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The Novel Drug Delivery System

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Abstract:

Evolution of an existing drug molecule from a conventional form to a novel delivery system can significantly improve its performance in terms of patient compliance, safety and efficacy. In the form of a Novel Drug Delivery System an existing drug molecule can get a new life. An appropriately designed Novel Drug Delivery System can be a major advance for solving the problems related towards the release of the drug at specific site with specific rate. The need for delivering drugs to patients efficiently and with fewer side effects has prompted pharmaceutical companies to engage in the development of new drug delivery system. This article covers the basic information regarding Novel Drug Delivery Systems and also different types of the same.

Key Wards: Nanomedicine, natural plant metabolite, biomedical application, carrier formulation, drug delivery

Introduction:

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all 1 . On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues.

From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio recognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), which are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bio conjugate chemistry, and molecular biology. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development 1 . Controlled and Novel Drug Delivery which was only a dream or at best a

possibility is now a reality. During the last decade and half pharmaceutical and other scientists have carried out extensive and intensive investigations in this field of drug research.

Among drug carriers one can name soluble polymers, microparticles made of insoluble or biodegradable, natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles. The carriers can be made slowly degradable, stimulireactive (e.g., pH- or temperature-sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release: (i) Passive and; (ii) Active targeting.

Definition:

A Novel Drug Delivery System (NDDS) can be defined as a new approach that **combines innovative development, formulations, new technologies**, novel methodologies for delivering pharmaceutical compounds in the body as needed to safely achieve its desired pharmacological effects.

Characteristics of Novel Drug Delivery System:

- Increase the bioavailability
- Provide controlled delivery of drug
- Transport the drug intact to the site of action avoiding the non-diseased tissue.
- Stable and delivery be maintained under various physiological variables.
- Easy to administer, safe and reliable.
- Cost-effective.

Benefits of NDDS:

- **Medical:** Optimum dose, at the right time and at the light location.
- **Industrial:** Efficient use of expensive ingredients, reduction in production cost.
- **Social:** Beneficial to patients, better therapy, improved compliance and standard of living.

Novel Drug Delivery Approaches:

Various drug delivery and drug targeting systems are currently under development to minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone. Among drug carriers one can name soluble polymers, micro particles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes and micelles. The carriers can be made slowly degradable, stimuli-reactive (e.g. pH- or temperature-sensitive) and even targeted (e.g. by conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release: (i) passive and (ii) active targeting. An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors as a result of the enhanced vascular permeability of tumor tissues compared with healthy tissue. A strategy that could allow active targeting involves the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest. Since ligand-receptor interactions can be highly selective, this could allow a more precise targeting of the site of interest.

Controlled drug release and subsequent biodegradation are important for developing successful formulations. Potential release mechanisms involve: (i) desorption of surface-bound / adsorbed drugs; (ii) diffusion through the carrier matrix; (iii) diffusion (in the case of nanocapsules) through the carrier wall; (iv) carrier matrix erosion and (v) a combined erosion / diffusion process. The mode of delivery can be the difference between a drug's success and failure, as the choice of a drug is often influenced by the way the medicine is administered. Sustained (or continuous) release of a drug involves polymers that release the drug at a controlled rate due to diffusion out of the polymer or by degradation of the polymer over time. Pulsatile release is often the preferred method of drug delivery, as it closely mimics the way by which the body naturally produces hormones such as insulin. It is achieved by using drug-carrying polymers that respond to specific stimuli (e.g. exposure to light, changes in pH or temperature)

For over 20 years, researchers have appreciated the potential benefits of nanotechnology in providing vast improvements in drug delivery and drug targeting. Improving delivery techniques that minimize toxicity and improve efficacy offers great potential benefits to patients, and opens up new markets for pharmaceutical and drug delivery companies. Other approaches to drug delivery are focused on crossing particular physical barriers, such as the blood–brain barrier, in order to better target the drug and improve its effectiveness; or on finding alternative and acceptable routes for the delivery of protein drugs other than via the gastrointestinal tract, where degradation can occur.

