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Review Article

NOVEL DRUG DELIVERY SYSTEM

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In the treatment of a patient, the route of administration of drug plays a pivotal role in producing the therapeutic effect and the drug delivery system is the tool with which the extent and rate of drug administration can be controlled. Conventional Drug Delivery system met the needs, but when the requirement for continuous delivery of drugs at predictable and reproducible kinetics over an extended period of time in the circulation is needed, Novel Drug Delivery System comes into play. Oral controlled-release drug administration applies principle of osmotic and hydrodynamic pressure to control the release of drug in GIT. Hydrophilic contact lenses have emerged as a novel method in ocular drug delivery system to improve the therapeutic efficacy by sustaining the duration of intimate drug-eye contact. Transdermal drug delivery system aims to achieve the objective of systemic medication through topical application to the intact skin surface. Injectables and implantable drug delivery has revolutionized the parenteral drug delivery system. Bio-adhesive vaginal formulations that are capable of delivering the active agent for an extended period at a predictable rate. Novel Drug Delivery system carries the advantages of sustained delivery, improved tissue macrophage distribution, protection from physical and chemical degradation and increased bioavailability and pharmacological activity. The present review gives an overview of various novel approaches in drug delivery system.

Key Words: Novel drug delivery system, ocular drug delivery system, nasal drug delivery system, transdermal drug delivery system.

INTRODUCTION

Novel drug delivery systems are designed to achieve a continuous delivery of drugs at predictable and reproducible kinetics over an extended period of time in the circulation. The potential advantages of this concept include minimisation of drug related side effects due to controlled therapeutic blood levels instead of oscillating blood levels, improved patient compliance due to reduced frequency of dosing and the reduction of the total dose of drug administered. Hence, the combination of both sustained release and control release properties in a delivery system would further enhance therapeutic efficacy.

Novel drug delivery can be broadly classified as sustained release formulations and controlled release formulations. The term "sustained release" is known to have existed in the medical and pharmaceutical literature for many decades. It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and prolonged and its plasma profile is sustained in duration. The onset of its pharmacologic action is often delayed, and the duration of its therapeutic effect is sustained.

The term "controlled release," on the other hand,



has a meaning that goes beyond the scope of sustained drug action. It also implies a predictability and reproducibility in the drug release kinetics, which means that the release of drug ingredient(s) from a controlled-release drug delivery system proceeds at a rate profile that is not only predictable kinetically, but also reproducible from one unit to another.

Based on their technical sophistication controlled-release drug delivery systems that have recently been marketed or are under active development can be classified as:

- Rate-preprogrammed drug delivery systems
- Activation-modulated drug delivery systems
- Feedback-regulated drug delivery systems
- Site-targeting drug delivery systems

1. ORAL CONTROLLED-RELEASE DRUG ADMINISTRATION

Types of oral controlled-release drug administration:

1.1 Osmotic Pressure-Controlled Gastro-intestinal Delivery Systems

These are systems fabricated by encapsulating an osmotic drug core containing an osmotically active drug (or a combination of an osmotically inactive drug with an osmotically active salt, e.g., NaCl) within a semi-permeable membrane made from biocompatible polymer, e.g., cellulose acetate. A delivery orifice with a controlled

diameter is drilled, using a laser beam, through the coating membrane for controlling the release of drug solutes. This polymer membrane is not only semi-permeable in nature but is also rigid and capable of maintaining the structural integrity of the gastrointestinal delivery system during the course of drug release.

1.2 Hydrodynamic Pressure-Controlled Gastro- Intestinal Delivery System

In addition to osmotic pressure, hydrodynamic pressure is also a potential energy source for controlling the release of therapeutic agents. A hydrodynamic pressure-controlled gastrointestinal drug delivery system can be fabricated by enclosing a collapsible drug compartment inside a rigid shape-retaining housing. The space between the drug compartment and the external housing contains a laminate of swellable, hydrophilic cross-linked polymer, e.g., polyhydroxyalkyl methacrylate, which absorbs the gastrointestinal fluid through the annular openings in the bottom surface of the housing. This absorption causes the laminate to swell and expand which generates hydrodynamic pressure in the system and forces the drug compartment to reduce in volume and induce the delivery of a liquid drug formulation through the delivery orifice.

1.3 Gel Diffusion Controlled Gastrointestinal Delivery Systems

This type of gastrointestinal delivery system is fabricated from gel-forming polymers. It can be prepared by first dispersing the therapeutic dose



of a drug in layers of water-soluble carboxymethylcellulose (CMC), sandwiching the drug-loaded CMC layers between layers of cross-linked carboxymethylcellulose (which is water insoluble but water swellable) and then compressing these layers to form a multi-laminated device.

1.4 pH-Controlled Gastrointestinal Delivery Systems

This type of gastrointestinal delivery system is designed for the controlled release of acidic (or basic) drugs in the gastrointestinal tract at a rate independent of the variation in gastrointestinal pH. It is prepared by first blending an acidic (or basic) drug with one or more buffering agents, e.g., a primary, secondary, or tertiary salt of citric acid, granulating with appropriate pharmaceutical excipients to form small granules, and then coating the granules with a gastrointestinal fluid-permeable film-forming polymer, e.g., cellulose derivatives. The polymer coating controls the permeation of gastrointestinal fluid.

