AN OVERVIEW: SUSTAINED RELEASE DRUG DELIVERY TECHNOLOGIES WITH POLYMERIC SYSTEM

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ABSTRACT
In recent years scientific and industrial advancements have been made in the research and development of oral drug delivery system. The reasons that the oral route achieved such reputation may be in part accredited to its ease of administration. Use of different release retardant for oral sustained release of drugs is a common practice in the pharmaceutical industry. In this study discusses formulation and manufacturing variables affecting the design and performance of the extended-release product by using selected practical examples. Optimal therapy of a disease requires an efficient delivery of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A controlled release dosage forms leads to better management of the acute or chronic disease condition. While the concept of using polymer-based sustained-release delivery systems to maintain therapeutic concentration of protein drugs for extended periods of time has been well accepted for decades, there has not been a single product in this category effectively commercialized to date despite Clinical and market demand. The present review addresses formulation, approaches, and a range of technologies with polymeric based sustained drug delivery system.

Keywords: Sustained/controlled release formulation, protein, stability, pre-determined rate.

INTRODUCTION
Sustained release oral drug formulations have been used since the 1960s to enhance performance and increase patient compliance. By incorporating the dose for 12 hours into one tablet from which the drug is slowly released, peaks of high plasma concentration and troughs of low plasma concentration can be prevented. This helps avoid the side effects associated with high concentrations and the lack of activity associated with low concentrations giving better overall therapy. In addition, in the treatment of diseases those are asymptomatic such as hypertension patients generally remember morning and evening medication, but tend to forget doses in between. Once- or twice-daily dosing thus improves therapy through the constant presence of the drug. Early drug delivery systems
(DDS) tended to give non-constant release rates, although this was still a large improvement over immediate release formulations.\textsuperscript{[1]}

Most conventional drug products, such as tablets and capsules are formulated to release the active drug immediately after administration to obtain rapid and complete systemic drug absorption. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in desired concentration.

Considerations for the formation of sustained-release formulation

\begin{itemize}
\item Factors of consideration in Design of sustained Release Dosage Forms
\item The therapeutic efficacy of drug under clinical conditions is not simply a function of its intrinsic pharmacological activity but also depends upon the path of the drug molecule from the site of administration to the target site. Different conditions encountered by the drug molecule while traversing the path of distribution may alter either the effectiveness of the drug or affect the amount of the drug reaching the receptor site.
\item A] Pharmaceutics: This refers to the development/manufacturing of an efficient delivery system in which the drug has maximum physiological stability and optimum bioavailability.
\item B] Biopharmaceutics/ pharmacokinetics: This involves the study of absorption, distribution, metabolism and excretion of the drug, before and after reaching the target site and evaluation of the relationship between delivery system and therapeutic response.
\item C] Pharmacodynamics/ Clinical Pharmacology: It is the study of the mechanism of action and clinical efficacy of a drug administered in dosage form in terms of onset, intensity and duration of pharmacological activity.\textsuperscript{[2]}
\end{itemize}

Approach in sustained drug delivery system

The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and non toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal. Sustained release, sustained action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug therapy systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose.
Example -
In the case of injectable dosage forms, this period is measured in hours and critically depends on the residence time of the dosage form in the gastrointestinal tract.

The term controlled release has become associated with those systems from which therapeutic agents may be automatically delivered at predetermined rates over a long period of time. Products of this type have been formulated for oral, injectable and topical use and inserts for placement in body cavities. The system attempts to control drug concentrations in the target tissues or cells. Prolonged or sustained release systems only prolong therapeutic blood or tissue levels of the drug for an extended period of time. Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as controlled release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered a prolonged release system. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subject to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.$[^3]$.

ADVANTAGES

1. The frequency of drug administration is reduced
2. Patient compliance can be improved
3. Drug administration can be made more convenient
4. The blood level oscillation characteristics of multiple dosing of conventional dosage form is reduced, because a more even blood level can be maintained
5. Better control of drug absorption can be attained, since the high blood level peak that may be observed after administration in an extended action form
6. The characteristic blood level variations due to multiple dosing of conventional dosage form can be reduced
7. The total amount of drug administration can be reduced, thus
a. Maximizing availability with minimum dose  
b. Minimize or eliminate local side effects  
c. Minimize or eliminate systemic side effects  
d. Minimize drug accumulation with chronic dosing  

8. Safety margin of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients  

9. Improve efficacy in treatment  
   a. Cure or control condition more promptly  
   b. Improve/ control i.e. reduces fluctuation in drug level.  
   c. Improve bioavailability of some drugs  
   d. Make use of special effect e.g. sustained release aspirin for morning relief of arthritis by dosing before bed time.  

