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## A Sequential Review on Intelligent Drug Delivery System

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### ABSTRACT:

Intelligent drug-delivery systems are described as novel technological innovations and clinical approaches to improve conventional treatments. These systems differ in methodology of therapeutic administration, intricacy, materials and patient compliance to address numerous clinical conditions that require various pharmacological therapies. Drug delivery systems (DDS) capable of releasing an active molecule at the appropriate site and at a rate that adjusts in response to the progression of the disease or to certain functions/biorhythms of the organism are particularly appealing. Biocompatible materials sensitive to certain physiological variables or external physicochemical stimuli (intelligent materials) can be used for achieving this aim. This new class of intelligent drug delivery includes pulsatile drug delivery, responsive delivery systems, systems utilizing enzymes and antibodies that are designed to perform various functions like detection, isolation and/or release of therapeutic agent for the treatment of diseased conditions. In pulsatile drug delivery system drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation etc. The most critical considerations for the design of these intelligent delivery systems include the controlled release, target specificity, on-demand dosage adjustment, mass transfer and stability of the pharmacological agents. Drug-delivery systems continue to be developed and enhanced to provide better and more sophisticated treatments, promising an improvement in quality of life and extension of life expectancy.

**KEYWORDS:** Intelligent drug delivery system, Biocompatible materials, In situ gel, Responsive systems, Microchips.

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### INTRODUCTION

The conventional manner of introducing drug to patient is inefficient and often leads to toxic side effects. The dramatic advance in controlled and targeted drug delivery systems over the past few decades has led to enormous expectations for the treatment of numerous complicated ailments with minimum side effects. One class of such systems is intelligent drug delivery systems. Intelligent drug delivery systems are capable of adjusting drug release rates in response to a physiological need. This system helps to maintain drug in therapeutic range with single, localized delivery of drug to particular compartments, preserve the medicament that is rapidly destroyed, and improve patient compliance.<sup>(1)</sup>

This new class of "intelligent therapeutics" refers to intelligent and responsive delivery systems that are designed to perform various functions like detection, isolation and/or release of therapeutic agent for the treatment of diseased conditions.<sup>(2)</sup> Intelligent drug delivery systems are mostly based on stimuli-responsive polymers which sense a change in a specific variable and activate the delivery; this phenomenon being reversible.<sup>(3)</sup> This review reports on recent

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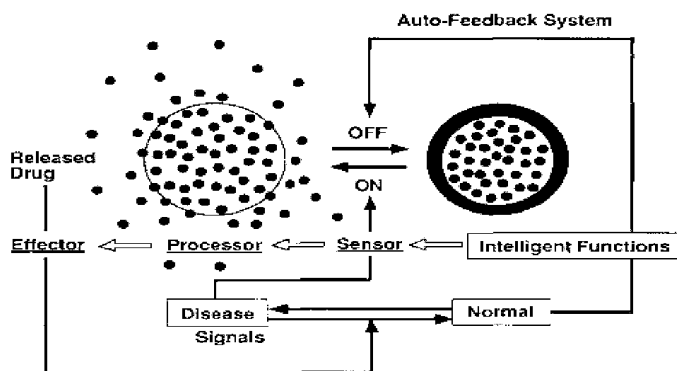
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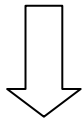
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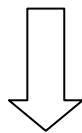
advances in the development of open-loop and closed-loop control systems based on stimuli-responsive polymers and their applications in the drug delivery field as pulsatile and self-regulated devices.<sup>(4)</sup>



It senses the signal caused by disease  
(SENSOR FUNCTION)



Judges the magnitude of signal  
(PROCESSOR FUNCTION)



Then act to release the drug in direct response  
(EFFECTOR FUNCTION)

Figure 1 Mechanism of Intelligent Drug Delivery System

### 1. Single Unit Capsular System

Single unit systems are mostly developed in capsule form. The lag time is continued by a plug, which gets pushed away by swelling or erosion, and the drug is released as a pulse from the insoluble capsule body.

**Pulsincap®** system is such a delivery in which a water insoluble body containing the drug formulation is closed with a swellable hydrogel and plugged (insoluble but permeable & swellable) at open end. Upon contact with, gastrointestinal fluid or dissolution medium the plug swells pushing itself out of the capsule after a lag time. For rapid release of water insoluble drug effervescent or disintegrating agents are added.

### 2. Pulsatile Delivery by Osmosis

This system consists of a capsule coated with a semi permeable membrane. Inside the capsule is an insoluble plug consisting of osmotically active agent and the drug formulation. This system shows good *in vivo* and *in vitro* correlation in humans.

**The Port® System** is a representative that consists of a gelatin capsule coated with a semi permeable membrane (e.g., cellulose acetate) housing an insoluble plug (e.g., lipidic) and an osmotically active agent along with the drug formulation.

#### Pulsatile Delivery by Solubilization (Erosion of Membrane)

These systems are based upon a drug reservoir surrounded with a soluble or erodible barrier layer that dissolves with time and the drug releases at once after the lag time.

**Time Clock®** system consists of solid dosage form coated with lipid barriers such as carnauba wax and beeswax along with surfactants like polyoxyethylene sorbitan monooleate represents such a delivery.

