# Design of Sustained Action Dosage Forms; Mini-Review

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### Abstract

Greatest idealized per-oral sustained action products have been formulated in the form of oral dosage forms such as capsules or tablets. The characteristic trouble of preparing sustained action liquids has controlled the availability of such dosage forms. Encapsulated long-acting dosage forms have two particular benefits over capsules and tablet designs. Firstly, the inability to be disintegrated which may persist in the stomach for long periods of time, extremely suspending in the stomach and retard the absorption of maintenance dose. Secondly, the disintegration of the capsule shell in the gastric fluid releases particles that pass across the pyloric valve. Also, the release of drug by a meaningful fraction of the granules is highly possible. If a tablet fails to release drug, the entire maintenance dose is lost. This review discusses the different methods for enhancing the sustained drug action.

**Keywords:** Sustained action; Dosage form; Controlled release

## Introduction

The purpose of any drug dosage form delivery system is to produce a therapeutic amount of drug to the precise site of action in the body in order to punctually achieve and then control the desired drug concentration. This idealized scientific features to the two appearances most essential to drug delivery, specifically, spatial placement and temporal delivery of a drug. Spatial arrangement correlates to the targeting of a medication to a specific organ or tissue, while temporary delivery points to establishing the rate of medication transport to the target sites. A properly designed sustained-release drug delivery system can be an important advance toward solving these two problems. The science and technology is a useful development of sustained-release pharmaceuticals and still continue to be the focusing of a great deal of care in both industrial and educational laboratories [1]. The term sustained-release drug product has been utilized to explain several types of oral prolonged release rate dosage forms, involving sustained-release, controlled-action, long-action, and retarded-release [2,3].

Multiple periodic dosing often is inaccessible for the patient and can result in missed doses, makeup doses and patient noncompliance with the curative regimen. When standard immediate release dosage forms are delivered on schedule and more than once daily, there are steady therapeutic blood level peaks and channels associated with the taking of each dose. Nevertheless, if doses are not given on schedule, the resulting peaks and gaps reflect less optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations (MTC) of the drug may be reached with toxic side effects resulting. If doses are required, terms of sub-therapeutic medication blood levels or the lowest effective concentration (MEC) may outcome, with no patient value [4,5].

Extended-release tablets and capsules are regularly taken only once or twice daily compared with equivalent conventional forms that may need to be taken three to four times daily to achieve the same therapeutic effect. Additionally, extended-release products present an immediate release of drug which quickly produces the wanted curative effect which then is reflected by the gradual and constant release of additional amounts of drug to control this effect over a decided period of time. The sustained plasma drug levels produced by extended-release drug products often times reduce the need for night dosing, which presents the benefit not only to the patient but to the caregiver as well [6,7].

Numerous studies showed that nanoparticles linked ligands or antibodies could be targeted to surface receptors over-expressed by cancer cells, such as the SSTRs, the folate receptor, and transferrin receptors. Moreover, nanoparticles coated cell-penetrating peptides and protein-transduction domains, such as oligoarginine and TAT facilitated the uptake of these nanoparticles which cannot successfully enter cancer cells [8].

This review discusses the different methods for enhancing the sustained drug action, the barrier principle, model based on diffusion, and model based on dissolution. Moreover, the review discusses the principle release from the matrix.

## These are the Barrier and the Embedded Matrix Principle

### The barrier principle

The barrier theory of controlled release suggests that a layer retardant material is forced between the medication and the elution medium. Moreover, a coating film of the retardant material forms around center composed of the effective ingredient. In addition, these coated particles form a system with the drug contained in the coating film system as well as in the central of the microparticles. Further, drug release from such systems obeys a dissolution mechanism, a diffusion mechanism or a combination of both mechanisms [9].

Moreover, the diffusion systems rate release depends on the ratio at which the drug dissolves through a barrier which is typically a type of polymer. Diffusion systems can be broken into two subcategories, reservoir devices and matrix devices [10].

Reservoir devices can coat the drug with polymers and in order for the reservoir devices to be in sustained release effects, also the polymer must not dissolve and let the drug be released through diffusion. The percentage of reservoir devices can be changed by changing the polymer and is possible be made to be zero-order release; nevertheless,

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drugs with higher molecular weight have difficulty diffusing through the barrier membrane [10].