Presently novel drug delivery systems have been widely utilized only for allopathic drugs, but they have their own limitations hence, turning to safe, effective and time-tested Ayurvedic herbal drug formulation would be a preferable option.

Potential of novel drug delivery for herbal drugs:

Our country has a vast knowledge base of Ayurveda whose potential is only being realized in the recent years. However, the drug delivery system used for administering the medicine to the patient is traditional and out-of-date, resulting in reduced efficacy of the drug. In case of herbal extracts, there is a great possibility that many compounds will be destroyed in the highly acidic pH of the stomach. Other components might be metabolized by the liver before reaching the blood. As a result, the required amount of the drug may not reach the blood. If the drug does not reach the blood at a minimum level, which is known as 'minimum effective level' then there will be no therapeutic effect.

Phytopharmaceuticals are pharmaceuticals using traditional compounds derived from botanicals instead of chemicals. Natural ingredients are more easily and more readily metabolized by the body. Therefore they produce fewer, if any, side effects and provide increased absorption in the bloodstream resulting in more thorough and effective treatments. Pharmaceuticals made from chemical compounds are prone to adverse side effects. The human body will have a tendency to reject certain chemical compounds which do not occur naturally. These rejections occur in the form of side effects; some as mild as minor headaches, and others as severe as to be potentially lethal. It is important to note while phytopharmaceuticals produce fewer to no side effects, chemical interactions with other prescription drugs can occur. Furthermore, as they are single and purified compounds, they can be easily standardized making it easier to incorporate them in modern drug delivery systems compared to herbs.

Lipid-based drug delivery systems have been investigated in various studies and have shown their potential in controlled and targeted drug delivery. Pharmacosomes are amphophilic phospholipid complexes of drugs bearing active hydrogen that bind to phospholipids. They impart better biopharmaceutical properties to the drug, resulting in improved bioavailability. Phytosomes are novel compounds comprising of lipophilic complexes of components of plant origin like *Silybum Marianum, Ginkgo Biloba*, *ginseng* and so on, with phospholipid. They are also called as phytolipids delivery system. They have high lipophilicity and improved bioavailability and therapeutic properties. These are advanced form of herbal extract that have improved pharmacokinetic and pharmacological parameter, whose result can advantageously be used in treatment of acute liver diseases, either metabolic or infective origin. Phytosomes are produced by a patent process in which individual component of herbal extract like flavonolignans and terpenoids are bound on a molecular level to the phospholipids like phosphatidylcholine through a polar end. Phytosomes are used as a medicament and have wide scope in cosmetology.

If the herbs themselves or the purified phytopharmaceuticals or phytosomes are incorporated in novel drug delivery systems, we can get the benefits of both. Thus it is important to incorporate the novel drug delivery system in Indian Ayurvedic medicines to combat serious diseases.

Design of the Review:

In this review, nanocarriers were being classified based on the types of nanocarrier, i.e. i) organic nanocarriers; ii) inorganic nanocarriers; iii) hybrid nanocarriers; and iv) biological nanocarriers. References were searched in Scopus data based using each class of nanocarriers as the keyword. Articles after the year 2010 were selected (unless the significant references for a particular type of nanocarrier, which were downloaded separately) and sorted based on the specific type of carrier for each of the above classes.

Nanocarrier:

Nanocarrier is hopefully utilized to overcome the difficulty and issues related to conventional drug delivery systems such as their nonspecificity, side effects, burst release and detrimental destroying of large populations of the normal cells. Nanocarrier improves the bioavailability and therapeutic efficiency of drugs, as well as providing a preferential accumulation at the target site.[10] Nowadays, a large number of nanocarriers have been produced but only some of them are clinically authorized for the delivery of materials because of their motivated actions at the targeted sites, especially antitumor agents.[11]

The particles of a nanocarrier vary in size, and those ranged from 10 to 100 nm give the most acceptable physicochemical characteristics. The main advantages of nanonization are improving solubility, reducing medicinal doses and side effects, and increasing the absorbency of medicinal herbs compared with the respective crude extract preparations.

