Advancements in Sustained Release Tablet Formulations: A Comprehensive Review

1Nikhil Santram Randil, 2Trusha P. Shangrapawar, 3Dr. Ashok Bhosale, 4Rohit Gaikwad, 5Komal Waster

1,4,5Student, 2Professor, 3Principal
PDEA'S Shankarrao Ursal College of Pharmaceutical Sciences & Research Center

Abstract- This review article delves into the latest developments in sustained release tablet formulations, exploring their significance in modern pharmaceutical research. The review systematically analyses diverse strategies employed to achieve prolonged drug release, encompassing various polymer matrices, coating technologies, and innovative drug delivery systems. Emphasis is placed on the therapeutic advantages, such as enhanced patient compliance and reduced side effects, associated with sustained release tablets. Additionally, the article critically evaluates the impact of formulation parameters, manufacturing techniques, and regulatory considerations on the overall success of sustained release tablet development. Through a synthesis of recent studies and emerging trends, the review aims to provide researchers, pharmaceutical professionals, and regulatory authorities with valuable insights to guide future advancements in sustained release tablet design and application. Ultimately, this comprehensive review contributes to the evolving landscape of drug delivery systems, fostering a deeper understanding of sustained release technologies and their potential in optimizing therapeutic outcomes.

Keywords: Sustained Release Tablets, Drug Delivery Systems, Pharmacokinetics, Controlled Release, Formulation.

Introduction:

The primary objective of drug administration is to treat diseases effectively. To achieve this, drugs are often formulated into various dosage forms, ensuring controlled onset, intensity, and duration of action. An ideal controlled drug delivery system aims to deliver the drug at a specific rate, either locally or systemically, over a defined period, minimizing fluctuations in plasma drug concentration, reducing toxicity, and maximizing efficiency. Traditional dosage forms are increasingly being replaced by novel drug delivery systems, with oral administration being the preferred route due to high patient compliance, cost-effectiveness, and ease of production. Approximately half of the drugs in the market are orally administered, with tablets being the predominant oral dosage form. Tablets range from immediate release to complex sustained or modified release formulations. Sustained release systems are designed to release medication at a delayed rate, particularly suitable for drugs with shorter half-lives. Matrix tablets, a promising approach in extended-release drug therapy, consist of drugs homogeneously dispersed within hydrophilic or hydrophobic polymeric matrices. Ideally, sustained release should mimic a zero-order mechanism, maintaining drug plasma levels similar to intravenous infusion. Matrix systems control drug release through erosion under gastric pH conditions. Two mechanisms, zero-order erosion and decreasing surface area, contribute to this process. Matrix tablets offer precise control over drug levels within a narrow therapeutic range. The introduction of matrix tablets as sustained release formulations represents a breakthrough in pharmaceutical technology, achieved through wet granulation or direct compression methods. These methods disperse solid particles within a porous matrix formed by hydrophilic and hydrophobic polymers, ensuring a sustained and controlled release profile.

Sustained Release Tablet:

Sustained Release Drug Delivery Systems (SRDDS) offer the advantage of reduced dosing frequency by optimizing the pharmacokinetic, biopharmaceutics, and pharmacodynamic properties of drugs, surpassing conventional dosage forms. Unlike conventional methods that involve complex procedures such as coating and pelletization, SRDDS manufacturing adopts simplified techniques. This innovation enhances patient adherence by delivering drugs at a controlled rate over an extended period, minimizing the need for frequent administration. By eschewing intricate processes, SRDDS not only streamline production but also contribute to the overall efficiency and effectiveness of drug delivery, presenting a notable advancement in pharmaceutical formulation.
Figure 1: Plasma drug concentration profiles for conventional tablet or capsule formulations, sustained release formulation and zero order controlled release formulation.

