations involves measuring the concentration or activity of the active pharmaceutical ingredient (API) in the formulation. The goal is to ensure that the desired amount of the API is present to achieve the intended therapeutic effect. Common methods for potency testing in liquid formulations include:

- High-performance liquid chromatography (HPLC)
- UV-Visible spectrophotometry
- Titration methods
- Bioassays

Stability Testing: Stability testing assesses the chemical, physical, and microbiological stability of the liquid oral preparation over time. The tests help determine the expiration date and appropriate storage conditions to maintain the product's quality, efficacy, and safety. Considerations specific to liquid formulations include:

- Physical stability: Evaluating changes in appearance, color, odor, and pH.
- Chemical stability: Monitoring API degradation, impurity formation, and potential drug-drug interactions in the liquid matrix.
- Microbiological stability: Assessing microbial growth and the effectiveness of preservatives.
- Packaging compatibility: Analysing the interaction between the formulation and the packaging material.

Stability Testing Methods

Stability testing is a routine procedure performed on drug substances and products and is employed at various stages of the product development. In early stages, accelerated stability testing (at relatively high temperatures and/or humidity) is used in order to determine the type of degradation products which may be found after long-term storage. Testing under less rigorous conditions i.e. those recommended for long-term shelf storage, at slightly elevated temperatures is used to determine a product's shelf life and expiration dates.

Accelerated Stability Testing: Similar to solid oral preparations, accelerated stability testing can be performed for liquid oral formulations. Elevated temperature and humidity conditions are applied to induce faster degradation and evaluate the stability of the product over a shorter period. The data obtained from accelerated testing can be used to estimate the product's long-term stability.

Real-Time Stability Testing: Real-time stability testing involves monitoring the stability of the liquid oral preparation under recommended storage conditions for the intended shelf life. Samples are periodically withdrawn and tested to assess changes in quality attributes, such as API degradation, pH, and microbial growth.

Assessment of Stability Through HPLC Method

High-performance liquid chromatography (HPLC) is a widely used analytical technique for stability studies of pharmaceuticals, including liquid oral preparations. HPLC allows for the separation, identification, and quantification of different components in a sample, including the active pharmaceutical ingredient (API) and related impurities. Here's how HPLC is utilized in stability studies:

1. **Method Development:** A suitable HPLC method is developed specifically for the analysis of the API and impurities in the liquid oral preparation. This involves selecting an appropriate stationary phase, mobile phase composition, column temperature, and detection wavelength. The method should be sensitive, selective, and capable of providing accurate and reproducible results.
2. **Sample Preparation:** Prior to HPLC analysis, the liquid oral preparation undergoes sample preparation to extract or isolate the API and impurities from the matrix. Sample preparation techniques can include filtration, dilution, extraction, or solid-phase extraction (SPE), depending on the specific characteristics of the formulation and the desired analytes.
3. **Separation and Detection:** The prepared sample is injected into the HPLC system, and the components are separated based on their physicochemical properties on the stationary phase (column). The mobile phase,

typically a mixture of solvents, flows through the column, carrying the analytes. The separated components are detected by a suitable detector, such as UV-Visible, diode array, or mass spectrometry detector.

4. **Quantification and Identification:** The HPLC system generates chromatograms, which provide information about the retention times and peak areas of the API and impurities. The peak area or height is used to quantify the analytes based on calibration curves prepared with known standards. The identity of the API and impurities can be confirmed by comparing retention times and spectra with authentic reference standards, if available.
5. **Forced Degradation Studies:** HPLC is also used in forced degradation studies, where the liquid oral preparation is subjected to various stress conditions, such as heat, light, humidity, and acid/base hydrolysis. The HPLC analysis of the degraded samples helps identify and quantify degradation products, providing insights into the stability and degradation pathways of the formulation.
6. **Stability-Indicating Method:** A stability-indicating HPLC method is developed to specifically detect and quantify the API and its degradation products. This method should be capable of separating the API from impurities and degradation products, even in the presence of excipients and matrix components present in the liquid oral preparation.