Additionally, the matrix device forms a matrix (drug(s) mixed with a gelling agent) [9] where the drug is dispersed. The drug is mostly dispersed within a polymer and then released by undertaking diffusion. Nevertheless, to style the drug SR in this device, the rate of dissolution of the drug within the matrix requests to be higher than the rate at which it is released. The matrix device cannot achieve a zero-order release but higher molecular weight molecules can be used, also tends to be easier to produce and protect from changing in the gastrointestinal tract. Further, the factors such as food can affect the release rate [11].

### Models based on diffusion

In this model, the barrier is comprised of a water-insoluble polymeric material that is water-resistant to the elution medium. Moreover, the drug is partitioning into the membrane and exchange with the fluid surrounding the particle. An extra drug is inflowing the polymer, dispersing to the boundary and exchange with the contiguous medium. At steady state, the release rate of the drug is expressed as:

$$R = SDC_{sm} / L \qquad (1)$$

Where, S is the surface area, D is the diffusion coefficient of the medication in the membrane. $C_{sm}$ is the solubility of the medication in the membrane. L is the thickness of the membrane. Two forms of release profiles may be observed in this case: a burst effect if the membrane is saturated with the medication and a time lag if the medication has not penetrated the membrane [12,13]. A second probable model established on the diffusion mechanism happens when a moderately soluble membrane encloses a medication core. Moreover, the dissolution of part of the membrane permits for diffusion of the forced medication through the pores in the polymer coat. The release rate can be expressed as:

$$R = SD (C_1 - C_2)/ L \qquad (2)$$

Where $C_1$ is the medication concentration in the core, $C_2$ is that in the adjacent surrounding medium. Moreover, the fraction of soluble polymer in the coating materials will be the dominant factor in monitoring drug release rates. If the medication is soluble in the membrane, the release rate can be described by the equations (1) and (2). Using of methylcellulose and ethyl cellulose films for coating aspirin by the air suspension coating technique was described previously [14], while the methylcellulose was dissolved out of the film leaving small networks in the film through which drug can be diffused. Furthermore, the ethyl cellulose barrier left on the particle aids as a preventive barrier to maintain constant diffusion area and constant diffusion path length [7,15].

### Models based on dissolution

The drug released from the coated particles could be also involved as a time dependent dissolution or erosion of barrier. These approaches generally refer to the coating of separate particles or granules of the medication with varying thicknesses of slowly soluble or erodible coating ingredients. Additionally, the time required for ending of the coat is a function of coating thickness and dissolution rate of the coating substance. With covered items one can acquire beat dosing impacts i.e., rehash the activity, by simply utilizing few distinctive thicknesses covered particles, or getting the more typical maintained impact by using a range of various thickness coatings. A few granules inside each gathering discharge the medication at interims covering different gatherings, bringing about a smooth as opposed to intermittent discharge, profile [2,16].

There are numerous conducts to produce drug-coated beads or particles. A common process is to coating nonpareil seeds with the medication and follow this with both a slowly dissolving wax or polymer coating of varying thickness. In this process some high milligram potency formulations, individual crystals of medication or palletized drug may be coated by pan or fluidized-bed procedures with a retardant barrier. This system can also be useful through microencapsulation, wherein the drug crystals are encapsulated with a coating substance employing one of the microencapsulation procedures [17,18].

An assortment of gradually dissolving coatings is accessible, for example, those in view of different blends of starch sugars and cellulose, polyethylene glycol, polymeric materials, and wax. A representation of this approach was portrayed the arrival of amobarbital and dextroamphetamine from managed discharge measurements frames utilizing wax-covered granules. The rate of medication discharge was found to diminish logically as the level of wax in the covering increments. In order to eliminate production complexity associated with the manufacture of mixed release granules, formulations were designed to produce granules with uniform rather than mixed release characteristics. Delayed release ascorbic acid consisting of ascorbic acid crystals encapsulated in partially hydrogenated cottonseed oil has been marketed for the food industry [19-21].