10. Economy  

DISADVANTAGES  
1. Administration of sustained release medication does not permit prompt termination of therapy  
2. Flexibility in adjustment in dosage regimen is limited  
3. Controlled release forms are designed for normal population i.e., on the basis of average drug biological half lives.  
4. Economy factors may also be assessed, since most costly process and equipment are involved in manufacturing so many controlled release dosage forms\(^4\).  

A RANGE OF TECHNOLOGIES OF SUSTAINED RELEASE  
Many current oral sustained release systems are of the matrix type, based on hydrophilic polymers. With these technologies, drug and excipients are mixed with polymers such as hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC), and then formed as a tablet by conventional compression. Release from these tablets takes place by a combination of physical phenomena. Water diffuses into the tablet, swells the polymer and dissolves the drug whereupon the drug may diffuse out to be absorbed. If the drug diffuses out faster than the polymer dissolves, the release rate declines with time. Water penetration also depends on factors such as tablet porosity, and this makes matrix tablets
inherently variable and difficult to formulate. If the medication is taken with food, the increased mechanical stress leads to an increased release rate and a higher risk of dose-dumping. In addition, these systems require a large amount of excipient, and drug loading is consequently comparatively low. Another method of obtaining controlled release is to employ diffusion-controlling membranes. Here, a core that may be pure drug is coated with a permeable polymeric membrane (see Figure 1). Water diffuses through the membrane and dissolves the drug which then diffuses through the membrane at a rate determined by the porosity and thickness of the membrane, the solubility of the drug and the membrane area. Available membrane polymers such as ethyl cellulose have relatively low permeability and, consequently, this technique is mainly used on small pellets to increase the total membrane area. [5]

Example - Poly (esters), Poly (lactic acid), Poly (glycolic acid), Poly (iminocarbonates)

![Figure 1](image_url)

**Figure 1**
Diffusion Controlling Membrane

A special version is the so-called osmotic pump. Here, the membrane is semi-permeable water can diffuse in through the membrane but the drug cannot diffuse out. However, by drilling a hole in the membrane, dissolved drug may flow out (see Figure 2). Drilling the hole is, however, an expensive step; furthermore, the existence of the hole must be assured since the system may otherwise explode leading to complete dose dumping.
Example- Azmacort® (triamcinolone acetamide), Ventolin® HFA (albuterol sulfate), Serevent® (salmeterol)

Figure 2
Osmotic pump

Amongst the stable of patented oral DDS is the diffusion controlled vesicle (DCV) platform which uses impenetrable water-insoluble polymers that are either dissolved in an organic solvent or used as aqueous dispersions. Water soluble pore former is suspended in the polymer solution dispersion, and this coating mix is then spray-coated onto drug-containing cores by conventional coating techniques. This process creates a macro porous membrane that controls the diffusion of the drug. Compared with the osmotic pumps, the membrane contains about one million holes. These are created by a stochastic process during coating, and consequently dose-dumping cannot take place by osmotic rupture of the membrane. Furthermore, the drug is released over the entire membrane surface, as compared with a single spot with the osmotic pump. This reduces the risk of side effects due to high drug concentrations close to gastric and intestinal mucosa[6].

MATHEMATICAL MODELS FOR SUSTAINED RELEASE

The release of drug from the system is described by a well-established mathematical model. The processes that may control the release include:

1. Dissolution of the drug at the surface of the solid depot,
2. Mixing of the drug into the dissolved phase inside the membrane,
3. Diffusion of the drug through the membrane, and
4. Mixing of the drug into the fluid outside the membrane

It can be assumed that the first two processes and the last process are much faster than diffusion through the membrane. Consequently, the release rate is given by Flick’s first equation of diffusion:

\[ J = -D \frac{dc}{dx} \]

\( D = \) diffusion coefficient in area/time
\( \frac{dc}{dx} = \) change of concentration 'c' with distance 'x'

Where \( J \) is the rate of mass transport (mg/time), \( Dd \) is the diffusion coefficient of the drug, and \( \frac{dc}{dx} \) is the diffusion gradient. The gradient can be approximated with the concentration difference (Cs) across the membrane and the thickness of the membrane (h). The tortuous porous membrane reduces diffusion of the drug and \( Dd \) is replaced by \( Dd(P) \), the diffusion coefficient as a function of membrane porosity. Finally, we have to multiply with the membrane area \( A \), which gives the release rate:

\[ \frac{dQ}{dt} = ADd(P) \times Cs / h \]

