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Alternate Drug Delivery System: Recent Advancement and Future Challenges

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For many decades treatment of an acute diseases or illness has been mostly accomplished by delivery of drugs to the patients by various conventional delivery systems. The drug delivery method is chosen based upon the physiological properties of drug, the desired site of action, the biological barrier including drug metabolism that must be overcome to deliver the drug. The most common conventional method to delivery is oral, parentral, transdermal, ophthalmic, nasal, rectal and anal. Three areas of potential challenges accounts in the exploration of alternate controlled release drug administration which are development of system which can be capable of delivering the drug at a therapeutically effective rate to a desired site for duration required for optimal treatment, modulation of gastrointestinal transit time and minimization of hepatic first pass elimination.

Alternate drug delivery systems are continuously being developed as many of the new drugs have low solubility and degradation against enzymatic acid catalyzed breakdown in the human body. Alternate drug delivery systems are the means of enhancing the therapeutic benefit of drug controlling the pharmacokinetics, pharmacodynamics, non specific toxicity immunogenicity and efficacy. Based on their technical sophistication Alternate drug delivery system can be classified as Rate preprogrammed, Activation modulated, Feedback regulated, Carrier based drug delivery system. There are many future challenges to be met like, technologies for self-assembly, virus-like systems for intracellular delivery, carriers for tissue engineering, cell and gene targeting systems, better disease markers in terms of sensitivity and specificity.

Key Words: Rate preprogrammed, Activation modulated, Feedback regulated, Electroporation

INTRODUCTION

For many decades treatment of an acute diseases or illness has been mostly accomplished by delivery of drugs to the patients by various conventional delivery system which is known to provide a prompt release of drugs, to achieve as well as maintain drug concentration within the therapeutic effective range, it is often necessary to take several times a day which result in significant fluctuation in drug level. [1] The therapeutic nature of the drugs dictates the methods of administration, for e.g. oral drug delivery may be the most logical choice for gastrointestinal disease. If the drug release is systemic then the choice of method often relies on the physiological and the therapeutic properties of the drug molecules. Transdermal drug delivery although having the advantages of being non invasive, it has to meet several criteria such as high potency, ready permeability through stratum cornea and non irritation. [2]

The drug delivery method is chosen based upon the physiochemical properties of drug, the desired site of action, the biological barrier including drug metabolism that must be overcome to deliver the drug. The most common conventional method of delivery are oral, parentral, transdermal, ophthalmic, nasal, rectal and anal each delivery route involves special challenges and requirements for proper and safe administration of drugs.

Recently several technical advancements have been made which resulted in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, and or targeting the delivery of drug to tissues. [3]

In the exploration of alternate controlled release drug administration one accounts three areas of potential challenges, a) Development of system which can be capable of delivering the drug at a therapeutically effective rate to a desired site for duration required for optimal treatment, b) Modulation of gastrointestinal transit time, c) Minimization of hepatic first pass elimination.

Alternate drug delivery systems are continuously being developed as many of the new drugs have low solubility and degradation against enzymatic acid catalyzed breakdown in the human body. Due to the recent advancement in biotechnology increasing number of drugs are based on bio molecules such as peptides, proteins, oligonucleotides and DNA which often shows low bioavailability and low membrane permeability requiring

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improved method for delivery of these drugs. Improvement in the delivery method for peptides, proteins are necessary as they may continue to be developed as drug. The efficacy of medicament can have an immense effect by the method by which it is delivered. Alternate drug delivery systems are the means of enhancing the therapeutic benefit of drug controlling the pharmacokinetics, pharmacodynamics, non specific toxicity immunogenicity and efficacy. These new strategies often called 'drug delivery systems' which are based on interdisciplinary approaches that combine polymer science, pharmaceutical bi-conjugate chemistry and molecular biology. [4]

Alternate drug delivery system may have highly desirable attributes and improved utilities like: [5]

- Targeting delivery to specific tissues
- Improved safety and efficacy
- Decreased in frequency of dosing and the amount of drug needed.
- Reduction of toxicity
- Eliminating or reducing pain related administration.
- Improved patient compliances.

