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SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Navin Dixit*, Sheo Dutt Maurya, Bhanu P.S.Sagar
I.E.C.College of Eng & Technology, Greater Noida (U.P)
***Corresponding author: ndixit515@gmail.com**

ABSTRACT

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug.

Key words: Sustained Release, Drug delivery system, Matrix, Drug Release

INTRODUCTION

Probably the earliest work in the area of sustained drug delivery dosage forms can be traced to the 1938 patent of Israel Lipowski. This work involved coated pallets for prolonged release of drug and was presumably forerunner to the development of the coated particle approach to sustained drug delivery that introduced in the early 1950s. Ideally, a drug should arrive rapidly at the site of action (receptor) in the optimum concentration, remain for the desired time, be excluded from other sites, and be rapidly removed from the site when indicated i.e. the basic goal of the therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. Generally, the time course of a dosage form (pharmacokinetics) in man is considered to be controlled by the chemical structure of the drug. Decreasing the rate of absorption and/ or changing the dosage form provide a useful adjunct. When it is feasible or desirable to modify the drug compound on a molecular level, often sought is a product that will requireless frequent administration to obtain the required biologic activity time profile; for example, a tablet that has the same clinical effect when administered every twelve hours. In another instance, it may be desirable to decrease the absorption rate in order to obtain a more acceptable clinical response (Girish K Jani, 2009).

Tablets are one of the most stable and commonly administered oral dosage forms. Since the later part of nineteen-century, tablets have been widespread and their popularity continues. Tablets remain popular as dosage form because of the advantages afforded both to the pharmaceutical manufacturers and patients. These includes: simplicity and economy of preparation, stable and convenient in packing, ease of transporting and dispensing, accuracy of single dosage regimen, compactness and portability, and blandness of taste and ease of administration. The goal in designing sustained or controlled delivery systems is to reduce frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, providing uniform drug delivery. If one were to imagine the ideal drug delivery system, two prerequisites would be required. First, it would be a single dose for duration of treatment, whether it is for days of weeks, as with infection, or for lifetime of the patient, as in hypertension or diabetes. Second, it should deliver the drug directly to the site of action, thereby minimizing or eliminating side effects. This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body.

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained release systems, oral route of administration has received most of the attention with respect to research on physiological and drug constraints as well as design and testing of products. This is because of the fact that there is more feasibility in dosage form design for oral route than for parenteral or any other route. The design of oral sustained release delivery systems is subject to several intercalated variables of considerable importance. Among these are the types of delivery systems, the disease being treated, the patient and the length of therapy and the properties of the drug. In conventional drug therapy, it can be seen from the Figure 1.1 that the administration of drug by either intravenous injection or an extravascular route e.g. Orally, intramuscularly, or

rectally does not maintain drug blood level within the therapeutic range for an extended period of time. The short action is due to the inability of conventional dosage forms to control temporal delivery (Banks Michael, 1991).

DRUG SELECTION FOR ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEMS

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 G. I. tract, the general absorbability, the drug's molecular weight, pKa, solubility at different pH and apparent partition coefficient.

Table.1. Parameter for drug selection

Parameter	Preferredvalue
Molecular weight/ size	< 1000
Solubility	> 0.1 µg/ml for pH 1 to pH 7.8
P_{ka}	Non ionized moiety > 0.1% at pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

The pharmacokinetic evaluation requires knowledge on a drug's elimination half- life, total clearance, absolute bioavailability, possible first- pass effect, and the desired steady concentrations for peak and trough.

Table.2. Pharmacokinetic parameter for drug selection

Parameter	Comment
Elimination half life	Preferably between 0.5 and 8 h
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution V_d	The larger V_d and MEC, the larger will be the required dose size.
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration Css av	The lower Css av and smaller V_d, the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

Matrix diffusion controlled drug delivery system: In this type of controlled drug delivery system, the drug reservoir results from the homogeneous dispersion of the drug particles in either a lipophilic or a hydrophilic polymer matrix.

