Novel drug delivery systems

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Administration of drugs using conventional dosage forms is sometimes unsatisfactory due to variability in systemic drug levels, incomplete absorption or poor patient compliance. This article reviews some novel drug delivery systems intended to overcome some of the above shortcomings. Emphasis is placed on controlled drug delivery systems, although mention is also made of other novel drug delivery systems not based on control release principle.

INTRODUCTION

Drug administration using conventional dosage forms may be associated with certain shortcomings leading to poor treatment outcome. For a drug with a narrow therapeutic index, high concentrations may lead to toxicity while low concentration may be ineffective. Other drugs have low aqueous solubilities or are degraded by enzymes in gastrointestinal wall/liver. Thus, alternative routes of administration or delivery systems are required. In addition, some drugs used for treatment/control of chronic diseases have short half-lives, necessitating frequent administration to maintain therapeutic levels in the body. This often leads to poor patient compliance. Thus new ("novel") drug delivery systems have been introduced to overcome some of the above problems.

A novel drug delivery system is a device (formulation) designed to release drug at a controlled rate into the general circulation or into a particular body compartment, or to deliver drug to a specified area (not necessarily in a controlled manner) by avoiding/ by-passing problems associated with conventional drug delivery. The term "controlled release" is broadly used when describing drug delivery aimed at achieving sustainability and/or predictability of drug release from a dosage form. When the term `sustained release' is used, this implies either rapid achievement of desired plasma drug level which are then "sustained" for a period of time, or it may imply gradual attainment of desired levels. In the former case, a rapid release component is usually incorporated into the formulation to allow for rapid attainment of desired drug levels. These levels are subsequently maintained by drug release from the sustained release component.

Other drug delivery systems are not designed to release drug at a controlled/sustained rate, but merely to exploit alternative routes (e.g. lungs) to maximise drug delivery into the body. In the present review, emphasis is placed on controlled release devices, although mention will be made of other devices not necessarily based on controlled release principles.

CONTROLLED RELEASE DRUG DELIVERY AND INTRAVENOUS DRUG INFUSION: COMMON FEATURES.

In order to understand the design of some novel drug delivery systems, an analogy with continuous intravenous infusion is helpful since intravenous (i/v) infusion is a prototype of a rate-controlled dosage form. Below is a summary of a simple infusion assembly and corresponding components of some controlled drug delivery devices.

Drug reservoir

This forms the core of the device and contains the "dose" required. For an i/v infusion, the reservoir is the bottle or bag containing drug solution. The quantity of drug (mg) divided by the intended rate of infusion (mg/hr) specifies the duration of drug administration (hr), before replenishment is needed. The infusion rate (mg/hr) is the product of the concentration (mg/ml) and the rate of solution flow (ml/hr).

Energy source

Energy is required to pump drug out of the delivery device. For a gravity flow i/v infusion, the energy source is the gravity acting on the infusate, creating a hydrostatic pressure higher than the venous pressure. In some drug delivery devices to be described later, the energy source is osmotic pressure.

Rate controlling device

For i/v infusion, a screw clamp or a drop counter controls rate of delivery. The corresponding component in some drug delivery devices is a membrane of defined permeability characteristics. In some devices, it is the nature of the polymer matrix within the reservoir that determines rate of drug release.

Delivery portal

Some drug delivery devices have an orifice through which drug solution leaves the device. This corresponds to the tip of the catheter for i/v infusion.

Platform

This is the physical structure that holds the functional elements together. For i/v infusion, it includes the bedside stand supporting the bottle/bag, and terminates at the delivery portal.

There are three basic approaches that have been used in the development of novel controlled drug delivery systems. These are:

(a) Delivery systems based on diffusion or osmosis.

(b) Chemical delivery systems

(c) Delivery systems based on other designs.

A — DELIVERY SYSTEMS BASED ON DIFFUSION OR OSMOSIS[1-10]

The general design of these drug delivery systems is based on the prototype analogous to intravenous infusion as described earlier.

Systems based on diffusion

These are further divided into two groups:

a) Diffusion matrix systems

b) Diffusion reservoir systems

a) Diffusion matrix systems

These systems have remained largely experimental with few products having reached clinical stage so far. The design involves mixing drug particles with suitable thermoplastic polymers or cross-linked elastomeric material. When such a system comes into contact with water in tissue, drug is released at a rate inversely proportional to the square root of time.

b) Diffusional reservoir systems

These systems have found application in ocular, ,intrauterine and transdermal drug delivery, as briefly described below.

i) Controlled release ophthalmic preparations

Chronic open-angle glaucoma is an example of a condition in which daily administration of drug in form of pilocarpine eye drops can lead to patient non-compliance. Given the "symptomless" nature of the disease, poor compliance is understandable. Moreover, administration of pilocarpine in form of eye drops is associated with side effects such as miosis and myopia.

