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R E V I E W A R T I C L E

Review on Activation of Modulated drug delivery systems

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A B S T R A C T

The number of controlled release drug delivery systems have been developed for various routes of administration. Controlled release drug delivery directly targeted to the organ and tissue. The present review describes that activation of modulated drug delivery systems. In modulated drug delivery systems drug release controlled by physical, chemical or biochemical process or facilitated by the energy supplied externally. In this system drug delivery achieved by based different physic chemical properties like magnetically, osmotically, enzymatic and activation of vapour pressure, nanoparticles etc. The review mainly discussed on the classification and concepts are explained about the various types of modulated drug delivery systems.

Keywords: Controlled release, Modulated drug delivery, energy, magnetically, vapour pressure

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

The science of controlled release was first originated from the development of oral sustained release products in the 1940s and early 1950s [1]. First of all, the controlled release of marine antifoul ants (the 1950s) and controlled release of fertilizer (1970s) were formulated which had only a single application in the soul science [2]. The development of the pharmacology and pharmacokinetics demonstrated the importance of drug release rate in determining therapeutic effectiveness of therapy. This becomes the reason behind the development of controlled release[1, 3]. A number of advancements have been made recently in the development of new techniques for drug delivery. These techniques are capable of regulating the rate of drug delivery, sustaining the duration of therapeutic action, and/or targeting the delivery of drug to a specific tissue [4,5] These advancements have already led to the development of several novel drug delivery systems that could provide one or more of the following benefits:

- Maintenance of drug concentration within an optimal therapeutic range for prolonged duration of treatment.
- Maximization of efficacy-dose relationship.

- ❖ Reduction of adverse side effects.
- ❖ Minimization of the needs for frequent dose intake.
- ❖ Enhancement of patient compliance.
- ❖ Controlled administration of a therapeutic dose at a desirable rate of delivery.

Based on the technical sophistication of the controlled-release drug delivery systems (CrDDSs) that have been marketed so far, or that are under active development, the CrDDSs can be classified as follows:

1. Rate-preprogrammed drug delivery systems.
2. Activation-modulated drug delivery systems.
3. Feedback-regulated drug delivery systems.
4. Site-targeting drug delivery systems.

2. Different Drug Delivery Systems

Activation of modulated drug delivery system

In this group of CrDDSs, the release of drug molecules from the delivery systems is activated by some physical, chemical, or biochemical processes and/or facilitated by an energy supplied externally. The rate of drug release is then controlled by regulating the process applied or energy input. Based on the nature of the process applied or the type of energy used [6,7].

The activation-modulated CrDDSs can be classified into the following categories:

1. Physical mean

a. Osmotic pressure activated drug delivery system.
b. Hydrodynamic pressure activated drug delivery system
c. Vapor pressure activated drug delivery system
d. Mechanically activated drug delivery system
e. Magnetically activated drug delivery system
f. Sonophoresis activated drug delivery system
g. Ionotrophoresis activated drug delivery system
h. Hydration activated drug delivery system

2. Chemical means

a. pH activated drug delivery system.
b. Ion exchange drug delivery system.
c. Hydrolysis activated drug delivery system.

3. Biochemical means

a. Enzyme activated drug delivery system.
b. Biochemical activated drug delivery system

Several CrDDSs have been successfully developed and applied clinically to the controlled delivery of pharmaceuticals and biopharmaceuticals. These are outlined and discussed below.

Osmotic Pressure-Activated Drug Delivery System

In this type of CrDDSs, the drug reservoir, which can be either a solution or a solid formulation, is contained within a semipermeable housing with controlled water permeability. The drug in solution is released through a special laser-drilled delivery orifice at a constant rate under a controlled gradient of osmotic pressure [8]. For a solution-type osmotic pressure-activated CrDDS, the intrinsic rate of drug delivery (V/t) is defined by:

$$dV/dt = A\ \theta\ \Delta\pi/l \ldots\ldots (1)$$

Where,

dV/dt = the water flow across the membrane area A and thickness l with permeability θ

Δπ = the difference in osmotic pressure between the two solutions on either side of the membrane.