Mode of action of hydrophilic matrix dosage form: Hydrophilic matrix dosage forms essentially consist of a compressed blend of hydrophilic polymer and drug. According to the generally accepted mechanism, the drug release from hydrophilic matrix dosage forms starts when the tablet comes in contact with gastrointestinal fluid. The surface of the tablet hydrates to release exposed drug and at the same time form a viscous polymer mucilage or gel. This gel fills the interstices within the tablet, retarding further ingress of liquid. The concentration of polymer within the hydrated layer ranges from dilution at the outer surface to around 90% at the boundary with the drug core. Within this layer, drug in various states of dissolution (undissolved in dilute solution; in saturated solution) is distributed amongst the other ingredients of the tablets.

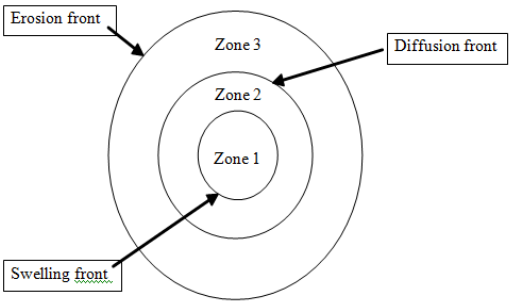

Fig.1.Matrix diffusion controlled drug delivery system

Drug release occurs immediately from the surface (burst effect) followed by diffusion through, and / or erosion of, the hydrated layer. The relative proportions of drug released by diffusion and erosion are determined by the drug's solubility properties and by the physical and chemical nature of the hydrated polymer. This in turn is influenced by other factors, including drug characteristics, dissolution medium and other, which continue to be investigated.

Modified-release drug delivery systems: In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of modified release drug delivery systems. The modified-release delivery systems may be divided conveniently into four categories[4]:

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

Delayed release system: Delayed-release systems are those that use repetitive, intermittent dosing of a drug from one or more immediate-release units incorporated into a single dosage form. Examples of delayed-release systems include repeat-action tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating.

Sustained release system: Sustained-release systems include any drug-delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this is of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled-release system.

Site-specific targeting: Site-specific and receptor targeting refer to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is adjacent to or in the diseased organ or tissue.

Receptor targeting: For receptor release, the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug-delivery systems.

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 desirable 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 1.2 shows the difference between the conventional and sustained release dosage forms.

Advantages of sustained release drug delivery: Following are the potential advantages of sustained release products

1. Decreased local and systemic side effects reduced gastrointestinal irritation.
2. Better drug utilization reduction in total amount of drug used.

3. Improved efficiency in treatment, optimized therapy, more uniform blood concentration.
4. Reduction in fluctuation in drug level and hence more uniform pharmacological response, cure of control of condition more promptly, less reduction in drug activity with chronic use.
5. Method by which sustained release is achieved can improve the bioavailability of some drugs e.g. drugs susceptible to enzymatic inactivation can be protected by encapsulation in polymer systems suitable for sustained release.
6. Improved patient compliance, less frequent dosing, reduced night-time dosing, reduced patient care time. The importance of patient compliance in successful drug therapy is well recognized. It has been found that there is an inverse relationship between the number of dosages per day and the compliance rate.
7. Although the initial unit cost of sustained release products is usually greater than that of conventional dosage forms because of the special nature of these products, the average cost of treatment over an extended time period may be less. Economy may also result from a decrease in nursing time and hospitalization time.

Disadvantages of sustained release drug delivery: The disadvantages of sustained release drug delivery system are

1. Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time complete release, site specific absorption, pH dependent stability, etc.
2. Poor *in vitro – in vivo* correlation.
3. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
4. Reduced potential for dose adjustment of drugs normally administered in varying strengths.

Classification of oral sustained/controlled release systems

Diffusion controlled Systems

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.

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.

Dissolution controlled systems

Matrix dissolution controlled systems: Aqueous dispersions, congealing, spherical agglomeration, etc. can be used.

Encapsulation dissolution controlled systems: Particles, seeds, granules can be coated by techniques such as microencapsulation.

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.

Sustained release matrix tablets: One of the least complicated approaches to the manufacture of sustained release dosage forms is the direct compression of drug, release retardant, and additives to form a tablet in which drug is embedded in a matrix core of retardant. Alternatively drug retardant blend may be granulated prior to compression. Such tablets are called as matrix tablets. Three classes of release retarding materials are used for the formulation of matrix tablets.