2. NASAL DRUG DELIVERY SYSTEM

Historically, nasal drug delivery has received intensive interest since ancient times. Therapy through intranasal administration has been an accepted form of treatment in the Ayurvedic system of Indian medicine. Psychotropic drugs and hallucinogens have been used in the form of snuff by Indians in South America. In more recent years many drugs have been shown to achieve a better systemic bioavailability by self-medication through the nasal route than by oral

administration. The systemic bioavailability by nasal delivery of some peptide and protein drugs with low nasal absorption has been improved by co-administering them with absorption promoters, enzyme inhibitors, and/or microspheres fabricated from bio-adhesive and bio-erodible polymers.

2.1 Physical and Chemical Parameters

The physical and chemical properties of a drug candidate should be evaluated before the development of nasal drug delivery system.

a) Effect of Molecular Size

It has been reported that nasal absorption falls off sharply for a drug molecule with a molecular weight of greater than 1000 Daltons; oral absorption declines even more steeply when the molecular weight goes beyond 400 Daltons.

b) Effect of Perfusion Rate

As the perfusion rate increases, the nasal absorption is first increased and then reaches a plateau level that is independent of the rate of perfusion.

2.2 Pharmacokinetics and Bioavailability

Factors that have been reported to affect the pharmacokinetics and bioavailability of drugs following intranasal administration include the following:

- Physiological factors:
 - Speed of mucus flow
 - Change in physiological state
 - Atmospheric conditions in the nasal cavity
- Dosage form factors:



- Physicochemical properties of the active drug
- Concentration of the active drug
- Physicochemical properties of the pharmaceutical excipients used
- Density, viscosity, and pH characteristics of the formulation
- Toxicity of the dosage form
- Administration factors:
 - Size of dose
 - Site of deposition
 - Mechanical loss posteriorly into the esophagus
 - Mechanical loss to other regions in the nose
- Mechanical loss anteriorly from the nose

2.3 Ex-Vivo Nasal Perfusion Model

During the perfusion studies a funnel is provided underneath the nose to lead the drug solution, which is flowing out of the nasal cavity, into the drug reservoir. The reservoir solution of a drug candidate to be evaluated is placed in the container, which is maintained at 37°C, and is circulated through the nasal cavity of the rat by means of a peristaltic pump. The perfusion solution passes out from the nostril and through the funnel and flows into the drug reservoir solution again. The reservoir is stirred constantly, and the amount of drug absorbed is then determined by measuring the drug concentration remaining in the solution after a period of perfusion. Because of the experimental

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conditions, the possible loss of drug activity due to physicochemical stability, such as the loss of peptides and proteins by proteolysis, aggregation, and other factors, must be considered.

3. OCULAR DRUG DELIVERY SYSTEM

Several types of dosage forms can be applied as the delivery systems for the ocular delivery of drugs. The most prescribed dosage form is the eye drop solution, for example, ocular decongestant eye drops and aqueous antiglaucoma pilocarpine solutions. The eye drop dosage form is easy to instill but suffers from the inherent drawback that the majority of the medication it contains is immediately diluted in the tear film as soon as the eye drop solution is instilled into the cul-de-sac and is rapidly drained away from the precorneal cavity by constant tear flow, a process that proceeds more intensively in inflamed than in the normal eyes, and lacrimal-nasal drainage. Therefore, only a very small fraction of the instilled dose is absorbed into the target tissues (e.g., 1.2% is available to the aqueous humor), and relatively concentrated solution is required for instillation to achieve an adequate level of therapeutic effect. The frequent periodic instillation of eye drops becomes necessary to maintain a continuous sustained level of medication.

3.1 Potential Development of Ocular Controlled Drug Delivery

Development of Epinephrine-Releasing Ocular Therapeutic Systems



Like pilocarpine, epinephrine is also recommended for the management of intraocular pressure. While pilocarpine is a parasympathomimetic drug that reduces intraocular pressure by increasing the facility of outflow of aqueous humor, epinephrine is a sympathomimetic drug that diminishes intraocular pressure by the dual actions of reducing the secretion of aqueous humor and increasing the facility of outflow. These two drugs are commonly used in separate eye drop solutions for controlling glaucoma, and sometimes they are used in combination for the same therapeutic purpose.

Hydrophilic Contact Lenses as Ophthalmic Drug Delivery Systems

As discussed in earlier sections, the therapeutic efficacy of an ophthalmically active drug can be greatly improved by sustaining the duration of intimate drug-eye contact. The drug-eye contact time can be substantially prolonged by the use of hydrophilic contact lenses.