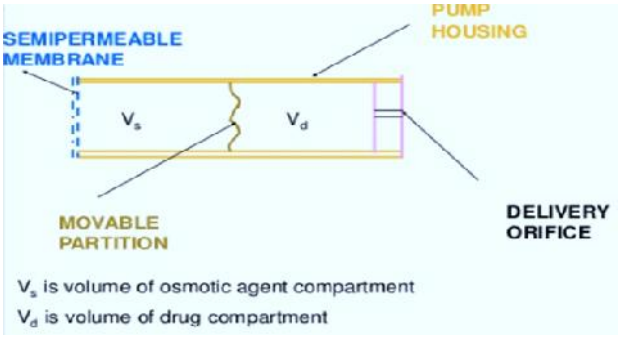

Fig 1: Schematic representation of Osmotic Pressure-Activated Drug Delivery Systems

Hydrodynamic Pressure-Activated Drug Delivery Systems: In addition to the osmotic pressure systems discussed above, hydrodynamic pressure has also been explored as the potential source of energy to modulate the delivery of therapeutic agents. A hydrodynamic pressure-activated drug-delivery system can be fabricated by placing a liquid drug formulation inside a collapsible, impermeable container to form a drug reservoir compartment. This is then contained inside a rigid, shape-retaining housing. A laminate of an absorbent layer and a swellable, hydrophilic polymer layer is sandwiched between the drug reservoir compartment and the housing. In the gastrointestinal tract, the laminate will imbibe the gastrointestinal fluid through the annular openings at the lower end of the housing and become swollen. This generates a hydrodynamic pressure in the system. The hydrodynamic pressure, thus created, forces the drug reservoir compartment to reduce in volume and causes the liquid drug formulation to release through the delivery orifice [9].

The drug release rate is defined by:

$$\frac{Q}{t} = \frac{P_f A_m}{h_m}(\theta_s - \theta_e)$$

Where,

Pf, A_m, and h_m are the fluid permeability, the effective surface area, and the thickness of the wall with annular openings, respectively; and θs- θe is the difference in hydrodynamic pressure between the drug delivery system (θs) and the environment (θe). The release of drug molecules from this type of CrDDS is activated by hydrodynamic pressure and controlled at a rate determined by the fluid permeability and effective surface area of the wall with annular openings as well as by the hydrodynamic pressure gradient.

Vapor Pressure-Activated Drug Delivery Systems

In this type of CrDDS, the drug reservoir, which is a solution formulation, is contained inside the infusion compartment. It is physically separated from the pumping compartment by a freely movable partition. The pumping compartment contains a vaporizable fluid, such as

fluorocarbon, which vaporizes at body temperature and creates a vapor pressure. Under the vapor pressure created, the partition moves upward and forces the drug solution in the infusion compartment to be delivered, through a series of flow regulator and delivery cannula, into the blood circulation at a constant flow rate. The process is defined by:

$$\frac{Q}{t} = \frac{d^4 \delta P}{40.74 \mu l}$$

Where,
d and l are, respectively, the inner diameter and the length of the delivery cannula;
Dp is the pressure difference between the vapor pressure in the pumping compartment and the pressure at the implantation site; and m is the viscosity of the drug formulation. The delivery of drug from this type of CrDDS is activated by vapor pressure and controlled at a rate determined by the differential vapor pressure, the formulation viscosity, and the size of the delivery cannula.
A typical example is the development of Infusaid, an implantable infusion pump by Metal Bellows, for the constant infusion of heparin in anticoagulation treatment, of insulin in the normoglycermic control of diabetics, and of morphine for patients suffering from the intensive pain of a terminal cancer.

Mechanical Force-Activated Drug Delivery Systems

In this type of CrDDS, the drug reservoir is a solution formulation in a container equipped with a mechanically activated pumping system. A metered dose of drug formulation can be reproducibly delivered into a body cavity, such as the nose, through the spray head upon manual activation of the drug-delivery pumping system. The volume of solution delivered is fixed and is independent of the force and duration of activation. A typical example of this type of drug-delivery system is the development of a metered-dose nebulizer for the intranasal administration of a precision dose of luteinizing hormone-releasing hormone (LHRH) and its synthetic analogs, such as buserelin [9,10]. Through nasal absorption, the hepatic first-pass elimination of these peptide drugs is thus avoided.