A pH-sensitive constituted of made out of the hydrolyzed styrene-maleic corrosive copolymer was applied to methylprednisolone. Coated granules can be put in a case for organization to the patient. On the other hand, the granules can be compacted into tablets. For this situation, the impact of excipients and pressure ought to be considered. The position of a typified item into tablet or case must be done precisely to limit fracture or combination of the particles and to keep up the respectability of the coat [22-25].

Osmotic delivery systems have a numeral of key advantages over the other controlled release mechanisms. They are greatly less affected by factors such as pH, food intake, GI motility and unusual bowel surroundings. The usage of an osmotic drug delivery pump has additional inherent advantages in controlling drug delivery rates. This allows much more particular drug delivery over a longer period of time, developing in widely more predictable pharmacokinetics [26,27].

### Models based on a combination of diffusion and dissolution

This case exists for the arrival of medication from covered particles if the barrier is penetrable to the elution medium. Disintegration liquid infiltrates through the coating film into the granules and breaks down the medication. The medication at that point diffuses through the flawless film at a rate corresponding to the penetrability of the layer, convergence of the medication inside the granule, and portability of medication particles. Medication discharge from coated particles can take after any of the past models. As a rule, a mix of atleast two of the models speak to the genuine method of the medication discharge [28-30].

### The Embedded Matrix Principle

The embedded matrix principle of sustaining drug action involves the dispersion of the drug in a matrix of retardant material. This may be encapsulated in a certain form or compressed into tablets. A solid drug dispersed in an insoluble matrix has a rate of release dependent on the rate of drug diffusion and not on the rate of solid dissolution. An equation describing drug release from this system was derived by Higuchi [17,28].

$$Q = [D \Sigma (2A - \Sigma C_s) C_s t / f]^{1/2} \qquad (3)$$

Where Q is the amount of drug released per unit area of the surface at time t, D is the diffusion coefficient of the drug in release medium. $\Sigma$ is the porosity of the matrix, Cs is solubility of the drug in the release medium, $f$ is the tortuosity of the matrix, and A is the concentration of drug in the matrix. A simple approach to disperse a drug in a matrix of the retardant material involves the direct compression of granulated drug and an insoluble plastic material so that a porous skeleton of matrix material forms around the drug. The release rate of various drugs incorporated into a plastic matrix type tablets has been studied. The kinetics of release of drugs dispersed in a methylmethacrylate-methyl acrylate matrix has been reported previously [17,28,30,31].

Another approach employed to prepare embedded matrix involves dissolving the drug into the plastic matrix prior to compression. In the first method, the prompt and extensive release of the drug is obtained when such tablet is chewed. This problem is somewhat alleviated in the second method. In this case, the drug is not free to be absorbed even upon mastication. Another approach based on the embedded matrix principle is to compress the drug with a slowly dissolving lipid carrier into a tablet form. Factors such as the porosity of the tablet matrix, the presence of hydrophobic additives, and the wettability of the tablet and particle surface, play important roles in the release rate of the drug. In a modification of this approach, a lipase-lipid-drug system was employed to provide sustained drug release where the matrix erosion was due to the lipolytic action of lipase on the substrate. Incorporation of lipase-activity accelerators such as calcium carbonate or glyceryl monostearate provides flexibility for controlling drug release [16,32-34].

The embedded matrix principle has also been applied to prepare sustained release encapsulations [32-34]. Medicaments are dispersed in molten lipid materials to form a slurry which may be spray congealed, or granulated after solidification. Some lipid retardant or carrier materials include hydrogenated oils, glyceryl stearates, fatty alcohols and microcrystalline wax. The addition of l to 10 % of channeling agents (wicking agents) e.g. methylcellulose, alginic acid, polyvinylpyrrolidone or polyethylene glycol, is claimed to produce a greater uniformity of drug release which more nearly approximates zero-order process. Water-soluble drugs dispersed in hydrophilic matrices were studied. The results showed that the release rate was controlled mostly by drug diffusion rather than polymeric dissolution. Thus, even when drugs are incorporated in a water-soluble matrix which will be subjected to erosion, the rate-limiting step is diffusion of the drug out of the matrix [9,35-37].