When this system comes in contact with the aqueous medium the coat emulsifies or erodes after the lag-time depending on the thickness of coat. The lag time of system is independent of the gastrointestinal motility, pH, enzyme and gastric residence.

### 3. Pulsatile Delivery by Rupture of Membrane

These systems are based upon a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents (or) swelling agent. Citric acid and sodium bicarbonate is incorporated as effervescent mixture in tablet core coated with ethyl cellulose.

When system comes in contact with water it produces carbon dioxide gas, which exerts pressure and after a lag time the membrane ruptures and rapid release of drug occurs.

A reservoir system with a semi permeable coating is proposed especially with drugs with high first pass effect in order to obtain *in vivo* drug pattern similar to the administration of several immediate release doses crosscarmellose sodium, sodium starch glycolate or low substituted hydroxyl propyl cellulose were used as swelling substances, which results in complete film rupture followed by rapid drug release. The lag time is controlled by composition of outer polymeric membrane

#### 4. Electrically Regulated Systems:

These systems exhibit drug release under the effect of an applied electric field due to action of an applied electric field on rate limiting membrane or directly on the solute thereby controlling its transport across the membrane.

Electric field-sensitive polyelectrolyte hydrogels have been developed for use in solute permeation control, artificial muscles and actuators utilizing their swelling-deswelling behavior.

#### 5. Photoresponsive Systems:

Photoresponsive gels change their physical or chemical characteristics reversibly upon exposure to photoradiation.

A photoresponsive polymer consists of a photoreceptor usually a photochromic chromophore and a functional part. The photochromic molecules capture the optical signal and subsequent isomerisation of the chromophores in the photoreceptors converts it to a chemical signal.

Phase transition in polymer gels is induced by visible light and the mechanism proposed was direct heading to the network polymer response to the light.

#### 6. Ultrasonically Modulated Systems:

The feasibility of ultrasonic-controlled polymeric delivery systems in which release rates of substances can be repeatedly modulated externally.

Both Non-erodible as well as Bio-erodible polymers can be used for the preparation of drug carrier matrices.

The bioerodible polymers: polylactide, polyglycolide, poly(bis(p-carboxyphenoxy)alkane anhydrides and their copolymers with sebacic acid.

The bioactives used:- p- aminohippurate, p-nitroaniline, insulin and bovine serum albumin.

On exposure to ultrasound an enhanced polymer erosion and drug release occurs. The response of system to the ultrasonic triggering is rapid (within 2 min) and reversible in nature.

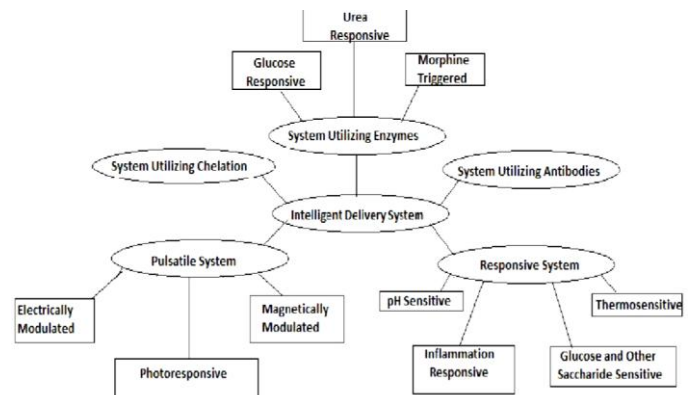
#### 7. Magnetically Modulated Systems:

This approach involves incorporation of magnetic beads in elastic polymers. It has been shown that when oscillating magnetic field is applied, more drug will be released.

Insulin and other macromolecular bioactives can be continuously released by embedding them in a carrier like ethylene vinyl acetate copolymer (EVAc).

Another system utilizing EVAc-protein matrices containing magnetic beads exhibit enhanced releases rates when placed in oscillating magnetic field.

#### Classification of intelligent drug delivery system



#### RESPONSIVE SYSTEMS:

- ✓ pH Sensitive Systems
- ✓ Thermo-responsive Systems
- ✓ Inflammation Responsive Systems
- ✓ Glucose and Other Saccharide Sensitive Systems
- ✓ Ionic Cross - linking In Situ Gelling System
- ✓ Enzymatic Cross - linking In Situ Gelling System

#### SYSTEMS UTILIZING ENZYMES:

Urea Responsive Delivery Systems  
 Glucose Responsive Insulin Delivery  
 Morphine Triggered Naltrexone Delivery System

#### SYSTEMS UTILIZING ANTIBODY INTERACTIONS:

This approach has proposed antibody mediated release of contraceptive agent.

The  $\beta$  subunit of Human Chronic Gonadotropin (HCG) is grafted on to the surface of the polymer, which in turn is exposed to antibodies to  $\beta$ -HCG. The appearance of HCG in the blood (indication of pregnancy) will cause release of contraceptive drug as HCG competes for the polymer bound antibodies to HCG and initiates the drug release.