After integration, we obtain the cumulated release:

\[ Q(t) = ADd(P) \times Cs / ht \]

While there is a solid depot of the drug present inside the membrane, all parameters are constant and, thus, the release rate is constant. The release rate declines exponentially when the depot is depleted

\[ \frac{dQ}{dt} = [ADd(P) Cs / h] \times e - [ADd(P) / Vh] \times t \]

The model accurately predicts drug release from the system, and the formulation is consequently constructed by computer simulation using the following parameters

- Drug dose,
- Drug solubility,
- Drug size (diffusion coefficient),
- Tablet size, membrane area,
- Membrane thickness, and
- Membrane porosity\(^\text{[7]}\).
Pharmacokinetic and pharmacodynamic Considerations

1. Release Rate and Dose

Immediate release from a conventional dosage form implies that kr >>> ka or alternatively, that absorption of drug across a biological membrane, such as the intestinal epithelium, is the rate limiting step in delivery of the drug to its target area. For non immediate-release dosage forms, kr <<< kw that is release of drug from the dosage form is the rate-limiting step. This causes the above kinetic scheme to reduce to, essentially, the absorptive phase of the kinetic scheme becomes insignificant compared with the drug release phase. Thus, the effort to develop a non-immediate-release delivery system must be directed primarily to altering the release rate by affecting the value of kr. Although it is not necessary or desirable to maintain a constant level of drug in the blood or target tissue for all therapeutic cases this is the ideal starting goal of an extended-release delivery system. In fact, in some cases optimum therapy is achieved by providing oscillating, rather than constant drug levels. An example of this is antibiotic therapy, where the activity of the drug is required only during the growth phase of the microorganism.30 the ideal goal in designing an extended-release system is to deliver drug to the desired site at a rate according to the needs of the body (i.e., a self-regulated system based on feedback control). However, this is a difficult assignment. Although some attempts have been made to achieve this goal, such as with the self-regulating insulin pump, there is no commercial product representing this type of system as yet. In the absence of feedback control, we are left with a simple extending effect. The pivotal question is at what rate a drug should be delivered to maintain a constant blood drug level. This constant rate should be the same as that achieved by continuous intravenous infusion where a drug is provided to the patient at a constant rate just equal to its rate of elimination. That is, release from the dosage form should follow zero-order kinetics, as shown

By,

\[ k_0 \]

\[ r = \text{Rate In} = \text{Rate Out} = k_e.C_d.V_d \]

Where,
k_0
r = Zero-order rate constant for drug release (amount/time),
Ke = First-order rate constant for overall drug elimination (time-1),
Cd = Desired drug level in the body (amount/volume),
VD = Volume of the space in which the drug is distributed.
The values of \( ke \), \( Cd \), and \( VD \) needed to calculate \( k_0 \)
r is obtained from appropriately designed single-dose pharmacokinetic studies. The above equation provides the method to calculate the zero-order release rate constant necessary to maintain a constant drug blood or tissue level for the simplest case, where drug is eliminated by first order kinetics. For many drugs, however, more complex elimination kinetics and other factors affecting their disposition are involved. This in turn affects the nature of the release kinetics necessary to maintain a constant drug blood level. For a system in which the maintenance dose release drug by a zero order process for a specified period of time, the total dose is,
\[
W = D_i + kr_0 T_d - kr_0 T_p
\]
Where,
\( T_d \) = Total time required for extended release from one dose. If the maintenance dose begins release of drug at the time of dosing \( (t = 0) \), it will add to that which is provided by the initial dose, thus increasing the initial drug level. In this case a correction factor is needed to account for the added drug from the maintenance dose,
\[
W = D_i + kr_0 T_d - Kr_0 T_p
\]
The correction factor \( kr_0 T_p \) is the amount of drug provided during the period from \( t = 0 \) to the time of the peak drug level \( T_p \). No correction factor is needed if the dosage form is constructed in such a fashion that the maintenance dose does not begin to release drug until time \( T_p \). It already has been mentioned that a perfectly invariant drug blood or tissue
level versus time profile is the ideal starting goal of an extended release system. The way to achieve this, in the Simplest case is use of a maintenance dose that releases its drug by zero-order kinetics. However, satisfactory approximations of a constant drug level can be obtained by suitable combinations of the initial dose and a maintenance dose that releases its drug by a first – order process. The total dose for such a system is,

\[ W = D_i + \left( \frac{k_e C_d}{k_r V_d} \right) \]

Where,

\( k_r \) = First-order rate constant for drug release (time-1),
\( k_e, C_d, V_d \) = as defined previously. If the maintenance dose begins releasing drug at \( t = 0 \), a correction factor is required just as in the zero-order case.

