SUSTAINED RELEASE DRUG DELIVERY SYSTEM – AN OVERVIEW

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ABSTRACT

Continuous drug delivery systems have shown promise as a method to improve drug efficacy and patient compliance. This review begins with an overview of the rationale for sustained drug delivery systems, emphasizing their ability to prolong drug release, minimize dosing frequency, and maintain therapeutic drug concentrations within desired ranges. It highlights the importance of selecting appropriate polymers, excipients, and manufacturing techniques to achieve sustained-release properties for specific drugs and therapeutic indications.

KEYWORDS: Controlled release, Systemic release, Matrix, Bilayer, Dosage form.

INTRODUCTION

The oral route is the most popular method of drug delivery, due in part to ease of administration and the fact that the physiology of the gut is more flexible in increasing volume than many other routes.[1] The term "controlled release" relates to systems that can automatically deliver a therapeutic agent at a predetermined rate over an extended period of time. However, there is some term confusion between controlled and sustained release.

Sustained release: The term "sustained release" is used to describe a pharmaceutical dosage form that is formulated to delay and/or prolong the release of a therapeutic agent, thereby delaying and/or prolonging its emergence in the systemic circulation and whose plasma
distribution is Maintain over time.

**Controlled release:** On the other hand, the meaning of this term goes beyond sustained drug action. Additionally, it refers to therapeutic components being released from a controlled delivery system at a rate profile that is both kinetically predictable and repeatable from one unit to another. This is known as predictable and reproducible drug release kinetics.[2]

A carefully thought-out controlled drug delivery system can address some of the issues with traditional therapies and enhance the therapeutic impact of a certain medicine. To achieve maximum therapeutic effect, the drug must be delivered to the target tissue in an optimal amount at the right time, while causing low toxicity and minimal side effects.[3] One of the easiest ways to produce an extended-release dosage form is to directly compress a mixture of drug, delaying material, and additives to formulate a tablet, where the drug is embedded in a matrix of the delaying agent.[4]

In order to achieve and maintain optimal therapeutic blood levels, extended-release dosage forms are designed to release the drug at a specified location at a specified rate for a specified period of time. Examples are delayed release, slow-release, controlled-release and extended release.[5]

![Figure 1](image.png)

**Figure 1:** Drug levels in the blood with a) Traditional drug dose systems and b) Controlled drug delivery dose systems.[6]
Advantages of extended-release drug delivery systems\(^{[7,8,9]}\)

- Reduce dosing frequency
- Reduce fluctuations in drug levels due to less frequent dosing.
- Drug accumulation is reduced.
- Enhanced effectiveness of the medicine.
- Decrease in harmful side effects and improvement in tolerance.
- Reduced patient compliance issues.
- Maximize bioavailability and minimize local side effects.
- Drug level maintenance within required range.

Disadvantages of extended-release drug delivery systems\(^{[7,9]}\)

- Effective drug release time is affected and limited by clinical gastric residence time.
- Dose dumping can occur with poorly developed strategies.
- Potential for increased first-pass metabolism.
- Dosage forms are more dependent on gastric residence time.
- In some cases, less precise dose adjustments may be made.
- The cost per unit dose is higher compared to conventional doses.
- Unpredictable and often poor in vitro-in vivo correlation.

Challenges to controlled release\(^{[6]}\)

- Cost - preparation and processing.
- If not biodegradable, drop of controlled release system.
- Biocompatibility.
- Fate of polymer additives, eg. Plasticizers, stabilizers, antioxidants, fillers.

Purpose of oral extended-release dosage forms

- The drug concentration is maintained at a constant level for a preferred period of time.
- Reduced dosing frequency compared to conservative dosage forms.
- It should deliver the drug directly to the site of action while minimizing or eliminating side effects.
- This may require delivery to specific receptors or localization to cells or specific regions of the body.
- The margin of safety of effective drugs can be increased.
- Insusceptible patients, the incidence of local and systemic side effects can be reduced.\(^{[7]}\)
Classification of sustained release systems

Classification of SR Formulation: The most common methods used to achieve sustained release of orally administered drugs are as follows.\textsuperscript{[10,11,12]}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{classification_of_sustained_release_systems.png}
\caption{Classification of sustained release system.}
\end{figure}

Introduction of the matrix tablet

A new release is available as a Continuous Release (SR). Novel drug delivery systems (NDDS) have made significant strides in the field of pharmaceutical technology. Multifaceted production processes such as coating and granulation are excluded in the production process, and the release rate of the drug from the dosage form is mainly controlled by the type and ratio of the polymer used in the preparation. Hydrophilic polymer matrices are often used to formulate SR dosage forms.\textsuperscript{[7]}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{matrix_type_systems.png}
\caption{Schematic of matrix type systems for controlled drug delivery. Matrix delivery systems can be constructed with drugs dissolved in matrix material (a) or Particles of drug dispersed to form a composite material (b and c).\textsuperscript{[1]}}
\end{figure}
Advantages of SR-Matrix-DDS
- Easy to make
- Versatile, Effective and Cheap
- Designed to release high quality compounds
- Sustained-release formulations maintain therapeutic levels for extended periods of time.
- High concentrations of the drug in the blood are avoided by using a sustained release formulation.
- Sustained-release formulations have the potential to improve patient compliance.[13]