Magnetic-Activated Drug Delivery Systems

Macromolecular drugs, such as peptides, have been known to release only at a relatively low rate from a polymer-controlled drug-delivery system. This low rate of release can be improved by incorporating an electromagnetism-triggering vibration mechanism into the polymeric delivery device. With a hemispheric-shaped design, a zero-order drug-release profile is achieved. By combining these two approaches, a subdermally implantable, magnetic-activated hemispheric drugdelivery device is developed [11]. It is fabricated by first positioning a tiny doughnut-shaped magnet at the center of a drug-dispersing biocompatible polymer matrix and then coating the external surface of the medicated polymer matrix, with the exception of one cavity at the center of the flat surface, with a pure polymer, for instance, ethylene–vinyl acetate copolymer or siliconeelastomers. This uncoated cavity is designed for allowing a peptide drug to release. The hemispheric magnetic delivery device produced can release macromolecular drugs, like bovine serum albumin, at a low basal rate, by diffusion process, and under a non-triggering condition, or it can release the same drug at a much higher rate, when the magnetic activated, to vibrate by an external electromagnetic field.

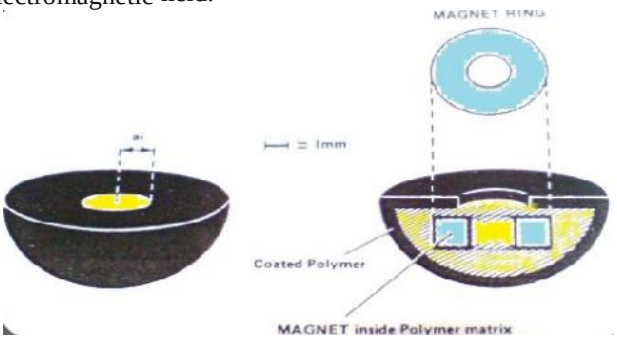

Fig 2: Magnetically activated drug delivery

Sonophoresis-Activated Drug Delivery Systems

This type of activation-controlled drug delivery system utilizes ultrasonic energy to activate (or trigger) the delivery of drugs from a polymeric drug delivery device. The system can be fabricated from either a non-degradable polymer, such as ethylene–vinyl acetate copolymer, or a bioerodible polymer, such as poly [bis(p-carboxy phenoxy) alkane anhydride].The potential application of sonophoresis (or phonophoresis) to regulate the delivery of drugs was recently reviewed.

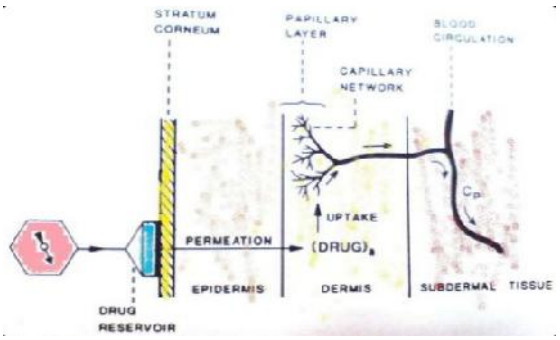

Fig 3: Sonophoresis-Activated Drug Delivery Systems

Iontophoresis-Activated Drug Delivery Systems

This type of CrDDS use electrical current to activate and to modulate the diffusion of a charged drug molecule across a biological membrane, such as the skin, in a manner similar to passive diffusion under a concentration gradient but at a much facilitated rate [12]. The iontophoresis-facilitated skin permeation rate of a charged molecule it consists of three components and is expressed by:

$$J_i^{isp} = J^p + J^e + J^c = \left(K_s D_s \frac{dC}{h_s}\right) \left(\frac{Z_i D_i F_i}{RT} C_i \frac{dE}{h_s}\right) + (kC_s I_d)$$