Drug Delivery Carriers:

Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter show great promise as drug delivery systems. When developing these formulations, the goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity. The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties.

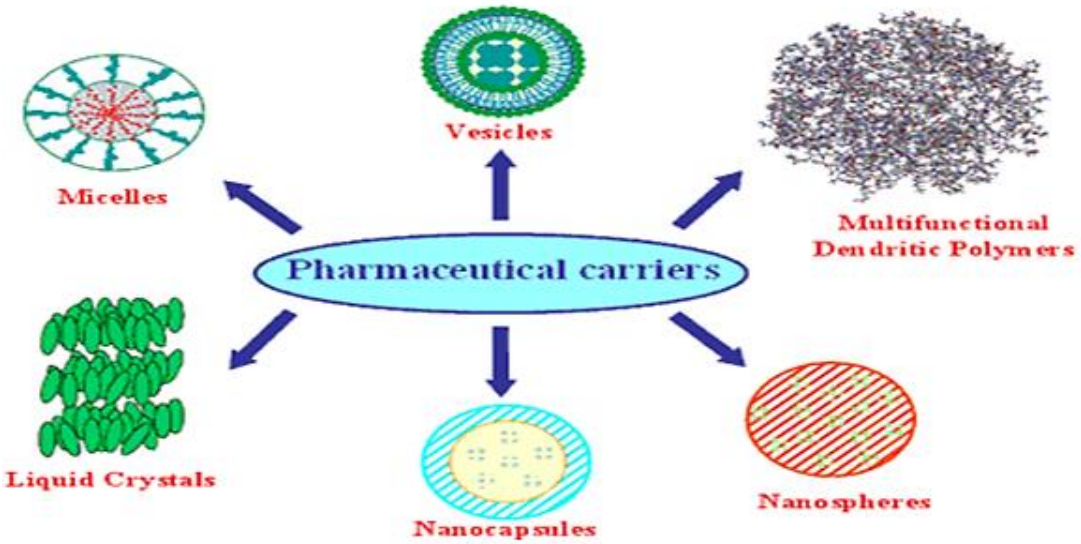


Fig. Pharmaceutical carriers

1. Micelles:

Micelles formed by self-assembly of amphiphilic block copolymers (5-50 nm) in aqueous solutions are of great interest for drug delivery applications. The drugs can be physically entrapped in the core of block copolymer micelles and transported at concentrations that can exceed their intrinsic water- solubility. Moreover, the hydrophilic blocks can form hydrogen bonds with the aqueous surroundings and form a tight shell around the micellar core. As a result, the contents of the hydrophobic core are effectively protected against hydrolysis and enzymatic degradation. In addition, the corona may prevent recognition by the

reticuloendothelial system and therefore preliminary elimination of the micelles from the bloodstream.

A final feature that makes amphiphilic block copolymers attractive for drug delivery applications is the fact that their chemical composition, total molecular weight and block length ratios can be easily changed, which allows control of the size and morphology of the micelles. Functionalization of block copolymers with cross linkable groups can increase the stability of the corresponding micelles and improve their temporal control. Substitution of block copolymer micelles with specific ligands is a very promising strategy to a broader range of sites of activity with a much higher selectivity.