Disadvantages of SR Matrix DDS
- Possibility of dose dumping.
- Reduced possibility of dose adjustments.
- Individual unit costs are higher than predictable dosage forms.
- Potential for increased first-pass metabolism.
- Requirement for additional patient education regarding proper medication.[7]

Classification of matrix tablets[8]
Matrix tablets can be divided into the following categories
A) Depending on the retardant material used
Within this category, matrix tablets are subdivided into 5 types
a) Hydrophobic matrix (Plastic matrix)
b) Lipid matrix
c) Hydrophilic matrix
d) Biodegradable matrix
e) Mineral matrix
B) Matrix based porosity
a) Macro porous system
b) Microporous system
c) Non porous system

a) Hydrophobic matrix (Plastic matrix): In this technique for inducing prolonged release from an oral dosage form, the medication is combined with an inert or hydrophobic polymer and crushed into a tablet. A network of channels between the compressed polymer particles allows the dissolved medication to spread, leading to a sustained release. As hydrophobic matrices, materials such as polyethylene, polyvinyl chloride,
ethylcellulose, and acrylate polymers and copolymers are employed.[14]

b) Lipid matrix: These matrices are made from fatty waxes and related materials. Drug release from such matrices occurs through pore diffusion and erosion. Therefore, the release profile is more sensitively dependent on the composition of the digestive fluid than that of a completely insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been used as an extended release base for many extended release formulations.[15]

c) Hydrophilic matrices: These transfer systems are also known as swelling soluble matrices. The system is prone to inflammation followed by gelation, erosion and dispersion of the aqueous medium. The components of the hydrocolloid readily form a liquid matrix when in contact with water. This controls the further distribution of water in the intermediate matrix. A hydrated drug delivery matrix layer controls the rate of release. On the outside, the hydrated matrix layer will corrode with increased cleaning. The rate of erosion depends on the state of the colloid.[14]

d) Biodegradable matrix: These consist of polymers that are composed of monomers linked to each other by functional groups and have unstable bonds in the basic structure. They are biodegraded or eroded by enzymes produced by surrounding living cells or by non-enzymatic processes into oligomers and monomers that can be excreted or metabolized. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly(Esters) and polyanhydrides.[15]

e) Mineral matrices: These are made up of polymers produced from various algal species. For example, alginic acid is a hydrophilic carbohydrate that is produced from the dilute bases of brown algal species. Matrix-based porosity: Matrix systems can be classified according to their porosity, thus macroscopically, with pores; microporous and anhydrous systems can be identified.[14]

Classification based on matrix porosity[15]

a) Macro porous system
In such systems, the diffusion of drugs occurs through the pores of the matrix, which range in size from 0.1 to 1 µm. The pore size is larger than the size of the diffusing agent molecules.
b) Microporous system
In this type of system, diffusion occurs mainly through pores. For microporous systems, the pore size ranges from 50 to 200 Å, slightly larger than the diffuser molecules.

c) Non-porous system
A nonporous system has no pores and molecules diffuse through the network. In this case, only the polymer phase exists and no pore phase exists.

Bilayer tablet
Today, several countries, both developing and developed, have begun to consider the use of combination therapies for the treatment of various diseases and conditions that require long-term treatment, such as diabetes, cardiovascular disease, and hypertension.[16,17] More than 90% of modern preparations are taken orally. This shows the worldwide prevalence of this type of formulation, which is why most researchers prefer to focus on it. The main aim of sustained drug delivery is to reduce the frequency of dosing.[16,7,17] Based on these factors, we developed a bilayer tablet in which the first layer is designed for rapid drug release, aiming to rapidly reach high blood levels.[18] The controlled-release hydrophilic matrix in the second layer is designed to maintain effective plasma levels over an extended period of time.[16,18]

The mechanical structure of such drug delivery systems has become quite complex, requiring more durable adhesives, advanced super disintegrants, and difficult tablet geometries and patient-friendly drug delivery methods, which bring challenges to pharmaceutical scientists.[19]

Fig. 4: Structure of bilayer tablet.[20]
Advantages of the bilayer tablet form\textsuperscript{[19,17,7]}

- Excellent chemical and microbiological stability compared to other oral dosage forms.
- Physical and chemical incompatibility can be minimized by separating incompatible components.
- Coating technology can mask unwanted odors and tastes.
- It can be designed in such a way that on the one hand the layer change discharge can be kept as large as possible and on the other hand an immediate discharge is possible.
- The price is slightly lower than any other oral dosage form.
- Tablet packaging is often simpler and less expensive.
- They are better suited for mass production.
- The pills are very easy to swallow.

Limitations of bilayer tablets\textsuperscript{[7,17,19,20]}

Due to the already discussed advantages of bi-layer tablets, a major shift has taken place in the pharmaceutical industry. However, there are some limitations to the manufacture and use of bilayer tablets, including.