Where,
J p, J e, and J c represent, respectively, the flux for the skin permeation by passive diffusion, for the electrical current-driven permeation, and for the convective flow-driven skin permeation; Ks is the partition coefficient for interfacial

partitioning from the donor solution to the stratum comeum; Ds and Di are, respectively, the diffusivity across the skin and the diffusivity of ionic species i in the skin; Ci and Cs are, respectively, the donor concentration of ionic species i and the concentration in the skin tissue; dE/hs is the electrical potential gradient across the skin; dC/hs is the concentration gradient across the skin; Zi is the electrical valence of ionic species i; Id is thecurrent density applied; F, k, and Rare, respectively, the faraday, proportionality, and gas constant; and T is the absolute temperature. A typical example of this type of activation controlled CrDDS is the development of an iontophoretic drug delivery system, named Phoresor by Motion Control, to facilitate the percutaneous penetration of antiinflammatory drugs, such as dexamethasone sodium phosphate, to surface tissues. Further development of the iontophoresis-activated drug delivery technique has yielded a new design of iontophoretic drug delivery system—the transdermal periodic iontotherapeutic system (TPIS). This new system, which is capable of delivering a physiologically acceptable pulsed direct current, in a periodic manner, with a special combination of waveform, intensity, frequency, and on/off ratio, for a specific duration, has significantly improved the efficiency of transdermal delivery of peptide and protein drugs [13,14]. A typical example is the iontophoretic transdermal delivery of insulin, a protein drug, in the control of hyperglycemia in diabetic animals.

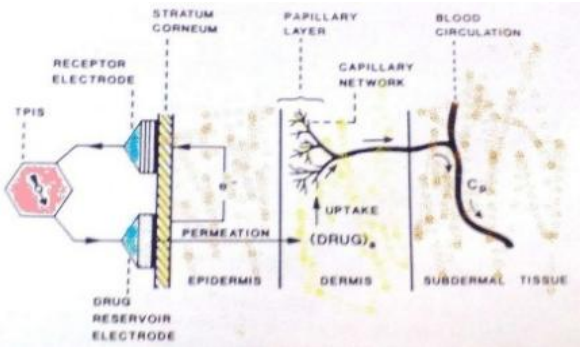

Fig 4: Iontophoresis-Activated Drug Delivery Systems

Hydration-Activated Drug Delivery Systems

In this type of CrDDS, the drug reservoir is homogeneously dispersed in a swellable polymer matrix fabricated from a hydrophilic polymer. The release of drug is activated and modulated by hydration-induced swelling of the polymer matrix [15]. Representatives of this type of CrDDS are outlined below.

Syncro-Male-B implant: This subcutaneous CrDDS is fabricated by dissolving norgestomet, a potent progestin for estrus synchronization, in an alcoholic solution of linear ethylene glycol methacrylate polymer (Hydron S). The drugpolymer mixture is then cross-linked by adding ethylene dimethacrylate, in the presence of an oxidizing catalyst, to form a cylinder-shaped subdermally implantable implant. This tiny subdermal implant can be activated by tissue fluid to swell and can be engineered to deliver norgestomet, at a rate of 504mg/cm2/day1/2, in the subcutaneous tissue for up to 16 days for the control and synchronization of estrus in livestock.

Val releasetablet: This oral CrDDS is prepared by granulating Valium, an antidepression drug, with hydrocolloids (20–75 wt%) and pharmaceutical excipients. The granules are then compressed to form an oral tablet. After oral intake, the hydrocolloids absorb the gastric fluid and are activated to form a colloid gel matrix surrounding the tablet surface. The release of Valium moleculesis then controlled by diffusion through the gel barrier, while the tablet remains buoyant in the stomach, due to a density difference between the gastric fluid (d > 1) and the gelling tablet (d < 1).