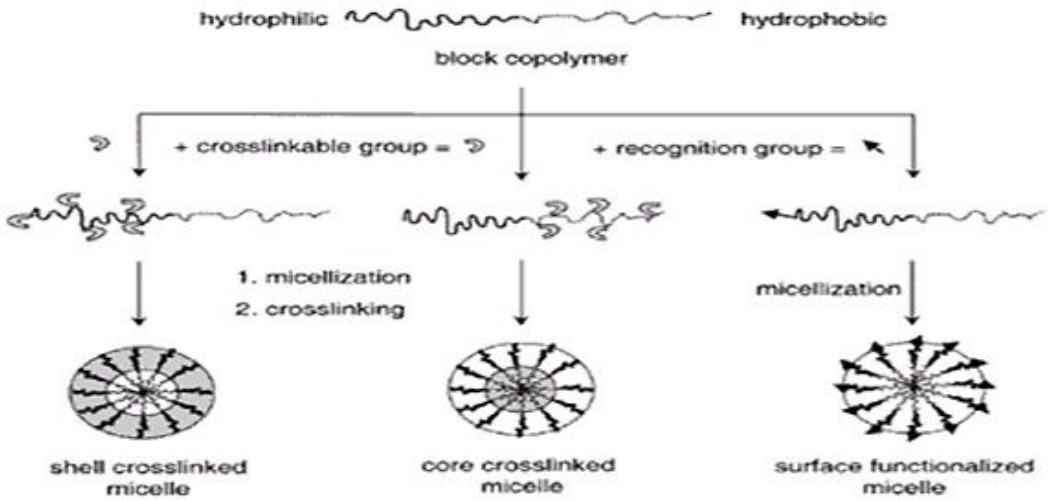


Fig. Block copolymer micelles.

2. Liposomes:

Liposomes are a form of vesicles that consist either of many, few or just one phospholipid bilayers. The polar character of the liposomal core enables polar drug molecules to be encapsulated. Amphiphilic and lipophilic molecules are solubilized within the phospholipid bilayer according to their affinity towards the phospholipids. Participation of nonionic surfactants instead of phospholipids in the bilayer formation results in niosomes.

Channel proteins can be incorporated without loss of their activity within the hydrophobic domain of vesicle membranes, acting as a size-selective filter, only allowing passive diffusion of small solutes such as ions, nutrients and antibiotics. Thus, drugs that are encapsulated in a nanocage-functionalized with channel proteins are effectively protected from premature degradation by proteolytic enzymes. The drug molecule, however, is able to diffuse through the channel, driven by the concentration difference between the interior and the exterior of the nanocage.

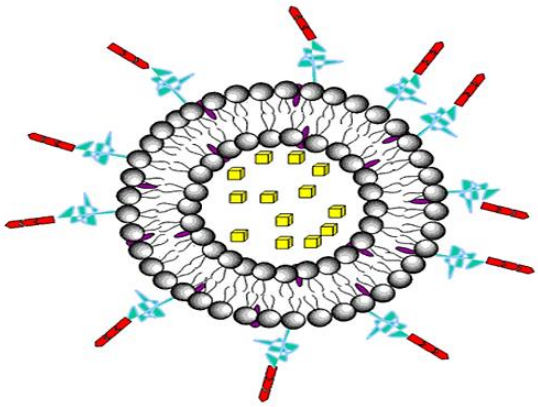


Fig. Drug encapsulation in liposomes

Methods of Liposome Preparation

- **Hydration Stage**

a. Mechanical Methods
b. Replacement of organic solvent by aqueous media method.
c. Detergent removal method.

- **Sizing Stage**
- **Removal of Non-encapsulated material.**

Applications of Liposomes:

1. Gene Delivery
2. Targeted Delivery
3. Ocular Therapy
4. Pulmonary Application
5. Cancer Therapy
6. Arthritis

3. Dendrimers:

Dendrimers are nanometer-sized, highly branched and monodisperse macromolecules with symmetrical architecture. They consist of a central core, branching units and terminal functional groups. The core together with the internal units, determine the environment of the nanocavities and consequently their solubilizing properties, whereas the external groups the solubility and chemical behavior of these polymers. Targeting effectiveness is affected by attaching targeting ligands at the external surface of dendrimers, while their stability and protection from the Mononuclear Phagocyte System (MPS) is being achieved by functionalization of the dendrimers with polyethylene glycol chains (PEG).