- One of the major problems with bilayer formulations is the lack of adequate bonding and adhesion at the interface between adjacent compacted layers, often resulting in interface cracking and delamination.
- If the compressed layers are too soft or too tight because they cannot fit tightly together, it can compromise mechanical integrity and cause the layers to separate.
- Due to their amorphous structure and low density, some drugs cannot be compressed into dense pellets.
- Drugs that taste bitter, have an unpleasant odor, or are sensitive to oxygen may require encapsulation or coating.
- The weight control of the individual layers is imprecise.
- Insufficient hardness, layer separation reduced yield.

Factors affecting the oral sustained release dosage form design

1. Biological factors

   1. Biological half-life: The half-life of a drug is a measure of how long the drug remains in the body. If the drug has a short half-life (Less than 2 hours), the amount of drug in the dosage form may be too high. On the other hand, drugs with an elimination half-life of eight hours or more will be adequately retained in the body when administered in
conventional doses and in a continuous delivery system.\[8\]

2. **Absorption:** The term "absorption window" refers to the region or extent of a region of the gastrointestinal tract where a drug is absorbed beyond which no or negligible absorption occurs. Different regions of the gastrointestinal tract have different pH values; therefore, the solubility and stability of some drugs vary from region to region due to pH changes and enzymatic degradation.\[9\]

3. **Distribution:** The distribution of a drug in the vascular and extravascular spaces in vivo is an important factor to consider in the overall elimination kinetics. Drug distribution is characterized by its apparent volume of distribution and the ratio of drug in tissue to drug in plasma (T/P). The larger the volume of distribution, the stronger the binding of the drug to the tissue and relatively less drug in the blood. Drugs present in circulating blood are affected by hepatic or renal clearance.\[9\]

4. **Metabolism:** The metabolic conversion to a drug is to be considered before converting into another form. Since as long as the location, rate and extent of metabolism are known a successful sustain release product can be developed.\[21\] Drugs with controlled release system should be able to be completely metabolized, but the speed of metabolism should not be too fast. Drugs that increase or decrease metabolism are not good candidates; because steady state is difficult to achieve.\[9\]

2. **Drug related factors**

1. **Drug stability:** An important factor in oral dosage forms is the loss of the drug in the gastrointestinal tract through acid hydrolysis and/or metabolism. Although solid drugs break down much more slowly than suspended or dissolved substances. The relative bioavailability of drugs that are toxic in the stomach could be significantly increased; the most effective control unit would be one that only activates its substance in the gut.\[8\]

2. **Water Solubility and pKa:** For a drug to be absorbed, it must first dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbent membrane.\[22\] The two most important physicochemical properties affecting the absorption activity of a drug are its aqueous solubility and, in the case of soft acids, its pKa.\[8\] The performance of controlled release systems is significantly influenced by these characteristics. The water solubility of a drug affects its dissolution rate, which in turn
determines its concentration in solution and thus the driving force for its transmembrane diffusion.\(^2\)

3. **Partition coefficient:** This is the ratio of the drug in the oil phase to the drug in the water phase. Drugs with high partition coefficients are not suitable for oral SRDDS because they do not partition out once they enter the lipid membrane. It can be calculated using the formula

\[ K = \frac{C_o}{C_w} \]

\(C_o = \) Concentration at equilibrium in the organic phase.

\(C_w = \) Concentration in aqueous phase at equilibrium.\(^8\)

### Polymers used in sustained release dosage form

**Table: Sustained release tablet polymers used.\(^{14}\)**

<table>
<thead>
<tr>
<th>Hydrophilic polymers</th>
<th>Non-Cellulosic (others)</th>
<th>Water Insoluble and Hydrophobic</th>
<th>Fatty Acids/Alcohols/Waxes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulosic</td>
<td>Sodium Alginate</td>
<td>Ethyl cellulose</td>
<td>Bees wax</td>
</tr>
<tr>
<td>Methylcellulose</td>
<td>Polyethylene oxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPC</td>
<td>Xanthan Gum</td>
<td>Hypromellose acetate succinate</td>
<td>Candelillla wax</td>
</tr>
<tr>
<td>HPMC</td>
<td>carrageenan</td>
<td>Cellulose acetate</td>
<td>Candelillla wax</td>
</tr>
<tr>
<td>HEC</td>
<td>Gaur gum</td>
<td>CAP</td>
<td>Paraffin waxes</td>
</tr>
<tr>
<td>Na-CMC</td>
<td>Locust bean gum</td>
<td>Methacrylic acid copolymers</td>
<td>Cetyl alcohol</td>
</tr>
<tr>
<td></td>
<td>Chitosan</td>
<td>PVA</td>
<td>Stearyl alcohol</td>
</tr>
</tbody>
</table>

### CONCLUSION

Extended-release dosage forms have proven to be a promising solution in the pharmaceutical field. This formulation offers numerous benefits, including improved patient compliance, reduced dosing frequency and improved patient outcomes. The controlled and gradual release of the drug ensures constant plasma concentrations, minimizes side effects and optimizes the drug's effectiveness. In addition, sustained-release dosage forms have shown great potential in the treatment of chronic diseases such as cardiovascular disease, Diabetes and Mental illness. Further research and development in this area promises to advance patient care and improve overall patient outcomes.
REFERENCE


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