Based on their technical sophistication alternate drug delivery system can be classified as:

1) Rate pre-programmed drug delivery system
2) Activation modulated drug delivery system
3) Feedback regulated drug delivery system
4) Carrier based drug delivery system

RATE PRE PROGRAMMED DRUG DELIVERY SYSTEM

Rate pre programmed drug delivery system accomplished by system design which controls the molecular diffusion of drug molecules in and or across the barrier medium within or surrounding the delivery system.

Polymer membrane permeation controlled drug delivery system:

In this system drug is partially or totally encapsulated within a drug reservoir compartment. This is covered by the rate controlling polymeric membrane having a specific permeability. Several potential development are feasible with membrane permeation process as microporous membrane permeation controlled gastrointestinal delivery device, gastric fluid resistance intestinal targeted controlled release gastrointestinal device and gel diffusion controlled drug delivery system.

e.g. Progestart IU – An intrauterine device engineered to deliver progesterone continuously for one year.

Norplant sub-dermal implants – An implant designed to release levonorgesterol continuously for seven days. [6]

Occusert system – It delivers pilocarpin continuously for seven days.

Transderm Nitro – It delivers nitroglycerine transdermally for providing daily relief of angina attack. [7]

Estraderm – It is engineered to deliver estradiol transdermally for 3-4 days. [8]

Catapress TTS – It controls the permeation of clonidine for seven days. [9]

Polymer matrix diffusion controlled drug delivery system:

It is prepared by homogeneously dispersing drug particles in a rate controlling polymer matrix. e.g. NitroDur - Designed for application onto intact skin for 24 hrs to provide continues transdermal infusion of nitroglycerine. [10] The recent developments are intragastric floating gastrointestinal drug delivery system, inflatable gastrointestinal drug delivery system and intralumen controlled release drug delivery system.

Microreservoir partitioned controlled drug delivery system:

It is designed by microdispersion of aqueous suspension of drug using high energy dispersion techniques in a biocompatible polymer. e.g. Nitrodisc system – Engineered to deliver transdermal administration of nitroglycerine. Syncromate implant – Engineered to deliver subdermal administration of norgestomet. [11]

ACTIVATION MODULATED DRUG DELIVERY SYSTEM

This type of delivery system can be achieved by physical means, chemical means and biochemical means.

PHYSICAL MEANS

Osmotic pressure activated drug delivery system: These systems are fabricated by encapsulating an osmotic drug core containing an osmotically active drug within a semi-permeable membrane made from biocompatible polymers. A delivery orifice with a controlled diameter is drilled using a laser beam, through the coating membrane for controlling the release the of drug molecules. [12]

e.g. Acutrim tablet – Designed to deliver phenylpropanolamine over a duration of 16 hrs,

Alzet pumps – Which may be implanted or inserted pump.

Hydrodynamic pressure controlled drug delivery system:

This 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 contain a laminates of swellable hydrophilic crosslinked polymer, which absorb the gastrointestinal fluid through the annual opening in the bottom surface of the housing. This absorbance causes the laminate to swell and expand which generates hydrodynamic pressure into the system and force the drug compartment to reduce in volume and induce the delivery of a lipid drug formulation through the delivery orifice. [13]

Vapour pressure activated drug delivery system:

This system engineered where the drug release is activated by vapor pressure. e.g. An implantable infusion pump (Infusaid) for the constant infusion of heparin [14] and insulin. [15]

Mechanically activated drug delivery system:

In this type of activation modulated drug delivery system the drug is a solution formulation retained in a container equipped with a mechanically activated pumpy system.

e.g. A metered dose nebulizer for intranasal administration of a precision dose of buserelin and insulin. [16]