4. Liquid Crystals:

Liquid Crystals combine the properties of both liquid and solid states. They can be made to form different geometries, with alternative polar and non-polar layers (i.e., a lamellar phase) where aqueous drug solutions can be included.

5. Nano-Particles:

Nanoparticles (including nanospheres and nanocapsules of size 10-200 nm) are in the solid state and are either amorphous or crystalline. They are able to adsorb and/or encapsulate a drug, thus protecting it against chemical and enzymatic degradation. Nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Nanoparticles as drug carriers can be formed from both biodegradable polymers and non-biodegradable polymers. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in the controlled release of drugs, in targeting particular organs / tissues, as carriers of DNA in gene therapy, and in their ability to deliver proteins, peptides and genes through the paroral route.

6. Hydrogels:

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids. The networks are composed of homopolymers or copolymers, and are insoluble due to the presence of chemical crosslinks (tie-points, junctions), or physical crosslinks, such as entanglements or crystallites. Hydrogels exhibit a thermodynamic compatibility with water, which allows them to swell in aqueous media. 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 analyst's 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.

Types of Hydrogels:

1. pH sensitive or ion sensitive hydrogels
2. Temperature sensitive hydrogels
3. Glucose sensitive hydrogels
4. Nano hydrogels

Preparation of Hydrogels;

- Isotonic ultra-high pressure (IUHP)
- Use of cross linkage
- Use of nucleophilic substitution reaction
- Use of gelling agents
- Use of irradiation and freeze thawing.

Pharmaceutical Application of Hydrogels:

- ❖ Wound Healing
- ❖ Colon specific drug delivery
- ❖ Topical drug deliver
- ❖ Ocular drug delivery
- ❖ Industrial applicability
- ❖ Tissue engineering

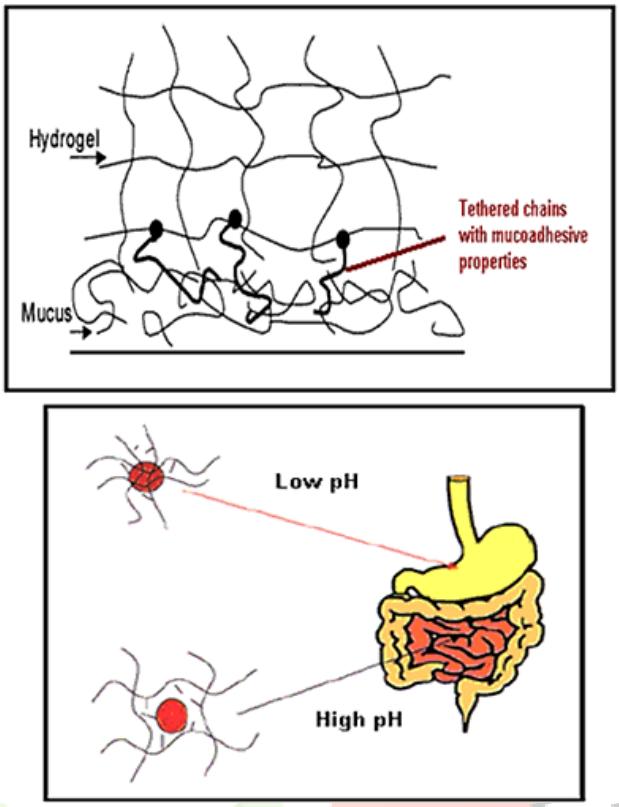


Fig. Pegylated and pH sensitive micro- or nanogels

ROUTES OF ADMINISTRATION:

A. Peroral route (oral):

The most important drug delivery route is the peroral route. An increasing number of drugs are protein- and peptide-based. They offer the greatest potential for more effective therapeutics, but they do not easily cross mucosal surfaces and biological membranes; they are easily denatured or degraded, prone to rapid clearance in the liver and other body tissues and require precise dosing. At present, protein drugs are usually administered by injection, but this route is less pleasant and also poses problems of oscillating blood drug concentrations. So, despite the barriers to successful drug delivery that exist in the gastrointestinal tract (i.e., acid-induced hydrolysis in the stomach, enzymatic degradation throughout the gastrointestinal tract by several proteolytic enzymes, bacterial fermentation in the colon), the peroral route is still the most intensively investigated as it offers advantages of convenience and cheapness of administration, and potential manufacturing cost savings.

B. Pulmonary route:

Pulmonary delivery is also important and is effected in a variety of ways - via aerosols, metered dose inhaler systems (MDIs), powders (dry powder inhalers, DPIs) and solutions (nebulizers), all of which may contain nanostructures such as liposomes, micelles, nanoparticles and dendrimers. Aerosol products for pulmonary delivery comprise more than 30% of the global drug delivery market. Research into lung delivery is driven by the potential for successful protein and peptide drug delivery, and by the promise of an effective delivery mechanism for gene therapy (for example, in the treatment of cystic fibrosis), as well as the need to replace chlorofluorocarbon propellants in MDIs. Pulmonary drug delivery offers both local targeting for the treatment of respiratory diseases and increasingly appears to be a viable option for the delivery of drugs systemically. However, the pulmonary delivery of proteins suffers by proteases in the lung, which reduce the overall bioavailability, and by the barrier between capillary blood and alveolar air (air-blood barrier).

C. Transdermal route:

Transdermal drug delivery avoids problems such as gastrointestinal irritation, metabolism, variations in delivery rates and interference due to the presence of food. It is also suitable for unconscious patients. The technique is generally non-invasive and aesthetically acceptable, and can be used to provide local delivery over several days. Limitations include slow penetration rates, lack of dosage flexibility and / or precision, and a restriction to relatively low dosage drugs.

D. Parenteral route:

Parenteral routes (intravenous, intramuscular, subcutaneous) are very important. The only nanosystems presently in the market (liposomes) are administered intravenously. Nanoscale drug carriers have a great potential for improving the delivery of drugs through nasal and sublingual routes, both of which avoid first-pass metabolism; and for difficult-access ocular, brain and intra-articular cavities. For example, it has been possible to deliver peptides and vaccines systemically, using the nasal route, thanks to the association of the active drug macromolecules with nanoparticles. In addition, there is the possibility of improving the occular bioavailability of drugs if administered in a colloidal drug carrier.

E. Trans tissue and local route:

Trans-tissue and local delivery systems require to be tightly fixed to resected tissues during surgery. The aim is to produce an elevated pharmacological effect, while minimizing systemic, administration-associated toxicity. Trans-tissue systems include: drug-loaded gelatinous gels, which are formed in-situ and adhere to resected tissues, releasing drugs, proteins or gene-encoding adenoviruses; antibody-fixed gelatinous gels (cytokine barrier) that form a barrier, which, on a target tissue could prevent the permeation of cytokines into that tissue; cell-based delivery, which involves a gene-transduced oral mucosal epithelial cell (OMEC)-implanted sheet; device-directed delivery - a rechargeable drug infusion device that can be attached to the resected site.