pH-Activated Drug Delivery Systems

For a drug labile to gastric fluid or irritating to gastric mucosa, this type of CrDDS has been developed to target the delivery of the drug only in the intestinal tract, not in the stomach. It is fabricated by coating a core tablet ofthe gastric fluid-sensitive drug with a combination of intestinal fluid-insoluble polymer, like ethyl cellulose, and intestinal fluid-soluble polymer, like hydroxylmethyl cellulose phthalate. In the stomach, the coating membrane resists the degrading action of gastric fluid (pH <3), and the drug molecules are thus protected from the acidic degradation. After gastric emptying, the CrDDS travels to the smallintestine, and the intestinal fluid-soluble component in the coating membrane is dissolved away by the intestinal fluid (pH >7.5). This produces a microporous membrane of intestinal fluid-insoluble polymer to control the release of drug from the core tablet [16]. The drug is thus delivered in a controlled manner in the intestine by a combination of drug dissolution in the core and diffusion through the pore channels. By adjusting the ratio of the intestinal fluid-soluble polymer to the intestinal fluid-insoluble polymer in the membrane, the rate of drug delivery can be regulated. Representative application of this type of CrDDS is in the oral controlled delivery of potassium chloride, which is highly irritating to gastric epithelium.

Ion-Activated Drug Delivery Systems

For controlling the delivery of an ionic or an ionizable drug, this type of CrDDS has been developed. Because the gastrointestinal fluid has regularly maintained a relatively constant level of ions, the delivery of drug by this type of CrDDS can be modulated, theoretically, at a constant rate. Such a CrDDS is prepared by first complexing an ionizable drug with an ion-exchange resin, such as complexing a cationic drug with a resin containing SO_3 group or an anionic drug with a resin containing $N(CH_3)3þ$ group. The granules of the drug–resin complex are further treated with an impregnating agent, like polyethylene glycol 4000, for reducing the rate of swelling upon contact with an aqueous medium. They are then coated by an air-suspension coating technique with a water-insoluble but water-permeable polymeric membrane, such as ethylcellulose. This membrane serves as a rate-controlling barrier to modulate the release of drug from the CrDDS [17]. In the GI tract, hydronium and chloride ions diffuse into the CrDDS and interact with the drug–resin complex to trigger the dissociation and release of ionic drug. This type of CrDDS is exemplified by the development of Pennkinetic system (by Pennwalt Pharmaceuticals), which permits the formulation of oral liquid-type dosage forms with sustained

release of a combination of hydrocodone, chlorpheniramine (Tussionex).

Hydrolysis-Activated Drug Delivery Systems

This type of CrDDS depends on the hydrolysis process to activate the release of drug molecules. In this system, the drug reservoir is either encapsulated in microcapsules or homogeneously dispersed in microspheres or nanoparticles. It can also be fabricated as an implantable device. All these systems are prepared from a bioerodible or biodegradable polymer, such as polylactide, poly (lactide–glycolide) copolymer, poly (orthoester), or poly(anhydride). The release of a drug from the polymer matrix is activated by the hydrolysis induced degradation of polymer chains, and the rate of drug delivery is controlled by polymer degradation rate. A typical example is the development of Lupron Depot, injectable microspheres for the subcutaneous controlled delivery of luprolide, a potent biosynthetic analog of gonadotropin-releasing hormone (GnRH) for the treatment of gonadotropin-dependent cancers, such as prostate carcinomainmenandendometriosis in the females, for up to 4 months [19]. Another example is the development of Zoladex system, an implantable cylinder for the subcutaneous controlled delivery of goserelin, also a potent biosynthetic analog of GnRH for the treatment of patients with prostate cancer for up to 3 months [20].

Enzyme-Activated Drug Delivery Systems

In this type of CrDDS, the drug reservoir is either physically entrapped in microspheres or chemically bound to polymer chains fabricated from biopolymers, such as albumins or polypeptides. The release of drugs is made possible by the enzymatic hydrolysis of biopolymers by a specific enzyme in the target tissue. A typical example is the development of albumin microspheres, which release 5-fluorouracil, in a controlled manner, by protease-activated biodegradation [21].

3. Conclusion

The present review concluded that brief outline and concepts of activation modulated drug delivery systems. This system mainly used to preparation of chemotherapic drugs, and these are directly targeted to the site of tumors in organ or tissue. There is a growing belief that many more of the conventional drug delivery systems we have been using for decades will be gradually replaced in the coming years by these CrDDSs.

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