The correct expression in this case is,

\[ W = D_i + \left( \frac{k_e C_d}{k_r} V_d - D_m k_e T_p \right) \]

To maintain drug blood levels within the therapeutic range over the entire time course of therapy, most extended-release drug delivery systems are, like conventional dosage forms, administered as multiple rather than single doses. For an ideal extended-release system that releases drug by zero-order kinetics, the multiple dosing Regimens is analogous to that used for a constant intravenous infusion. Since an extended-release system is designed to alleviate repetitive dosing, it naturally will contain a greater amount of drug than a corresponding conventional form. The typical administered dose of a drug in a conventional dosage form will give some indication of the total amount of drug needed in an extended release preparation. For the drugs requiring large conventional doses, the volume of the sustained dose may be too large to be practical or acceptable, depending on the route of administration. The same may be true of drugs that require large release rate from the extended release system (For example, drugs with short half-lives). If the dose of a drug is high (For example, those that requiring a daily dose exceeding 500 mg), it becomes more challenging to develop sustained release oral dosage forms. For short half-life drugs, to provide a once a day tablet, it requires not only that a large amount of drug to be incorporated in a dosage unit to provide the daily dose, but also the dosage units be small in size to allow for ease of swallowing by the human.
requirement for small sizes would leave little space in the dosage unit for other ingredients needed to control the drug release. The size of the dosage unit becomes even more critical with highly water-soluble drugs since even a larger amount of inactive in gradients (For example, more than 50% of the total weight) is usually needed to provide the sustained release property, according to the conventional SR methods\textsuperscript{[8]}.

POLYMER-BASED SUSTAINED-RELEASE DOSAGE FORMS

This restriction certainly does not reduce the impact and significance of C-C backbones for controlled release applications but is simply a mechanism to focus on an important subset of materials. To illustrate the diverse range of functionalities available from non biodegradable systems based on C-C backbones to heteroatom-containing polymer backbones that may confer biodegradability’s is provided that overviews polymers used in controlled release applications as a function of the composition of the polymer backbone.

Protein drugs represent a group of the most effective, natural, and the fastest growing medicines for treatment of nearly 150 indications including various severe chronic conditions such as cancer, diabetes, hepatitis, leukemia, and rheumatoid arthritis. A critical problem in protein therapy is that most protein drugs are currently administered by frequent injections due to their tissue impermeability and short in vivo life. In the case of chronic conditions, daily or multiple weekly injections for years or even lifetime have resulted in poor patient compliance. For tissue regeneration therapy on the other hand, the in vivo life of some cytokines are limited to hours or even minutes after injection, far from sufficient to exert biological functions in vivo. Sustained-release technology offers the promise for reducing dosing frequency, maximizing the efficacy–dose relationship, and decreasing adverse side effects. To achieve in vivo or in situ sustained-release of protein drugs, various polymer-based formulation strategies have been examined since 1970s\textsuperscript{[9]}.

APPLICATIONS OF SUSTAINED-RELEASE DELIVERY OF PROTEINS

1. Stimulating homing and differentiation of stem cells at targeted tissues in addition to treatment of chronic conditions
In which reduction of injection frequency is demanded for improving patient’s compliance, sustained-release delivery of proteins is found useful in tissue regeneration therapy and in medical devices. For tissue regeneration, the homing, differentiation, and proliferation of stem cells at the site of the tissue to be repaired rely on therapeutic level of administrated cell growth factors within the targeting tissue for sufficient period of time, normally several weeks. However, in vivo life of these proteins range from several hours to several days, far from therapeutic needs. While tissue regeneration by mobilized or administrated stem cells is not a chronic process, many tissues, such as cardiac muscles, can only be injected for very limited times. Thus, having therapeutic level of cell growth factors extended for weeks after a single injection is essential. Reported examples in this area of applications are the collagen-based matrix system for extended release of bone morphogenetic proteins for bone regeneration. Collagens, however, are usually derived from animal sources, which can be a source of pathogen transmission. In addition, collagen-based carriers can only retain soluble proteins in their matrix for 1–2 weeks (with half life of 2 days) substantially less than therapeutically preferred duration (>6 weeks). The protein retention time will be even shorter when an injectable form of collagen is used (to some tissues that require small volume of injection). Partially, due to the unavailability of appropriate system to deliver proteins for tissue regeneration, methods to deliver genes to express cell growth factors in targeted tissues actively studied. However, gene delivery, by either viral or non-viral systems, also encounters a series of technical challenges, such as immunogenicity, chemo toxicity, and control of gene expression. Sustained-release systems that deliver cell growth factors to targeted tissues for sufficient period of time will offer a direct, effective, and safe solution to regeneration therapy of tissue and organs.