Objectives of Oral Sustained-Release Matrix Dosage Forms:
1. **Maintaining Consistent Drug Concentration**: Ensure a steady and constant drug concentration over a predetermined duration, optimizing therapeutic efficacy.
2. **Reducing Dosing Frequency**: Minimize the number of administered doses compared to traditional drug forms, enhancing patient compliance and convenience.
3. **Precise Drug Delivery to the Site of Action**: Directly transport the active ingredient to the target site with minimal or no side effects, improving drug delivery precision.
4. **Targeting Specific Receptors or Localizing to Cells/Regions**: Facilitate targeted drug delivery by aiming for specific receptors, cells, or localized regions within the body, enhancing therapeutic outcomes.
5. **Enhancing Safety Margins of Potent Drugs**: Improve the safety margins of potent drugs, ensuring effective treatment with minimized risk of adverse effects.
6. **Reducing Incidence of Adverse Side Effects**: Decrease the occurrence of both local and systemic adverse side effects, particularly in sensitive patients, promoting the overall safety and tolerability of the medication.

Advantages:
1. **Maintains Constant Therapeutic Concentrations**: Sustained release ensures a steady and constant level of therapeutic concentrations over time.
2. **Uniform Blood Drug Concentrations**: Achieves uniform drug concentrations in the bloodstream, optimizing therapeutic effectiveness.
3. **Reduced Dosing Frequency**: Decreases the frequency of dose administration, enhancing patient compliance.
5. **Reduced Drug Accumulation**: With less frequent administration, there is a reduction in the accumulation of drugs in the system.
6. **Improved Treatment Adherence**: Addresses deficiencies in treatment by improving patient adherence to prescribed regimens.
7. **Enhanced Patient Compliance**: Mitigates compliance issues among patients, leading to improved treatment outcomes.
8. **Maximizes Bioavailability, Minimizes Side Effects**: Optimizes bioavailability while minimizing local side effects.

Disadvantages:
1. **High Production Costs**: Sustained release formulations may incur higher production costs compared to conventional dosage forms.
2. **Poor In Vivo and In Vitro Correlation**: Exhibits poor correlation between in vivo and in vitro performance, posing challenges in predicting drug behaviour.
3. **Increased First-Pass Metabolism Potential**: Raises the potential for increased first-pass metabolism, impacting the bioavailability of the drug.
Classification of Sustained Release Drug Delivery Systems:

1. Continuous Release Systems:
   - **Diffusion Controlled Release Systems**: Release drug steadily over the entire length of the gastrointestinal tract, with the rate limited by the diffusion of dissolved drug through a polymeric barrier.
   - **Dissolution Controlled Release Systems**: Achieve controlled release by slowing the dissolution rate of the drug or incorporating it in an insoluble polymer. Two types include matrix dissolution-controlled and reservoir dissolution-controlled systems.
   - **Dissolution and Diffusion Controlled Release Systems**: Encase the drug in a partially soluble membrane, allowing both drug dissolution and diffusion.
   - **Ion Exchange Resin-Drug Complexes**: Formulated through the interaction of an ionic solution with ionic resins, leading to the creation of a drug-resin complex. Drug release occurs when there is an excess of specific ions, often involving a salt-forming function group in a polymer chain.

2. Delayed Transit and Continuous Release Systems:
   - **Mucoadhesive and Size-Based Systems**: Designed to prolong their stay in the gastrointestinal (GI) tract, including mucoadhesive systems that adhere to the stomach and size-based systems that detain in the stomach for an extended period.
   - **Delayed Release Systems**: Restrict drug release to specific positions in the gastrointestinal tract, suitable for drugs causing gastric distress, those easily destroyed, or those requiring extended local effects. Two types include intestinal release systems and colonic release systems.

3. Various Mechanisms of Medicament Release:
   - **Diffusion is Rate Limiting**: The drug is formulated in an insoluble matrix, allowing for controlled drug release as the matrix dissolves. Drug particles are coated with a polymer, facilitating slow diffusion and maintaining a constant drug level in the bloodstream.
   - **Dissolution is Rate Limiting**: For drugs with low water solubility, sustained release is inherent. Water-insoluble carriers prevent drug dissolution, and polyethylene glycol may be used as a coating material.
   - **Osmotic Pressure is Rate Limiting**: Utilizes osmosis, where liquid flows through a semipermeable membrane. The entire drug is covered with a semipermeable membrane, with a laser-cut hole for controlled release.

