Sustain Release Drug Delivery: A Theoretical Prospective

ABSTRACT

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Now a day, sustained release pharmaceutical products became a very useful tool in medical practice, offering a wide range of actual and perceived advantages to the patients. It also provides promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body because it will continue to account for the largest share of drug delivery systems. Compared to investigate a new molecule, it is better to do the research and development of already existing molecules by solving the problem of confrontation due to their awkward use particularly in case of drugs like antibiotics. This article contains the basic information regarding sustained-release formulation.

Key words: Sustained release, Drug absorption, Therapeutic concentration and Antibiotic.

INTRODUCTION

Sustained Release Drug Delivery Systems

During the past few years, conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst, these the controlled release/sustained release dosage forms have become extremely popular in modern therapeutics. The basic rationale for sustained release drug delivery is to alter the pharmacokinetics and pharmacodynamics of drugs by using novel drug delivery systems or by modifying the molecular structure or physiological parameters inherent in a selected route of administration.

It is that the duration of drug action becomes more a design property of a rate controlled dosage form and less or not at all a property of the drug molecule’s inherent kinetic properties. Thus, optimal design of a sustained/controlled release system necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug. When the drug is administered in a conventional dosage form, it results in a fluctuation of drug concentration at the site of action (peak and valley pattern) and therefore in systemic circulation and tissue compartment. Figure 1 shows the difference between the conventional and sustained release dosage forms.

Disadvantages of sustained release drug delivery

The disadvantages of sustained release drug delivery system are

· Toxicity due to dose dumping.
· Increased cost.
· Unpredictable and often poor in vitro-in vivo correlation.
· Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
· Local irritation or damage of epithelial lining (lodging of dosage forms).
· Need for additional patient education and counselling.
· Increased potential for first-pass clearance.

Advantages of sustained release drug delivery

Following are the potential advantages of sustained release products

· Decrease incidence and/or intensity of adverse effects and toxicity.
· Predictable and reproducible release rates for extended duration.
· Maintenance of optimum therapeutic drug concentration in the blood with minimum fluctuations.
· Delivery of drug in the vicinity of site of action.
· More efficient utilization of active agent.
· Improved patient compliance.
· Elimination of frequent dosing and wastage of drug, inconvenience of night time administration of drug.
· A greater selectivity of pharmacological activity.
· Reduction in GI irritation and other dose-related side effects.
· Enhanced bioavailability.
· Reduction of the incidences and degree of toxic and side effects and irritation of gastro intestinal tract caused by some orally administrated drugs.
· Greater effectiveness in treatment of chronic conditions.
· Enhanced duration of activity for short half-life drugs.

Sustained release drug administration means not only prolongation of duration of drug delivery, similarly to the action in the sustained and prolonged release, but the term also implies the predictability and reproducibility of drug release kinetics. The controlled release of drug substances and their effective transport to sites of action can be exploited to maximize the beneficial clinical response and to minimize the incidence of unfavorable adverse reactions and side effects.
Release of Medicament can Follow Various Mechanisms\textsuperscript{12-15}

I) Diffusion is rate limiting
Diffusion is driving force where the movement of drug molecules occurs from high concentration in the tablet to lower concentration in gastrointestinal fluids. This movement depends on surface area exposed to gastric fluid, diffusion pathway, drug concentration gradient and diffusion coefficient of the system (Figure 2).

In practice, we can follow either of the two methods,

a. The drug is formulated in an insoluble matrix; the gastric fluid penetrates the dosage form and dissolves the medicament and release the drug through diffusion.

b. The drug particles are coated with polymer of defined thickness so as the portion of drug slowly diffuse through the polymer to maintain constant drug level in blood.

II) Dissolution is rate limiting
The drugs with poor water solubility (BCS class 2 and 4) are inherently sustained release forms. While for water soluble drugs, it’s possible to incorporate a water insoluble carrier to reduce dissolution of the drug particles are coated with this type of materials e.g. Polyethylene Glycol. One may skip the use of disintegrating agent to promote delayed release.

III) Osmotic pressure is rate limiting
Osmosis is a phenomenon in which the flow of liquid occurs from lower concentration to higher concentration through a semi permeable membrane which allows transfer of liquid only. The whole drug is coated with a semi permeable membrane with a hole on one end of tablet made by a laser beam. The gastric fluid penetrates through the membrane, solubilizes the drug and increases the internal pressure which pumps the drug solution out of the aperture and releases the drug in gastric environment. The delivery rate is constant provided that the excess of drug present inside the tablet. But, it declines to zero once the concentration drops below saturation (Figure 3).

IV) Release is controlled by ion exchange
Ion exchangers are water insoluble resinous materials containing salt forming anionic or cationic groups. While manufacturing, the drug solution is mixed with resin and dried to form beads which are tableted. The drug release depends upon high concentration of charged ions in gastro intestinal tract where, the drug molecules are exchanged and diffused out of the resin into the surrounding fluid. This mechanism relies upon the ionic environment of resin and not pH or enzyme on absorption site.

Classification of Oral Sustained Release Systems\textsuperscript{16-20}

[1]. Diffusion controlled Systems
(a) Reservoir devices
A core of drug (reservoir) surrounded by a polymeric membrane characterizes them. The nature of the membrane determines the rate of drug release. The characteristics of reservoir diffusion systems are:
1. Zero order drug release is possible.
2. The release rate is dependent on the type of polymer.
3. High molecular weight compounds are difficult to deliver through the device.