When hydrophilic gums are employed as the matrix material and showed that drug diffusion from a gel barrier at the periphery of the tablet was rate limiting. If the drug is freely soluble in the elution medium i.e., Cs>A in equation (3), so that the dissolution rate is relatively rapid, the release process is described as the release of a solution of the drug entrapped in an insoluble matrix and the following equation applies.

$$Q = 2A \left( Dt / Cs\, f \right)^{1/2} \tag{4}$$

Where Q is the amount of drug released per unit area of the surface at time t, D is the diffusion coefficient of the drug in release medium, Cs is the solubility of the drug in the release medium, $f$ is the tortuosity of the matrix, and A is the concentration of drug in the matrix. It was reported that if the drug dissolves in the matrix in which dispersed, both matrix and partition control is possible. If drug has low solubility in the elution medium, partition control dominates and the release is zero order [38-40], that is;

$$Q = K\, D\, Cs\, t / h \tag{5}$$

Where K is the partition coefficient and h is the thickness of the hydrodynamic diffusion layer [9,23,24].

Physicochemical properties that affect drug product design and performance:

The design of a sustained action medication is restricted by certain properties that may render such design more difficult to attain; not all drugs are suitable candidates for formulation as sustained action medications. The performance of a drug is a function of its physicochemical properties which may prohibit placement of the drug in a sustained release form [9].

The first problem facing construction of a sustained action dosage form is the volume of drug that must be administered. For solid oral dosage forms, there is an approximate upper limit of the product bulk that is acceptable to the patient. Drugs with large single oral dose are poor candidates for oral sustained release products since the addition of the sustaining dose and possibly the sustaining mechanism will in most cases generate a substantial volume product. The solubility of the drug in the aqueous medium is another important limitation for its formulation in controlled release forms. Generally, extremes in aqueous solubility are undesirable in the preparation of suitable sustained action drugs. Highly insoluble drugs, whose availability is controlled by dissolution, would present problems in controlled release product design since the amount of drug available for absorption is limited by the poor solubility of the compound [41-44].

The oil/water partition coefficient is another factor that may limit the selection of drugs to be formulated in sustained release forms. This property determines the ability of the drug to cross biological membranes. Generally, drugs which are highly oil soluble, i.e. with high partition coefficients, will either readily penetrate into body membranes producing an accumulation in body tissues with subsequent slow elimination, or since the drug must cross both oil and water barriers in its permeation through tissues, will remain localized in the lipid phase of the tissue. In either case, a sustained release system for such drugs is inappropriate. Meanwhile, drugs with very low oil/water partition coefficients are also not suitable for such formulations, since they cannot penetrate biological body membranes. A balanced partition coefficient is required for successful formulation into a controlled release system [45-47].

The molecular size of drugs is an important parameter that must be considered if a polymeric membrane is employed as the controlled release mechanism. The ability of drugs to diffuse through membranes is influenced by molecular size. Drugs with high molecular weights usually possess a very low diffusion coefficient and hence a low permeability through many polymeric films [22,48].

To maintain a constant blood level of drug it should be uniformly released from the sustained release system and then uniformly absorbed. Drugs absorbed by a specialized transport process and drugs absorbed at special sites of the G.I.tract are poor candidates for controlled release products. A more prohibitive aspect for the formulation of sustained action medications is the low magnitude of absorption rate constant. In order to formulate drugs with the low magnitude of absorption rate constants into controlled release systems, the desired rate constant of release from dosage form would have to be less than that of absorption. As the G.I.tract transit time is finite, a suitable controlled release system, giving a high fraction of the dose absorbed, may be difficult to design [7].

The biological half-life and hence the duration of action of the drug is another factor that should be considered when dealing with controlled release medications. Factors that influence the biological half-life of a drug include the rates of its elimination, metabolism, and distribution [49]. Drugs with long biological half-lives are inherently

long-acting and thus are questionable candidates for sustained action formulations. It has been shown that there is no appreciable difference in effectiveness when such drug is formulated either into sustained action medications or conventional dosage forms [50].

## Conclusion

The encapsulated and coated long-acting dosage forms have particular advantages over the other oral dosage forms. Furthermore, the release of drug by a significant fraction of the granules is extremely probable. The main principles of sustained drug release are the retardation of drug release from highest practically sustained action formulations including dosage form modification.

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