Another reversible antibody system for controlled release of Ethinyl Estradiol (EE):- EE stimulates biosynthesis of sex hormone binding globulin (SHBG). It has been observed that high serum levels of EE stimulates the production of SHBG, which increases the concentration of SHBG attached to the polymer surface and reduces the EE release rate.

**SYSTEMS UTILIZING CHELATION:**

These include some antibodies vis-à-vis chelates used for treatment of metal poisoning.

The concept is based on the property of metals to accelerate the hydrolysis of carboxylate or phosphate esters and amides.

Tagging of the chelator to a polymer chain by a covalent ester or amide link prevents its premature loss by excretion and reduces its toxic effects.

In the presence of specific ion, the bound chelating agent forms a complex followed by metal accelerated hydrolysis and subsequent elimination of the metal chelate.

**TAILOR - MADE MEDICINE:**

Scientific achievements have had an immeasurable influence on the uses of innovative biopharmaceuticals and methods in medicine. These breakthrough discoveries have contributed to an irreversible change in the perception and use of diagnostics in contemporary treatment of many illnesses.

Today, in addition to the well-established types of physical and chemical examination and our growing understanding of biochemical processes occurring in the body, we now have at our fingertips state-of-the-art diagnostics and therapies based on the molecular pathomechanisms of illnesses.

A gradual change is occurring in the treatment strategies that have been used for years, based on the format: specific pathogenic factor pathogenesis illness.

Although the discovery of specific pathogens revolutionized medicine in the 19th and 20th centuries, making it possible to create pharmaceuticals essential to treat certain illnesses, generally improve health, or extend patients' lives, nowadays more attention is being paid to the lower than expected success of those medications. Their efficacy tends to fall between 25–62%. Such variation may result from different, difficult to predict responses to the same therapy within a population of patients with the same illness, hence in cases that are seemingly the same.

**MICROFABRICATED DRUG DELIVERY SYSTEMS:**

Microelectronic devices have become integral part of our lives. They are present in our automobiles, cellular phones and computers. Here we discuss application of microfabrication technologies to the development of devices for the controlled release of drugs. Possible applications include micromachined silicon membranes to create implantable biocapsules for the immune isolation of pancreatic islet cells as a possible treatment for diabetes and sustained release of injectable drugs needed over long time periods. The use of micro technology to tailor the size, shape, reservoir number,

reservoir volume, unidirectional openings and surface characteristics of the drug delivery vehicle in conjunction with appropriate surface chemistry is potentially influential in the area of controlled release. The development of microneedles for transdermal drug delivery came about as an approach to enhance the poor permeability of the skin by creating microscale conduits for transport across the stratum corneum. To fabricate microneedles, a deep reactive ion etching process is commonly used. In this process, a chromium masking material is deposited on to silicon wafers and patterned into dots that have a diameter approximately equal to that of the base of the desired needles. When placed in the reactive ion etcher, the wafers are exposed to carefully controlled plasma off fluorine and oxygen, which causes a deep vertical, etch and slight lateral under etching. The regions on the wafer that are protected by chromium remain and eventually form the microneedles. Etching is allowed to proceed until the masks are undercut and fall off, leaving behind an array of silicon spikes.

**RECENT ADVANCES:****INSULIN PUMP:**

The ultimate goal of insulin treatment in diabetes mellitus is to control the blood glucose level and prevent or stabilize long - term diabetic complications.

Administration of insulin through subcutaneous injection is currently the major therapy of diabetes. Two or three injections are required a day to maintain the normal blood glucose level. Because this method is burdensome and invasive to living organisms, the patient's situation would not be good regarding the quality of life.

Therefore, An insulin pump constructed with polymer materials has been studied. Wang developed an insulin reservoir consisting of silicone rubber, which releases insulin stored inside by generation of a pressure gradient by compression.

Segmented polyurethane (SPU) can be used as an elastic material for preparation of the insulin reservoir. For enhancement of insulin permeability and biocompatibility, a novel copolymer composed of 2-methacryloyloxyethyl phosphorylcholine (MPC) and 2-EthylHexyl Methacrylate (EHMA) can be designed. Addition of the MPC polymer to other polymers enhances the biocompatibility to the original polymer.

Two main mechanisms are generally involved in under delivery events: insulin aggregation in the pump insulin pathway and

catheter occlusions. Moreover, these aggregates, which are likely to be generated by hydrophobic interactions with the pump circuits, seem to promote an increased production of anti -insulin antibodies in many patients treated by implantable pumps. Concomitant improvements of catheter design also contributed to the reduction of under delivery. Despite these problems, implantable pumps currently provide the most effective and physiological insulin delivery.

#### GLUCO WATCH:

GlucoWatch™ biographer is non-invasive, watchlike device that measures glucose. A plastic part of Gluco watch that snaps into the biographer and sticks to the skin. Automatic reading every 10 min up to 13 hrs is taken by it.

Gluco watch presently takes the lead among user-friendly techniques aimed at glucose monitoring. This system is based upon the principle of reverse iontophoresis.

A low electric current pulls glucose through the skin. Glucose is accumulated in two gel collection discs in the auto sensor. Another electrode in the auto sensor measures the glucose. A signal in proportion to interstitial glucose level can thus be generated.

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