Example - PEG-Intron, Pegasys PEGylated interferon

PEGylated interferon + ribavirin. [10]

II. Protein drug eluting cardiovascular stents

Protein-eluting cardiovascular stents represent another potential application of protein sustained-release technology. The chemical drugs used on current drug eluting stents, although prevent after-stinting rest enosis; inhibit healing of the blood vessel endothelium
damaged by stent installation. The delayed endothelium recovery causes incident bleeding and thrombus forming. Several proteins have been found effective to suppress vascular smooth muscle proliferation and to stimulate vessel endothelium recovery when directly introduced to the stenting site. However, loading these proteins onto stents resulted in ineffectiveness. In these work, stents pre-coated with a layer of hydrophobic polymer was impregnated in a protein solution to adsorb proteins on the polymer surface. However, adsorbing proteins on hydrophobic polymer surfaces is a known cause for protein denaturing. In addition, only limited amount of proteins can be adsorbed on a stent surface (<20 μg/). A recent work reported by Jin et al. suggests that mixing protein-loaded polysaccharide glassy particles into the polymer solution for stent coating is an effective yet simple method to improve loading capacity, stability, and release kinetics of proteins.


THE CHALLENGES IN DEVELOPING POLYMER-BASED PROTEIN SUSTAINED-RELEASE SYSTEMS

Protein Instability in Formulation Processes As compared with peptide drugs, the greatest difficulty in formulating proteins into polymer-based sustained-release dosage forms is that protein molecules possess fragile advanced structures which may easily denature during formulation processes involving water–organic solvent interfaces and during a sustained-release period by protein aggregation and protein adsorption onto the hydrophobic polymers. The energy barrier for dissolved protein molecules to unfold was reported to be around 5–20 kcal/mol similar to that of a hydrophobic interaction and water–oil or water–air interfacial tension. Because of such close energy level, protein molecules may easily be denatured due to the interfacial tension between water and organic solvents used to dissolve biodegradable polymers for sustained-release, or due to the contact with the hydrophobic polymer matrix[12].

RECENT APPROACHES IN DEVELOPING SUSTAINED-RELEASE DOSAGE FORMS FOR PROTEIN DRUGS
To prevent protein denaturing by microencapsulation processes, most recent studies in developing sustained-release system for protein drugs have involved efforts to avoid exposing dissolved protein molecules to the interface of water and organic solvents. Reported formulation strategies may be classified into three categories:

1. TO formulate proteins into solid particles or some other stabilized form to gain resistance to organic solvents prior to microencapsulation processes
2. To microencapsulate proteins with polymeric materials soluble in water, and
3. To form sustained-release depots by an in vivo gelling process. To address protein aggregation and on polymer adsorption during the prolonged course of sustained release, some researchers suggested blending hydrophilic polymers or basic inorganic salts into polylactide-co-glycolide (PLG) systems to reduce hydrophobicity of the protein-loading matrix.\[13\].

Example – Lupron Depot, Nutropin Depot

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<tr>
<th>TABLE 1: EXAMPLE OF MARKETED SUSTAINED RELEASE PRODUCT</th>
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<tr>
<td>Name</td>
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<tr>
<td>Carrboro</td>
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<td>Glucotrol XI</td>
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<td>Adderall XR</td>
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CONCLUSION
Sustained release formulation is helpful in increasing the efficiency of the dose as well as they are also improving the patient’s compatibility. More over all these comes with reasonable cost. Among various recent formulation strategies, the methods to preload
proteins into polysaccharide fine particles prior to microencapsulation and those to load proteins into hydrophilic in vivo gelling systems seem to be comprehensive.

REFERENCE


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