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Microparticles formulation as a targeting drug delivery system

Abstract

A great interest has been centered on the idea of replacing daily administration of a drug with delivery devices which release a constant effective dose to the target tissues via a controlled release mechanism. Many pharmaceutical investigations have been carried out to develop controlled release oral dosage forms that sustain drug release. A sustained release system is defined as one in which the drug is initially made available to the body in an amount sufficient to give a rapid onset of the desired therapeutic response, after which the level of the therapeutic concentration is maintained constant for the desired duration of time. This review discusses the formulation of sustained release drugs by different kinds of microparticles as a targeting tool for new drug delivery.

Keywords: Microparticles; Targeting; Sustained release; Controlled release

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Introduction

Prolonged action drugs

The ideal sustained release products should not only have a prolonged drug releasing function, but should also offer once or twice a day dose treatment and better control of therapeutic drug level; this will have two benefits: the first is fewer side effects and the second is improved disease management. Hence a good patient compliance is obtained due to reduction in the frequency of daily dosing .[1,2] The problem of patient compliance and its considerable effect on drug therapy is the great advances and extensive research work considering drug absorption and its pharmacokinetics, the rapid growth of polymer technology and some other factors are behind the interest and rationale design of prolonged action dosage forms .[3] Prolonged or controlled release drugs are classified into three basic types: (1) Sustained release, (2) Prolonged action, and (3) repeat action dosage forms.[4] A sustained release product is made so that part of the drug is initially available in an amount sufficient to cause pharmacological response (initial or loading dose), and the other part is for maintenance of activity at the initial level for a desirable number of hours in excess of the activity resulting from the usual single dose of drug (maintenance dose). To maintain a certain level of activity, the maintenance dose should release the drug for absorption at constant rate, which is equal to the rate of elimination of drug from the body .[5] Prolonged action products may be considered as those in which drug is initially made available to the body in an amount sufficient to cause the therapeutic effect; these products also provide for replacement of the drug at some rate which gives a measurable increase in the duration of activity when compared to the conventional single dose. On the other hand, a repeat action preparation is one that provides a usual single dose of drug and is so constructed to provide another single dose at some later time after administration.[6]

Prescribing a long acting dosage form offers several advantages to the conventional dosage forms. By the virtue of eliminating the necessity for drug administration several times a day, patient compliance is greatly improved. Patient compliance is a chronic problem for all self-administered drugs and the minimization of this problem through prolonged acting drugs is very desirable .[7] The blood level oscillations characteristic of multiple dosing conventional dosage forms are greatly reduced after using long acting medications. With oscillating blood level, drug side effects tend to predominate at the high peak concentration in the blood, whereas, an inadequate therapeutic effect may be obtained at the valley level. On the other hand, maintenance of the blood levels constant at predetermined value reduces the incidence of adverse effects and increases the safety margin of drugs .[8-10]

Prolonged action dosage forms provide a slow and constant supply of drug to the body. This leads to a better control of the disease condition and to improve disease management. Proper drug delivery should lead to more prompt cure of the condition as well as better management of acute and chronic conditions .[11] Another advantage of prolonged acting drugs is economy. This economy should be viewed in a broad sense, since the unit cost of most prolonged action medications is usually greater than conventional dosage forms because of the special nature of these products. However, the use of less total drug. The total cost saving to the patient in terms of reduced lost work days, shorter periods of hospitalization, and fewer visits to the physician, make it reasonable to assume that these long-acting products are economical .[12] So, the importance and the usefulness of sustained release dosage forms are well-known and offer many advantages over the conventional dosage forms.

The disadvantages of administering prolonged action drugs

Administration of long acting medications does not permit the prompt termination of therapy. Accidental or intentional poisoning with long acting dosage forms are more difficult to manage than conventional oral solid dosage forms. The slow release of drug into the gastrointestinal tract and its extended absorption often leads to slow clearance of drug from the body .[13,14] With long acting medications, the physician has less flexibility in adjusting dosage regimen since this is affected by the dosage form design. Patient-to-patient variation is another troublesome variable in the design of prolonged action dosage forms. Prolonged action dosage forms are designed for the normal population. Thus, significant patient's variation or any disease state that alters drug disposition presents a problem.[1,2]

Design of prolonged action dosage forms

Most per-oral prolonged action products have been formulated in the form of capsules or tablets .[15,16] Also, can be formulated in nanoparticles and microparticles .[17,18] The inherent difficulty of preparing prolonged action liquids has limited the availability of such dosage forms. Encapsulated long acting dosage forms have two specific advantages over tablet designs. Firstly, undisintegrated tablets may remain in the stomach for extended periods of time, excessively delaying the absorption of maintenance dose. Disintegration of the capsule shell in the gastric fluid releases particles that pass unimpeded through the pyloric valve. Also, release of drug by a significant fraction of the granules is highly probable. If a tablet fails to release drug, the entire maintenance dose is lost. Two general principles are involved in retarding drug release from most practically prolonged action formulations involving dosage form modification. These are the barrier and the embedded matrix principle.[19-22]