Magnetically activated drug delivery system:

In this type of activation modulated drug delivery system the drug reservoir is a dispersion of peptide or protein powders in a polymer matrix from which macromolecular drugs can be delivered, which can be slowly delivered by incorporation or electromagnetically triggered vibration mechanism into the polymeric delivery device.

e.g. Delivery of protein drugs like bovine serum albumin. [17]

Electrically activated drug delivery system:

It is a process that facilitates the transport of ionic species by the application of physiologically acceptable electric current.[18] Iontophoresis and Electroporation techniques use the application of low voltage and high voltage pulses for a short duration and long duration respectively to deliver much large molecules through skin like proteins and oligonucleotides. More recently the transdermal delivery of peptide based drugs like insulin has became feasible by the application of Iontophoresis. [19] In future it may be feasible to use this as an alternative non viral approach for gene therapy. [20]

Ultrasound activated drug delivery system:

Sonophoresis enhances transdermal transport through affecting skin structure or through inducing convection across the skin. The potential application of sonophoresis to regulate delivery of drug was recently reviewed. [21]

Hydration activated drug delivery system:

This type of drug delivery system depends on the hydration induced swelling process to activate the release of drugs. The representative of these type of activated system are Syncro-Mate-B implants[22] for the delivery of Norgestrine, a potent progestrin and Valrelease tablet for delivery of valium, a tranquilizer.[23]

CHEMICAL MEANS

pH activated drug delivery system: This type of activation controlled drug delivery systems permits the targeting the delivery of drugs only in the region with a selected pH range.

Ion activated drug delivery system: Ionic or charge drugs can be delivered by this type of system. e.g. Development of Pennkinetic which permits the formulation of liquid suspension with sustained release property for oral administration. [24]

Hydrolysis activated drug delivery system: It depends on the hydrolysis process to activate the release of drugs. e.g. Development of LHRH releasing biodegradable sub dermal implants to deliver Goserelin, a synthetic LHRH analogue.

BIOCHEMICAL MEANS

Enzymes activated drug delivery system: It depends on enzymatic process to activate the release of drugs. e.g. Development of albumin microspheres that release 5-fluorouracil by protease activated biodegradation.

FEEDBACK REGULATED DRUG DELIVERY SYSTEM

The release of the drug molecules from the delivery system is activated by a triggering agent such as biochemical substances in the body and also regulated by its concentration via some feedback mechanism.

Bio-erosion regulated drug delivery system: The system consists of drug dispersed bioerodable matrix fabricated from poly (vinyl methyl ether) half ester, which was coated with a immobilized urease. In the presence of urea, urease at the surface of the drug delivery device metabolized to urea to form ammonia. In this case the pH is increased and a rapid degradation of polymer matrix as well as the release of drug molecule.

e.g. Bio-erosion regulated hydrocortisone dispersion. [25]

Bio-responsive drug delivery system: In this system the drug reservoir is contained in a device enclosed by a bio-responsive polymeric membrane whose drug permeability is controlled by the concentration of a biochemical agent in the tissue where the system is located. e.g. Glucose triggered insulin drug delivery system. [26]

Self regulated drug delivery system: This type of feedback regulated drug delivery systems depends on a reversible and competitive binding mechanism to activate and regulate the release of drugs. Recent development utilizes complex of Glycosylated insulin concanavalin-A which is encapsulated inside a polymer membrane. The amount of insulin delivered is thus self regulated by the concentration of glucon penetrating the insulin delivery system. [27]

CARRIER BASED DRUG DELIVERY SYSTEM

Colloidal particulates carrier system: Such as vesicular system like hydrogels, liposomes, niosomes, nanocapsules, nanoparticles, polymeric complexes, microspheres, nanoerythrosomes, transferosomes, dendrimers, aquasomes, etc.