F. Gene delivery:

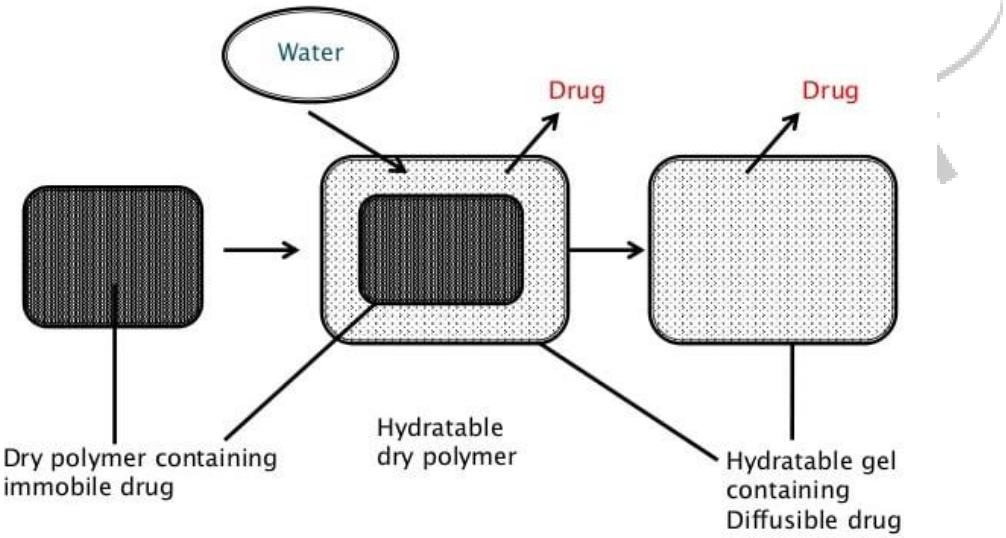
Gene delivery is a challenging task in the treatment of genetic disorders. In the case of gene delivery, the plasmid DNA has to be introduced into the target cells, which should get transcribed and the genetic information should ultimately be translated into the corresponding protein. To achieve this goal, a number of hurdles are to be overcome by the gene delivery system. Transfection is affected by: (a) targeting the delivery system to the target cell, (b) transport through the cell membrane, (c) uptake and degradation in the endolysosomes and (d) intracellular trafficking of plasmid DNA to the nucleus.

Modified Release Drug Formulation:

A. Sustained Release drug formulations:

A way of formulating a medicine so that it is released into body steadily, over a long period of time.

- ❖ Increases duration of action of a drug.
- ❖ Reducing dosing frequency.
- ❖ Once-daily oral preparations.
- ❖ Long lasting depot injections (E.g. Contraceptives, Hormone replacements, Antipsychotic drugs).



B. Controlled Release drug formulations:

- ❖ It closely mimics the way by which the body naturally produces hormones such as insulin.
- ❖ A way of formulating the medicine so it is released into the body in respond to specific stimuli e.g. Exposure to light, Changes in pH or temperature.

MICROENCAPSULATION:

Microencapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules, of many useful properties. In general, it is used to incorporate food ingredients, enzymes, cells or other materials on a micro metric scale.

Definition: It may be defined as, " The process of surrounding or enveloping one substance within another substance on a very small scale, yielding capsules ranging from less than one micron to several hundred microns in size". It is mean of applying thin coating to small particle of a solid or droplet of liquid and dispersion.

There are two phases:

a. **Core Material**
b. **Coating Material**

Reasons for Microencapsulation:

1. To protect reactive substances from the environment.
2. To convert liquid active components into a dry solid system.
3. To separate the incompatible components for functional reasons.
4. To protect the immediate environment of the microcapsules, from the active components.
5. Isolation of core from its surroundings, as in isolating vitamins from the deteriorating effects of oxygen.
6. Retarding evaporation of a volatile core.
7. Improving the handling properties of a sticky material.
8. Isolating a reactive core from chemical attack.
9. For safe handling of toxic materials.
10. To get targeted release of drug.

Advantages of Microencapsulation:

1. Reliable mean to deliver the drug to the target site and to maintain the desired concentration at the site of interest without untoward effects.
2. Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.
3. Microspheres received much attention for targeting of anticancer drugs to tumor.
4. Reduces the dosing frequency and thereby improve the patient compliance.

Disadvantages of Microencapsulation:

1. It is an expensive process.
2. Requires skills.
3. Difficult to obtain continuous and uniform film.

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