Biological Factors Influencing the Design of Oral Sustained Release Dosage Forms:

1. Biological Half-life:
   - Drugs with a biological half-life of 2-8 hours are deemed suitable for sustained-release formulations, aiming to reduce dosing frequency. However, drugs with extremely short half-lives may necessitate large amounts per dosage unit, limiting the practicality of the dosage form. Generally, drugs with a half-life less than 2 hours are unsuitable for sustained release systems.

2. Absorption:
   - The rate, extent, and uniformity of drug absorption play a crucial role in formulating extended-release systems. For oral administration, it is critical that the rate of release (Kr) is much less than the rate of absorption (Ka). The transit time of the drug through the gastrointestinal tract should be considered, and a minimum absorption rate constant (Ka) is necessary for optimal absorption. Drugs with very slow rates of absorption or those absorbed by active transport may pose challenges for sustained release systems.

3. Metabolism:
   - Metabolism, occurring primarily in the liver, can either inactivate an active drug or activate an inactive drug molecule. Predictable metabolism allows for incorporation into product design. However, complex metabolic patterns, especially when biological activity relies on a metabolite, can complicate design. Drugs inducing or exhibiting enzyme synthesis on chronic administration are poor candidates for sustained release products due to difficulty in maintaining uniform blood levels.

4. Therapeutic Index (TI):
• The Therapeutic Index ($TI$), measuring the margin of safety of a drug ($TI=TD_{50}/ED_{50}$), is crucial. A higher $TI$ indicates a safer drug. Drugs with a very small therapeutic index are considered poor candidates for sustained release formulations. A drug is deemed safe if its $TI$ value is greater than a certain threshold.

**Physiological Factors Influencing the Design of Oral Sustained Release Dosage Forms:**

1. **Molecular Size and Diffusivity:**
   - Drug absorption requires diffusion through various biological membranes and, in controlled-release systems, through rate-controlling polymeric membranes or matrices. Drugs with a molecular weight between 150-400 Da are optimal candidates for sustained release. Molecular weights greater than 500 Da often have small diffusion coefficients, making quantification challenging.

2. **Dosage Size:**
   - The maximum dose size for conventional dosage forms, typically 500-1000 mg, also applies to sustained release formulations.

3. **Aqueous Solubility:**
   - The fraction of drug absorbed is influenced by the drug's solubility. Aqueous solubility is crucial for dissolution and absorption. Drugs with low aqueous solubility face challenges in oral bioavailability. The lower limit of solubility for sustained release systems is 0.1 mg/ml. Drugs with good aqueous solubility are preferred for sustained release formulations.

4. **Partition Coefficient ($K$):**
   - Large $K$ values indicate high oil solubility, leading to easy partitioning into membranes and prolonged localization in the body. An optimum $K$ value of approximately 1000/1 in n-octanol/water is ideal for drug activity. Values higher or lower than this optimum are generally unsuitable for extended-release formulations.

5. **Drug Stability:**
   - Drugs unstable in the stomach may require a controlling unit that releases contents only in the intestine. Conversely, drugs unstable in the intestinal environment may need a unit releasing contents only in the stomach. Drugs with stability issues in specific regions of the gastrointestinal tract are less suitable for controlled release systems aiming for uniform delivery along the GIT length.

**Matrix Tablets in Drug Delivery Systems:**

Matrix systems, a prevalent oral extended-release technology, consist of both active and inactive ingredients homogeneously dispersed within a dosage form. The popularity of matrix systems is attributed to various factors, and their release is governed by Fick's first law of diffusion.

In a matrix system, the drug is dispersed as solid particles within a porous matrix, formed of either a hydrophobic polymer (e.g., wax, polyethylene, polypropylene, ethyl cellulose) or a hydrophilic polymer (e.g., hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methylcellulose, sodium carboxymethylcellulose, alginates, and scleroglucan). The term "matrix" refers to the three-dimensional network containing the drug and other necessary substances.