Hydrogels: Hydrogels are three dimensional hydrophilic polymeric networks capable of imbibing large amounts of water or biological fluids. They are used to regulate drug release in reservoir-based, controlled release systems or as carriers in swellable and swelling-controlled release devices. On the forefront of controlled drug delivery, hydrogels as enviro-intelligent and stimuli-sensitive gel systems modulate release in response to pH, temperature, ionic strength, electric field, or specific analyte concentration differences. In these systems, release can be designed to occur within specific areas of the body (e.g., within a certain pH of the digestive tract) or also via specific sites (adhesive or cell receptor specific gels via tethered chains from the hydrogel surface). Hydrogels as drug delivery systems can be very promising materials if combined with the technique of molecular imprinting. Despite the already developed interesting applications of MIPs, the incorporation of the molecular imprinting approach for the development of drug delivery system is just at its incipient stage. Nevertheless, it can be foreseen that, in the next few years, significant progress will occur in this field, taking advantage of the improvements of this technology in other areas. A group of research scientist developed mucoadhesive Insulin delivery system using lectin functionalized complex Hydrogels. [28]

Liposomes : Liposomes may be prove to be efficient carrier for targeting the drug to the site of action, because of biodegradable, innocuous nature and being identical to biological membrane. Liposomal drug delivery systems have been used as carrier for anticancer drugs, antimicrobial agents and the delivery of macromolecules including DNA and proteins. [29]

Recent development is triggerable liposome which triggers the release in response to external or cellular stimuli, such as thermosensitive liposomes for the delivery of anticancer drugs [30], PH sensitive liposomes, and light sensitive liposomes. [31]

Thermosensitive liposomes have found applications in the treatment of benign prostatic hyperplasia (BPH). Animal studies

have shown that heat-sensitive liposomes can improve chemotherapy delivery to tumors. [32]

Recently engineered liposomes such as, Fusogenic liposomes and virosomes, which fuse and merge with cell membrane and directly introduced entrapped and anchored molecules into cytoplasm thus avoiding the pathways followed by conventional liposomes. Fusion spike glycoproteins of sendi virus, rabbies virus, influenza, herpes, HIV, and vesicular stomatitis virus have been incorporated in liposomes and these virosomes have been investigated for their immunoadjuvant gene and oligonucleotides delivery. [33] Liposomes have been used as "Lysosomotropic carriers" to enroute the enzymes and supplement it therapeutically in enzyme deficiency disease like Gauchers disease or Pompes disease. In the recent years mucosal immunoadjuvant activity of liposomes, involving the induction of strong secretory IGA responces by delivering the system in gastrointestinal or respiratory is highly appreciated. [34]

Niosomes: Niosomes are the non ionic surfactant vesicles which can entrapped both hydrophilic and hydrophobic drugs either in aqueous layer or in vesicular membrane made up of lipid. These are found to have selective drug delivery potential for cutaneous application of 5-α dihydrostosterone, triamcinolone, acetonide and intravenous administration of methotrexate for cancer treatment and sodium stilbogluconate in the treatment of leishmaniasis. Vesicular drug carriers like niosomes can be transported by macrophages which are known to infiltrate tumor cells. It may be possible to take advantage of these activated macrophages system in delivery the antitumor agents within vesicles quantitatively to tumor sites. [35]

Polymeric micelles: Micelles formed by PEG-phosphating ethanolamine conjugates can accumulate in tumors and can be loaded with anticancer drugs which decrease the systemic concentration of drugs, diminish intracellular uptake but normal cell thus reducing unwanted interaction with healthy tissues. [36]

Microspheres: Attachment of antibodies to microsphere loaded with drugs offered opportunity to target them to the neoplastic tissue. The possibility of loading cytotoxic drugs, vaccines and polypeptides into preformed microspheres of proteins and polysaccharides allows the most native form of the therapeutic substance to be incorporated into the carrier thus avoiding the adverse effects of undesirable organic solvents, cross-linking agents, pH of the medium, temperature, ultrasound etc. Recent studies on the uptake of microspheres by peyers patches have opened the possibility of deliver many vaccines by oral route. [37]