A therapeutic system for continuous delivery of pilocarpine has been developed. The system (OCUSERT®) consists of a pilocarpine core surrounded by two flexible biocompartible ethylene- vinyl acetate (EVA) co-polymer membranes. The system is capable of controlled (zero-order) release of pilocarpine (20mg/hr or 40mg/hr) for one week. It provides ocular hypotensive action without causing marked myopia or miosis.

ii) Controlled release intrauterine drug delivery

One problem with oral contraception products is non-compliance in taking them. Controlled drug release devices have therefore found application in delivery of contraceptive hormones. One such device (PROGESTASERT^R) delivers drug directly into the uterus. It consists of a reservoir containing 36mg of progesterone dispersed in silicone oil, and surrounded by polymeric rate-controlling EVA co-polymer membrane. The system continuously releases 65 µg of progesterone daily for one year. Delivery of hormone directly to the uterus decreases systemic side effects. Moreover, the system can easily be removed as required.

iii) Controlled Transdermal drug delivery

Transdermal drug delivery refers to delivery of drug across the skin for systemic effect. The main barrier to transdermal drug delivery is the stratum corneum. Thus, drug candidates for transdermal administration must have optimal lipophilicity characteristics to enable them cross the stratum corneum. In general, these drugs are also very potent (i.e, they produce desirable pharmacological effects at very low concentrations).

Advantages of transdermal drug delivery include ease of termination of drug input (if necessary) and avoidance of "first pass" metabolism associated with oral administration of some drugs. Some problems with transdermal drug delivery include possibility of allergic skin reactions and variable skin permeability. The following are examples of drugs which have been formulated for transdermal delivery.

Nitroglycerin

Nitroglycerin is used in control of pain associated with angina. It is ineffective when administered orally, due to extensive "first-pass" metabolism. Although it can be administered sublingually, rapid absorption via this route often leads to transient high concentrations in plasma leading to side effects such as headache. Moreover, repeated sublingual doses are needed since nitroglycerin is rapidly cleared from the body.

A controlled-release formulation of nitroglycerin (TRANSDERM NITRO^R) has been developed (other formulations are NITRO-DUR^R and NITRODISC^R). It is applied as a patch on the chest and provides continuous release of nitroglycerin for 24 hours. The main drawback with these controlled release devices is development of tolerance to nitroglycerin within a few days.

Hyoscine

Hyoscine is an effective agent for prevention of motion sickness. However, when administered orally or intramuscularly, side effects such as tachycardia, decreased saliva output and drowsiness are common. A controlled-release formulation for transdermal administration of hyoscine (TRANSDERM SCOP^R) is now available. It is applied as a patch behind the ear, and has

been used to control vomiting associated with space travel and radiation therapy.

Other drugs which have been formulated for transdermal administration include clonidine, nicotine (for those wishing to stop smoking) and oestradiol.

Systems based on osmosis

The so-called elementary osmotic pump is a prototype of drug delivery systems based on the principle of osmosis. These devices have been used for oral, rectal and subcutaneous drug delivery.

The elementary osmotic pump was originally developed by the Alza company, as the OROS^R delivery system. It consists of a biocompartible semi-permeable membrane surrounding a core consisting of drug and an osmotically active material. The resultant solution cannot diffuse through the semi-permeable membrane. A small laser-drilled hole in the membrane allows drug solution to be pumped out at a constant rate. The energy source is the osmotic pressure created in the device. An example of such a system is VOLMAX^R, a controlled release preparation for oral administration of salbutamol.

B — CHEMICAL DELIVERY SYSTEMS[11-19]

Delivery of some drugs involves chemical modification of a drug molecule to allow targeting to a specific anatomical site, or to overcome some barrier associated with conventional delivery. Such approaches are usually considered as "chemical delivery systems".

Much of the work in this area is still experimental and has been directed at delivering drug into brain. Examples are neurotransmitters, amino acids and antiviral agents. Other products are already in use in form of pro-drugs for administration via various routes. The reader should consult the above references for detailed reviews.

C — DELIVERY SYSTEMS BASED ON OTHER DESIGNS [20-22]

There are numerous other drug delivery systems which don't fall within the categories described above. For example, for oral drug administration, there are controlled drug delivery systems based on differentially coated drug pellets contained in a capsule, e.g some cold remedies. There are slow release oral or non-erodible cores. There are also slow release oral preparations based on the principle of microencapsulation.

For subcutaneous administration, there are controlled drug release devices formulated as biodegradable or non-biodegradable implants. An example of the latter is NORPLANT®, a contraceptive hormone implant consisting of six silicone-rubber tubes filled with levonorgesterel solution and surgically implanted under the skin. It provides contraception for 5 years.

Special carriers, e.g. liposomes, have also been used to target drug delivery to a particular site such as lungs and the reticuloendothelial system.

CONCLUSIONS

Novel drug delivery systems offer opportunities for treatment/control of disease conditions that cannot be adequately controlled using conventional dosage forms. These devices tend to be expensive and have not found much utility in Tropical medicine, but may be useful in future for example in delivery of some vaccines or drugs for treatment chronic diseases.

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