HPLC Method Can be Used to Assess Following Stability Parameters:

- **Chemical stability:** Monitoring API degradation, impurity formation, and potential drug-drug interactions in the liquid matrix.
- **Assay/Potency:** HPLC analysis can determine the concentration of the active pharmaceutical ingredient (API) in a formulation. By comparing the assay results at different time points, the stability of the API can be assessed.
- **Microbiological stability:** Assessing microbial growth and the effectiveness of preservatives.
- **Packaging compatibility:** Analyzing the interaction between the formulation and the packaging material.
- **pH:** Some liquid formulations may undergo pH changes during stability studies. HPLC methods can be used to measure pH directly or indirectly by assessing the retention times or peak shapes of analytes sensitive to pH variations. Etc.

Physical Stability Assessment

Physical stability refers to the ability of an oral liquid formulation to maintain its physical characteristics over time. It involves assessing changes in appearance, color, odor, pH, and other physical attributes.

Appearance:

- **Visual inspection:** Monitor the formulation for any changes in clarity, color, presence of particles, or phase separation.
- **Turbidity:** Measure the turbidity of the liquid using techniques such as nephelometry or spectrophotometry. An increase in turbidity may indicate the presence of suspended particles or phase separation.

Color:

- **Visual inspection:** Compare the color of the formulation with its initial color and monitor for any noticeable changes or discoloration.

Odor:

- **Sensory evaluation:** Assess the formulation for any changes in odor or the presence of an off-putting odor.

pH measurement: Monitor the pH of the oral liquid formulation using a suitable pH meter. Deviations from the specified pH range may indicate degradation or other stability issues.

Homogeneity:

- **Visual inspection:** Look for any signs of phase separation, settling, or floating particles.
- **Shake test:** Vigorously shake the formulation and observe for the ease of re-dispersion and any changes in appearance or texture upon standing.

Sign of Physical/Chemical Instability

Signs of instability in oral liquid compounding can manifest in various ways. Here are some common signs that indicate a formulation may be unstable:

Phase Separation:

- Formation of distinct layers or separation of the formulation into two or more phases.
- Visible oil droplets or sedimentation at the bottom of the container.

Color Change:

- Alteration in the original color of the formulation.
- Development of a darker or lighter color, or the appearance of new color tones.

Appearance of Particulate Matter:

- Presence of visible particles or foreign matter in the formulation.
- Suspended solids, precipitates, or undissolved API or excipients.

Change in Clarity:

- Loss of transparency or opalescence.
- Cloudiness, haziness, or turbidity.

Odor Change:

- Foul or unpleasant odor development.
- Change in the characteristic odor of the formulation.

pH Shift:

- Significant deviation from the initial or target pH range.
- Acidic or alkaline pH changes beyond the acceptable limits.

Viscosity Alteration:

- Drastic increase or decrease in viscosity, leading to a change in the formulation's consistency.
- Formation of gels, thixotropy, or stringiness.

Gas Formation:

- Release of gas bubbles or effervescence.
- Foaming or frothing upon agitation or opening the container.

Container Integrity:

- Leakage or damage to the container, leading to exposure of the formulation to air, light, or contaminants.
- Signs of container deformation, cracks, or discoloration.

Loss of Efficacy:

- Decreased potency or loss of therapeutic effect.
- Failure to meet the specified assay or potency requirements.

Conclusion:

Stability testing is a critical component of the pharmaceutical development process, ensuring that a product maintains its quality, efficacy, and safety throughout its shelf life. For oral liquid compounding, stability testing plays a crucial role in evaluating the physical and chemical stability of the formulation, as well as assessing the potency, degradation products, and impurities that may arise over time.

By conducting stability studies, compounding pharmacists can determine the appropriate storage conditions, recommended shelf life, and handling instructions for the oral liquid formulation. This information is essential for maintaining the quality of the product and preventing any potential risks associated with its use.

HPLC analysis is a valuable tool in stability testing, as it provides accurate and reliable quantification of the active pharmaceutical ingredient (API), detection of degradation products, and identification of impurities. It allows for the monitoring of the API's potency and degradation kinetics, aiding in the determination of the formulation's stability profile.

Physical stability assessments are equally important, as they help identify changes in appearance, color, odor, pH, and other physical attributes. These changes may indicate potential problems such as phase separation, particle formation, container incompatibility, or other physical instabilities that can impact the usability and patient acceptance of the oral liquid formulation.

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