Nanoparticles: Also called as ultrafine colloidal carriers**.** The motivation to develop an alternate drug delivery system using nanoparticles are [38]

- Able to deliver drug across the biological surface such as blood brain barrier and cellular membrane
- Shows excellent adhesion to biological surface
- Particle size below 100 nm can evade mechanical filtration
- Larger surface area to volume ratio

Nanoparticles with different composition and characteristic have been investigated for various therapeutic applications in cancer therapy, DNA delivery, ocular delivery, oral delivery of peptides, and intracellular targeting. The most promising application of nanoparticle is their possible use as carrier for antitumor agents. [39] Biosante pharmaceuticals has developed delivery system based on calcium phosphate to administered an oral form of insulin called CAPIC which way create through a nanoparticulate techniques, using microscopic particles of calcium phosphate. [40]

Dendrimers: Dendrimers surfaces provide an excellent platform for the attachment and presentation of cell-specific targeting groups, solubility modifiers, stealth moieties that reduce immunological interactions and imaging tags. The ability to attach any or all of these molecules in a well-defined and controllable manner on to a robust dendritic surface clearly differentiates dendrimers from other vectors such as micelles, liposomes, emulsion droplets or engineered particles. The use of dendrimers as targeting vectors for diagnostic imaging, drug delivery and gene transfection had been proposed in the patent literature nearly a decade ago. [41] Recently it has been shown that efficient gene delivery can be mediated to a variety of cell types using dendrimers. A major advantage of dendrimers for in vivo applications is their ability to

protect DNA from the action of DNAase found in serum. [42]

Aquasomes: Jain et al. studied self-assembled carbohydrate-stabilized ceramic nanoparticles for the parentral delivery of insulin. Aquasomes were found to be promising for protection of the spatial qualities of the peptide drug for exhibiting better therapeutic effect. [43] The hemoglobin aquasomes prepared using hydroxyapatite cores may be of interest to pharmaceutical industry as potential artificial oxygen carrying system. [44]

Transferosomes: These are self aggregates, with ultraflexible membrane are able to delivery of drug reproducibly enter into or through the skin. These vesicular vesicles are several orders of magnitude more elastic than the standard liposomes. Transferosomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of the stratum corneum. [45] Delivery of peptides by transferosomes provides a very successful means for the non-invasive therapeutic use of large molecular wt. drug like insulin on the skin. [46] Hafer et al. studied the formulation of interleukin-2 and interferon-α containing transferosomes for potential transdermal application. [47]

Cellular carriers system: Among the various carriers used for targeting of drugs to various body tissues, the cellular carriers meet several criteria desirable in clinical applications, among the most important being biocompatibility of carrier and its degradation products. Resealed erythrocytes, leucocytes and platelets have all been engineered to use as potential delivery of drugs. [48] Resealed erythrocytes can be use targeting of bioactive agents to RE system used to delivery of lysosomal enzymes to erythrophagocytic cells and used to treat Gauchers disease with glucocartisone encapsulated in erythrocytes. [49] These can also be used as circulatory carrier to discriminate bioactive agents for prolonged period of time in circulation. Mitchel, et al. used erythrocytes for slow release of an immunomodulator interleukin-2. [50] Al Achi, et al. has successfully reported erythrocyted membrane vesicular delivery of insulin and doxorubicin. [51] For prevention of thromboembolism Eicher et al. encapsulated heparin in erythrocytes. [52] Magnetically responsive erythrocytes used for targeting of drugs other than reticuloendothelial system. [3] Recently nanoerythrosomes were developed. Significant advances have been made with the use of erythrocytes for specific targeting to cells of the immune system. [53] In near future, erythrocytes based drug delivery system will revolutionize disease management.