4. TRANSDERMAL DRUG DELIVERY SYSTEM

These are devices in the form of adhesive patches of various shapes and sizes (5–20 cm²) which deliver the contained drug at a constant rate into systemic circulation via the stratum corneum. The drug (in solution or bound to a polymer) is held in a reservoir between an occlusive backing film and a rate controlling micropore membrane, the under surface of which is smeared with an adhesive impregnated with

priming dose of the drug. The adhesive layer is protected by another film that is to be peeled off just before application. The drug is delivered at the skin surface by diffusion for percutaneous absorption into circulation. The micropore membrane is such that rate of drug delivery to skin surface is less than the slowest rate of absorption from the skin. This offsets any variation in the rate of absorption according to the properties of different sites. As such, the drug is delivered at a constant and predictable rate irrespective of site of application. Usually chest, abdomen, upper arm, lower back, buttock or mastoid region are utilized.

5. PARENTERAL DRUG DELIVERY SYSTEMS

Parenteral drug delivery, especially intravenous injection, can gain easy access to the systemic circulation with complete drug absorption and therefore reach the site of drug action rapidly. Parenteral drug delivery via intramuscular or subcutaneous administration, although not as fast as intravenous injection, still achieves therapeutically effective drug levels rapidly if the drugs are administered in aqueous solution. Continuous intravenous infusion has been recognized as a superior mode of systemic drug delivery that can be tailored to maintain a constant and sustained drug level within a therapeutic concentration range for as long as required for effective treatment. It also provides a means of direct entry into the systemic circulation for drugs that are subjected to hepatic



first-pass metabolism and/or suspected of producing gastrointestinal incompatibility.

Types of parenteral delivery system:

5.1 Injectable Drug Delivery

• Approaches

Several pharmaceutical formulation approaches may be applied to the development of parenteral controlled-release or sustained-release formulations. The most commonly used techniques are as follows.

- Use of viscous, water-miscible vehicles, such as an aqueous solution of gelatin or polyvinylpyrrolidone.
- Utilization of water-immiscible vehicles, such as vegetable oils, plus water-repelling agent, such as aluminum monostearate.
- Formation of thixotropic suspensions.
- Preparation of water-insoluble drug derivatives, such as salts, complexes, and esters.
- Dispersion in polymeric microspheres or microcapsules such as lactide-glycolide homopolymers and co-polymers.
- Co-administration of vasoconstrictors.

5.2 Implantable Drug Delivery

Over the years a number of approaches have been developed to achieve the controlled administration of biologically active agents via implantation (or insertion) in tissues. These approaches are outlined as follows:

Controlled drug delivery by diffusion

process

- Polymer membrane permeation-controlled

drug delivery using

- Nonporous membranes
- Microporous membranes
- Semipermeable membranes

- Matrix diffusion-controlled drug delivery using

- Lipophilic polymers
- Hydrophilic (swellable) polymers
- Porous polymers

- Microreservoir partition-controlled drug delivery using

- Hydrophilic reservoir in lipophilic matrix
- Lipophilic reservoir in hydrophilic matrix

- Membrane-matrix hybrid-type drug delivery using

- Lipophilic membrane with hydrophilic matrix
- Hydrophilic membrane with lipophilic matrix

Controlled drug delivery by activation process

- Osmotic pressure-activated drug delivery
- Vapor pressure-activated drug delivery
- Magnetically activated drug delivery
- Phonophoresis-activated drug delivery
- Hydration-activated drug delivery
- Hydrolysis-activated drug delivery

Controlled drug delivery by feedback-regulated process

- Bioerosion-regulated drug delivery
- Bioresponsive drug delivery



6. Vaginal Drug Delivery Systems

Using the vagina as the route of administration for contraceptive steroids has several advantages. Among these the most practical is that a drug-releasing vaginal device allows insertion and removal by the user and provides continuous administration of an effective dose level, thus, ensuring better patient compliance.

6.1 Bio-adhesive delivery systems

Bio-adhesive vaginal formulations that are capable of delivering the active agent for an extended period at a predictable rate. Bio-adhesive formulations have been found to reduce the conventional treatment time of fungal infections by at least 25%. A bio-adhesive formulation might not necessarily contain a therapeutic agent and can be used as a moisturizer for the treatment of dry vagina. Tablets that are placed directly between the vaginal mucosal surfaces have been demonstrated to be excellent bio-adhesive formulations.

MERITS OF DRUG DELIVERY SYSTEM:

- Better treatment of many chronic illnesses. eg. Cancer, Asthma, Arthritis.
- Increased Bio- availability.
- Reduction in the occurrence and badness of untoward systemic side effects related to high blood plasma drug concentration.
- Sustenance of the total amount of drug administered over the period dose periods.

- Reduction in the total amount drug administered over the period of drug treatment which reduce occurrence of systemic and local side effects.
- Prevention from first pass metabolism and gastrointestinal tract degradation.
- Better patient compliance effect from the reduction in the number and frequency of doses needed to maintain the want therapeutic responses.
- Targeting the drug molecule towards the affected tissue or organ make smaller the toxicity to the normal tissues.
- Versatile and pH dependent system release the drug whenever the body demands.
- Biocompatibility.
- Fewer expenses are made from better disease management achieved with this system.

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