The barrier principle

The barrier concept of controlled release implies that a layer retardant material is imposed between the drug and the elution medium; a coating film of the retardant material forms around core composed of the active ingredient. In most instances, these coated particles form a system where drug is contained in the coating film as well as in the core of the micro particles. Drug release from such systems follows a diffusion mechanism, a dissolution mechanism or a combination of both mechanisms.[23-25]

Models based on diffusion

In this case, the barrier is composed of water-insoluble polymeric material that is impermeable to the elution medium. Drug will partition into the membrane and exchange with the fluid surrounding the particle. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding medium. At steady state, release rate of drug is expressed as:

$$R = \frac{SDC_{sm}}{L} \quad \ldots\ldots (1)$$

Where S is the surface area, D is the diffusion coefficient of the drug in the membrane; Csm is the solubility of drug in the membrane, and 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 drug and a time lag if drug has not penetrated the membrane.[26-28] A second possible model based on the diffusion mechanism occurs when a partially soluble membrane encloses a drug core. Dissolution of part of the membrane allows for diffusion of the constrained drug through the pores in the polymer coat. Release rate in this case can be expressed as:

$$R = \frac{SD\,(C_1 - C_2)}{L} \quad \ldots\ldots (2)$$

Where C1 is the drug concentration in the core, C2 is that in the surrounding medium. The fraction of soluble polymer in the coat will be the dominant factor in controlling drug release rates. If the drug is soluble in the membrane, the release rate will be described by equations (1) and (2). The use of methylcellulose and ethyl cellulose films to coat aspirin particles using the air suspension coating technique was reported. In this case, the methylcellulose dissolves out of the film leaving small channels in the film through which drug can diffuse. The ethyl cellulose barrier left on the particle serves as restraining barrier to maintain constant diffusion area and constant diffusion path length.[29-32]

Models based on dissolution

Drug release from coated particles might also involve timed dissolution or erosion of the barrier. These methods generally refer to the coating of individual particles or granules of drug with varying thicknesses of slowly soluble or erodible coating materials. The time required for dissolution of the coat is a function of coating thickness and dissolution rate of the coating substance. With coated products, one can obtain pulsed dosing effects i.e., repeat action, by merely employing a small number of different thickness coated particles, or obtaining the more common sustained effect by utilizing a spectrum of different thickness coatings. Some granules within each group release the drug at intervals overlapping other groups, resulting in a smooth rather than discontinuous release, profile .[29-32]

There are several ways to produce drug-coated beads or granules. A common procedure is to coat non-peril seeds with the drug and follow this with either a slowly dissolving wax or polymer coat of varying thickness. In the case of high milligram potency formulations, individual crystals of drug or palletized drug may be coated by pan or fluidized-bed processes with retardant barrier. This technique can also be applied through micro encapsulation, wherein the drug crystals are encapsulated with a coating substance employing one of the micro encapsulation techniques .[33-35] A variety of slowly dissolving coatings are available, such as those based on various combinations of carbohydrate sugars and cellulose, polyethylene glycol, polymeric materials, and wax. An illustration of this approach is given by Rosen et al.[36] who described the release of amobarbital and dextroamphetamine from sustained release dosage forms employing wax-coated granules. The rate of drug release was found to decrease progressively as the percentage of wax in the coating increases.

A pH sensitive barrier composed of hydrolyzed styrene-maleic acid copolymer was applied to methylprednisolone. Coated granules can be placed in a capsule for administration to the patient. Alternatively, the granules can be compressed into tablets. In this case, the influence of excipients and compression should be considered. The placement of encapsulated product into tablet or capsule must be done carefully to minimize fragmentation or fusion of the particles and to maintain the integrity of the coat.[37,38]

Models based on combination of diffusion and dissolution

This case exists for the release of drug from coated particles if the barrier is permeable to the elution medium. Dissolution fluid penetrates through the coating membrane into the granules, and dissolves the drug. The drug then diffuses through the intact membrane at a rate proportional to the permeability of the membrane, concentration of the drug within the granule, and mobility of drug molecules. Drug release from coated particles can follow any one of the previous models. In many cases, a combination of two or more of the models represents the actual mode of the drug release.[39,40]

Conclusion

Thus, sustained release dosage forms are formulated to maintain constant drug level in either the plasma or target tissue so that, the rate of drug release after initial concentration must be equal to the rate at which drug is eliminated or deactivated. This review discussed the formulation of sustained release and controlled drugs by altered kinds of microparticles as a targeting tool for new drug delivery.

Conflicts of interest

The authors declare no conflict of interest.

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