They include

1. Insoluble or ‘skeleton’ matrices
2. Water insoluble, erodable matrices
3. Hydrophilicmatrices.

Table1.1. Some important materials used for preparing sustained release tablets.

Matrix characteristics	Release retarding material
Insoluble, inert	Polyethylene, Polyvinyl Chloride Methyl acrylate-methacrylate copolymer Ethyl Cellulose
Insoluble, erodible	Carnauba wax, Steryl alcohol Stearic acid, Polyethylene glycol Polyethylene glycol monostearate Triglycerides
Hydrophillic	Methyl cellulose, Hydroxyethyl cellulose Hydroxypropyl methycellulose Sodium carboxymethylcellulose Carboxypolymethylene Sodium alginate, Galactomannose

Tablets prepared from these materials are egested intact and not break apart in GI tract. The rate-liming step in controlling the release of drug from these formulations is liquid penetration into the matrix unless channeling agents are included in the formulation to promote permeation of water into the matrix. This allows drugs dissolution and diffusion from the channel created in the matrix. In these tablets, drug bioavailability is dependent on polymer-ratio. The bioavailability may be modified by addition of diluents such as lactose. These forms of matrix tablets are not useful if dose of drug is high or if the drug is insoluble in water. Waxes, lipids and related materials form matrices that control the release through both pore diffusion and erosion. Release characteristics are more sensitive to digestive fluid composition than the tablets preparation by insoluble material. Total release of drug from the wax-lipid matrices is not possible, since a certain fraction of the dose is coated with impermeable wax films. For dispersion of drug with the base, three methods are used, which include the fusion technique. In absence of additives, the drug release is non-linear from these systems. Additives like polyvinyl pyrrolidone or polyoxyethylene lauryl esters can lead to apparent zero-order release.

The third group of matrix formers represents non digestible materials, which form gels in situ. The release of drug from these systems is controlled by penetration of water through a gel layer produced by hydration of polymer and diffusion of drug through the swollen, hydrated matrix, in addition to the erosion of gelled layer. The extent to which the erosion or diffusion controls the release depends on polymer selected as well as on the drug-polymer ratio used in the formulation. High drug polymer ratios results in formulations from which drug release is controlled attrition.

Mechanism of drug release: On exposure to aqueous fluid, hydrophilic matrices take up water, and polymer starts hydrating to form a gel layer. An initial burst of soluble drug may occur due to surface leaching when a matrix containing a swellable glassy polymer comes in contact with an aqueous medium, there is an abrupt change from a glassy to a rubbery state which is associated with swelling process with time, water infiltrator deep into the case increasing the thickness by the gel layer. Concomitantly the outer layer becomes fully hydrated and states dissolving or eroding. When water reaches the center of the system and the concentration of drug fells below the solubility value, the release rate of drug begins to reduce. At the same time, an increase in thickness of the barrier layer with time increases the diffusion path length, reducing the rate of drug release. Drug release kinetic associated with these gel – layer dynamic, range initially from Fickian to annomalous (Non – Fickian) and subsequently from quasi – Constant (near Zero order) to constant. In general, two major factors control the drug release from swelling controlled matrix system. They include many processes given below.

1. The rate of aqueous medium infiltration into the matrix, followed by a relaxation process (hydration, gelatin or swelling).
2. The rate of matrix erosion

As a result of these simultaneous processes, two front are evident, a swelling front, where the polymer get hydrated, and an eroding front. The distance between these two fronts are called diffusion layer thickness. Diffusion layer thickness depends on the selective rate at which the swelling and eroding fronts move in relation to each other. If the polymer gets slowly, solvent can penetrate deep into the glassy matrix the dissolving the drug; there for gel layer thickness and it stability are council in controlling drug release. Swelling of HPMC

matrix tablet was higher for higher a molecular weight. They attributed this to the large hydrodynamic volume occupied by higher molecular weight chain when hydrated. As the polymer chain becomes more hydrated and the gel becomes more dilute, the disentanglement concentration may be reached that is the critical polymer concentration below which the polymer chain disentangle and detached from gelled matrix.

CONCLUSION

There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. If one were to develop an ideal drug delivery system, two pre-requisites would be required: Firstly single dose for the duration of treatment whether for days or weeks as with infection, diabetes or hypertension. Second it should deliver the active entity directly to the site of action minimizing the side effects.

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