Prodrugs: These can be described as compounds which undergo chemical as well as biological biotransformation prior to exhibit their pharmacological effect. Prodrug and pro-prodrugs were found wide application in oral, parentral, ocular, topical delivery systems for controlling and targeting the drug molecules. The concept of pro-prodrug is also gaining importance where a pro-prodrug is a prodrug of prodrug. Newly synthesized dibenzyl bispilocarpates, a new class of pilocarpine, pro-prodrug with adequate amount of aqueous solubility, improved delivery characteristics of pilocarpine and stability. [54] Types of prodrugs used as delivery systems are: bioprecursor prodrug, macromolecular prodrug, drug antibody conjugates, enzymatically activated reduction reaction-reaction prodrug, enzymatically activated hydrolysis reaction-reaction prodrug, oxidation activated prodrug, reduction activated prodrug, hydrolysis activated prodrug and gene directed enzyme prodrug therapy (GDEPT) and antibody directed enzyme prodrug therapy (ADEPT).

The approaches are based on the activation of specially designed prodrug by antibody-enzyme conjugates targeted to tumor associated antigens or by enzymes expressed by exogenous genes in the tumor cells. Recent advances in molecular biology provide direct availability of enzymes and carrier proteins, including their molecular and functional characteristic. The targeted prodrug approaches, which can be combined with gene therapy and controlled expression of enzymes and carrier proteins, are promising strategy for precise and efficient drug delivery. Enzymes activated prodrug approach was designed as purine nucleoside prodrug used for the treatment of viral infection like Hepatitis and AIDS. Recently VIRAMIDIN a prodrug of RIBAVARIN is being investigated for human use for the treatment of chronic Hepatitis C. Recently antibody directed enzymes prodrug

therapy (ADEPT) for anticancer molecules to target tumor cells. [55]

FUTURE OPPORTUNITIES AND CHALLENGES

In the exploration of alternate controlled release drug administration, one encountered three areas of potential challenges, [56]

1) Development of drug delivery system which can be capable of delivering of drug at a therapeutically effective rate to a desired site for duration required for optimal treatment.
2) Modulation of gastrointestinal transit time.
3) Minimization of hepatic first pass elimination.

Carrier based nano-formulations have already been applied as drug delivery systems with great success; and nanoparticulate drug delivery systems have still greater potential for many applications, including anti-tumor therapy, gene therapy, AIDS therapy, radiotherapy, in delivery of proteins, antibiotics, virostatics, vaccines and as vesicles to pass the blood-brain barrier. They provide massive advantages regarding drug targeting, delivery and release with their additional potential to combine diagnosis and therapy, also emerge as one of the major tools in nanomedicine. The cytotoxicity of nanoparticles or their degradation products remains a major problem, and improvements in biocompatibility obviously are a main concern of future research.

There are many technological challenges to be met, in developing the following techniques:

- Nano-drug delivery systems that deliver large but highly localized quantities of drugs to specific areas to be released in controlled ways;
- Controllable release profiles, especially for sensitive drugs;
- Materials those are biocompatible and biodegradable;
- Technologies for self-assembly;
- Functional delivery such as active drug targeting, on-command delivery, intelligent drug release devices bioresponsive triggered systems, self-regulated delivery systems, systems interacting with the body, smart delivery;
- Virus-like systems for intracellular delivery;
- Development of devices such as implantable devices/nanochips for nanoparticles release, or multi reservoir drug delivery-chips;
- Carriers for tissue engineering;
- Advanced polymeric carriers for the delivery of therapeutic peptide/proteins;
- Universal formulation schemes that can be used as intravenous, intramuscular or per oral drugs
- Cell and gene targeting systems;
- User-friendly lab-on-a-chip devices for point-of-care and disease prevention and control at home;
- Devices for detecting changes in magnetic or physical properties after specific binding of ligands on paramagnetic nanoparticles that can correlate with the amount of ligand;
- Better disease markers in terms of sensitivity and specificity.

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