Matrix drug delivery systems release the drug continuously, utilizing both dissolution-controlled and diffusion-controlled mechanisms. Initially, surface drug particles dissolve rapidly, followed by successive dissolution of particles at increasing distances from the surface, releasing the drug through diffusion in the pores.

The drug reservoir in this system is prepared by uniformly dispersing drug particles in a rate-controlling polymer matrix, which can be lipophilic or hydrophilic. This dispersion can be achieved through blending finely ground drug particles.
with a liquid or highly viscous polymer, followed by cross-linking, or by dissolving both the drug and polymer in a common solvent and evaporating the solvent at an elevated temperature or under a vacuum. The rate of drug release from this polymer matrix, a diffusion-controlled drug delivery system, is time-dependent and defined at steady state by the equation:

\[ Q = (2ACRD_p)^{1/2} \]

Where:
- \( A \) is the initial loading drug dose in the polymer matrix,
- \( CR \) is the drug reservoir concentration in the system,
- \( D_p \) is the diffusivity of the drug molecules in the polymer matrix

Controlling drug release in this system involves managing the loading dose, polymer solubility of the drug, diffusivity in the polymer matrix, and the porosity of the release unit.

**Classification of Matrix Tablets:**

**A. On the Basis of Retardant Material Used:**

1. **Hydrophobic Matrices (Plastic Matrices):**
   - Active drug dispersed within a tablet in a porous structure using plastic materials. Examples include polyethylene, polyvinyl chloride, ethyl cellulose, and acrylate polymers. Sustained release is achieved through the diffusion of the dissolving drug in a network of channels. Mechanism: Diffusion.

2. **Lipid Matrices:**
   - Prepared using lipid waxes and related materials. Drug release involves both pore diffusion and erosion. Carnauba wax, combined with stearyl alcohol or stearic acid, has been utilized. Mechanism: Pore diffusion and erosion.

3. **Hydrophilic Matrices:**
   - Utilize hydrophilic polymer matrix systems for controlled drug delivery. Formulated through wet granulation or direct compression of drug and hydrophilic matrix materials. Gel diffusion barrier controls drug release upon immersion in fluid. Mechanism: Gel diffusion barrier and erosion.

4. **Fat-Wax Matrix Tablet:**
   - Involves the addition of the drug into fat wax, incorporating drug into fat wax granulations through various methods. Release occurs through straining and hydrolysis mechanisms. Mechanism: Straining and hydrolysis.

5. **Mineral Matrices:**
   - Prepared using polymers from seaweeds, such as alginic acid. Alginic acid, a hydrophilic carbohydrate, is obtained from brown seaweeds. Mechanism: Diffusion.

**B. On the Basis of Porosity of Matrix:**

1. **Macro Porous Systems:**
   - Diffusion occurs through pores with a size range of 0.1 to 1 \( \mu \)m, larger than diffusant molecule size.

2. **Micro Porous Systems:**
   - Diffusion occurs through pores with a size range between 50-200 \( \text{Å} \), slightly larger than diffusant molecules.

3. **Non-Porous System:**
   - No pores exist, and molecules diffuse through the network meshes.

**C. On the Basis of the Way of Matrix Preparations:**

1. **Floating Matrix System:**
   - Matrix has lower bulk density than gastric fluid, creating buoyancy in the stomach. Slow release prolongs gastric residence time, enhancing bioavailability.

2. **pH-Sensitive Matrix System:**
   - Enteric coating protects the drug in the acidic stomach environment, releasing it at a specific high pH in the gastrointestinal tract. pH-sensitive polymers like HPMC-phthalate can be used.

3. **Mucoadhesive Matrix System:**
   - Designed for prolonged retention in the gastric region, significantly extending gastric residence time and improving bioavailability. Uses swellable hydrophilic polymers interacting with mucous layer glycoproteins. Can be applied to various mucosal tissues in the body.