Compounding
Slow-Release
Pharmaceuticals

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Slow-release tablets or capsules theoretically release the amount of drug at a rate that produces desirable therapeutic effect while decreasing the variability of drug level in the blood. Drugs suitable for formulation into a slow-release dosage form are those with relatively short half-life, and require frequent dosing during the course of 24 hours. Infrequent dosing produces more steady blood level of the drug and diminishes side effects associated with peak and trough levels.[1] Compounding pharmacies have been providing slow-release formulations to patients and physicians in their quests for individualized therapy for more than a decade. Limited studies with patients who received hormone replacement products suggested good clinical response in a dose-related manner to hormones administered in slow-release capsules.[2-4] A blend of slow-release liothironine (T3) and levothyroxine (T4) customized to a specific patient had enabled better dose adjustment for resolution of hypothyroid symptoms.[3] Likewise, compounded slow-release bioidentical hormone replacement therapy (BHRT) allowed therapy to be tailored to accommodate individual differences in drug disposition and responses.[2] The need for customized therapy is clearly established in these cases, but safety concerns do exist due to poor compounding procedures and processes. This report discusses quality-control testing strategy for slow-release capsules and tablets.
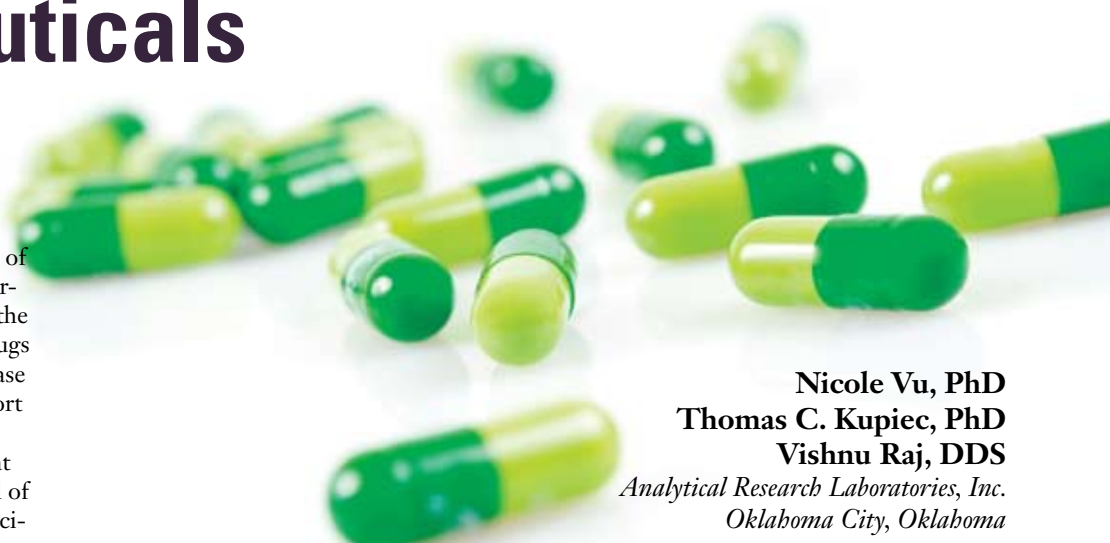
Abstract
Slow-release dosage forms are designed to release active drugs at slower rates for prolonging drug effects. These unconventional dosage forms are complex drug delivery systems, which require specialized technical knowledge and skills in their formulation. Verification of the compounding process for slow-release oral dosage forms can be accomplished through quality-control testing of pilot batches to ensure acceptable preparation and patient safety.

Composition of Slow-Release Medication

The most common polymers used in formulation of slow-release compounded preparations are cellulose derivatives.[3-4] Drugs are blended with the cellulose along with added excipients to ensure even distribution of the active ingredients. The powder mixture is used in filling capsules of appropriate size, which form hydrophilic gel systems and provide a mechanism for slow drug release. In a tablet format, the outer tablet surface forms a gel layer upon hydration. The rate of diffusion of drug out of the gel layer and the rate of tablet erosion control the overall dissolution rate and drug delivery. The matrix viscosity and its rate of hydration are independent of pH, but are functions of the percentages of methoxyl-side chains and hydroxypropoxyl-side chains in the cellulose backbone.[4-5] Slow release of drugs over 20 hours was achieved in some applications using these polymers.[4]

Quality-Control Testing Requirements for Slow-Release Tablets or Capsules

Quality-control testing of slow-release tablets or capsules follows Chapter <1075> Good Compounding Practices published in the *United States Pharmacopeia (USP)– National Formulary (NF)*.[6] Accordingly,

compounding pharmacists are required to ascertain the identity, strength, quality, and purity of compounded preparations. The following tests are specified for typical oral solid dosage forms.

Uniformity of Dosage Units and Assay

Uniformity of a dosage unit is defined by *USP* Chapter <905> as the degree of uniformity in the amount of the drug substance among dosage units.[6] The content uniformity test uses a specified number of dosages (e.g., 10 unit doses) in an assay procedure to determine the drug content for each unit dose. If one of the unit doses is not within the required range (±15% of label claim), then additional dosage units are required to be tested (20 dosage units). Content uniformity is met if all of the 30 dosage units fall within the ±15% range and none are outside the ±25% range. Content uniformity information is especially critical when the processes involved in compounding have not shown, or the personnel have not demonstrated, the compounding of a homogeneous preparation.[7]

Dissolution

Dissolution test is an important quality-control tool for process validation and for determining the slow-release performance of capsules and tablets. The loading capacity of slow-release tablets and capsules is usually larger than conventional unit dose, and may pose significant risk of toxicity as a result of dose dumping due to formulation failure. *USP* Chapter <711> sets specifications for dissolution test of extended-release products,[6] which can be applied to slow-release dosage forms. Generally, dissolution of drug is measured at 37ºC in water or buffers in the pH range of 1 to 7 depending on solubility and stability of the drug. Dissolution may be conducted using *USP* apparatus 1 or 2. A typical dissolution study for slow-release medication administered every 12 hours requires at least three time points (e.g., at 1, 4, and 8 hours). These time intervals may be changed to accommodate longer drug release profile. The cumulative percent drug dissolved (or Q) at each time interval is reported, with the last time point representing not less than 80% drug release.[6]

Conclusion

Monograph testing represents the pharmaceutical industry standard and may be very costly to a compounding pharmacy. However, dissolution and content uniformity tests are important quality-control components for the compounding process to ensure acceptable product and patient safety. Furthermore, dissolution test may be performed using one or two dosage units as representative samples, and content uniformity may be derived from a pool of several dosage units that represent the batch. As discussed previously, these strategies are designed to make testing more cost effective for compounding laboratories.[7]

References

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