(b) Matrix devices
It consists of drug dispersed homogenously in a matrix. The characteristics of matrix diffusion systems are:
1. Zero order release cannot be obtained.
2. Easy to produce than reservoir devices.
3. High molecular weight compounds are delivered through the device.

[2]. Dissolution controlled systems
(a) Matrix dissolution controlled systems
Aqueous dispersions, congealing, spherical agglomeration, etc. can be used.
(b) Encapsulation dissolution controlled systems
Particles, seeds, granules can be coated by techniques such as micro encapsulation.
(c) Diffusion and dissolution controlled systems
In a bioerodible matrix, the drug is homogenously dispersed in a matrix and it is released either by swelling controlled mechanism or by hydrolysis or by enzymatic attack\textsuperscript{21}.

Factors influencing Oral Sustained Release Dosage Form Design

A. Biological factors influencing oral sustained-release dosage form design\textsuperscript{22-24}

1) Biological half-life
Therapeutic compounds with short half-lives are excellent candidates for sustained-release preparations, since this can reduce dosing frequency.

2) Absorption
The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. If a drug is absorbed by active transport, or transport is limited to a specific region of the intestine, sustained-release preparations may be disadvantageous to absorptions.

3) Distribution
The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. For design of sustained/ controlled release products, one must have information of disposition of drug.
4) Metabolism
Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period, allowing more complete conversion of the drug to its metabolite.

B. Physicochemical factors influencing oral sustained-release dosage form design26-30

1) Dose Size
In general, single dose of 0.5 – 1.0 g is considered maximal for a conventional dosage form. This also holds true for sustained-release dosage forms. Another consideration is the margin of safety involved in administration of large amounts of drug with a narrow therapeutic range.

2) Ionization, pKₐ, and aqueous solubility
Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pKₐ of the compound and the absorptive environment. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of drug in the aqueous media. For dissolution or diffusion sustaining forms, much of the drug will arrive in the small intestine in solid form, meaning that the solubility of the drug may change several orders of magnitude during its release. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1 mg/ml.

3) Partition coefficient
Compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility. Furthermore these compounds can usually persist in the body for long periods, because they can localize in the lipid membranes of cells.

4) Stability
Orally administered drugs can be subjected to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transit in the GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form.

5) Molecular size and diffusivity
The ability of drug to diffuse through membranes its so called diffusivity & diffusion coefficient is function of molecular size (or molecular weight). Generally, values of diffusion coefficient for intermediate molecular weight drugs, through flexible polymer range from 10-8 to 10-9 cm2 / s. With values on the order of 10-8 being most common for drugs with molecular weight greater than 500, the diffusion coefficient in many polymers frequently are so small that they are difficult to quantify i.e. less than 16-12 cm2/sec. Thus high molecular weight drugs and / or polymeric drugs should be expected to display very slow release kinetics in sustained release device using diffusion through polymer membrane.

6) Protein binding
It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are for the most part re-circulated and not eliminated, drug Protein binding can serve as a depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for drugs and such drugs generally most require a sustained release dosage form. However drugs that exhibit high degree of binding to plasma proteins also might bind to bio-polymers in GI tract which could have influence on sustained drug delivery. The presence of hydrophobic moiety on drug molecule also increases the binding potential.

Drug Selection for Oral Sustained Release Drug Delivery Systems31-36
The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the GI tract, the general absorbability, the drug’s molecular weight, solubility at different pH and apparent partition coefficient (Table 1 and 2).

Table 1: Physicochemical Parameters for drug selection.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preferred value</th>
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<tbody>
<tr>
<td>Molecular weight/ size</td>
<td>&lt; 1000</td>
</tr>
<tr>
<td>Solubility</td>
<td>&gt; 0.1 mg/ml for pH 1 to pH 7.8</td>
</tr>
<tr>
<td>Apparent partition coefficient</td>
<td>High</td>
</tr>
<tr>
<td>Absorption mechanism</td>
<td>Diffusion</td>
</tr>
<tr>
<td>General absorbability</td>
<td>From all GI segments</td>
</tr>
<tr>
<td>Release</td>
<td>Should not be influenced by pH and enzymes</td>
</tr>
</tbody>
</table>

Table 2: Pharmacokinetic parameters for drug selection.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Elimination half life</td>
<td>Preferably between 0.5 and 8 h</td>
</tr>
<tr>
<td>Total clearance</td>
<td>Should not be dose dependent</td>
</tr>
<tr>
<td>Elimination rate constant</td>
<td>Required for design</td>
</tr>
<tr>
<td>Apparent volume of distribution Vd</td>
<td>The larger Vd and MEC, the larger will be the required dose size</td>
</tr>
<tr>
<td>Absolute bioavailability</td>
<td>Should be 75% or more</td>
</tr>
<tr>
<td>Intrinsic absorption rate</td>
<td>Must be greater than release rate</td>
</tr>
<tr>
<td>Therapeutic concentration Css av</td>
<td>The lower Css av and smaller V, the loss among of drug required</td>
</tr>
<tr>
<td>Toxic concentration</td>
<td>Apart the values of MTC and MEC, safer the dosage form</td>
</tr>
</tbody>
</table>

REFERENCES
35. Yie W., Chien, Rate controlled drug delivery systems., 2nd Ed.,Marcel Dekker; New York, Revised and expanded, 2005.

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