The Pharmaceutical and Chemical Journal, 2024, 11(3):180-188
AVAILABLE online www.tpcj.org

Review Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

An Overview on Advance Approach of Novel Drug Delivery System

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Abstract Plants are nature's remedies and have been used by human beings on earth since ancient times for food and medicine. Today there are global movements towards finding of herbal medicaments in plants to bring them in market via a suitable drug delivery system for mankind. The basic thought behind it is treatment of each disease is hidden in nature. However, delivery of herbal drugs also requires modification with the purpose to achieve sustain release, to increase patient compliance etc. previously herbal drugs could not attract scientists towards the modifications of novel drug delivery systems due to processing, standardizing, extracting and identification difficulties. But now days with the advancement in the technology, novel drug delivery systems (NDDS) open the door towards the development of herbal novel drug delivery system. With use of advance techniques protection from toxicity, enhancement in stability, improved bioavailability of herbal formulations, protection from physical and chemical degradation can be achieve. 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.

Keywords Global movement, Herbal medicaments, Bioavailability, NDDS

Introduction

Novel drug delivery system (NDDS) is an expression mainly associated with the formulation of new pharmaceutical forms which have optimized characteristics such as smaller particle size, higher permeability parameters, and selective site targetting. NDDSs can be used to enhance the performance of biotherapeutic agents when compared with their effect in the conventional dosage forms. The efficacy of a medication can be significantly impacted by the way it is administered. Certain medications have an ideal concentration range where the most therapeutic benefit may be obtained; dosages above or below this range may be hazardous or have no effect at all. Conversely, the sluggish advancement in the effectiveness of treating severe illnesses has indicated an increasing demand for a multidisciplinary strategy in delivering medicines to targets within tissues. This led to the development of novel concepts for managing the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and effectiveness of pharmaceuticals. These innovative techniques, which go by the name "drug delivery systems" (DDS), are founded on multidisciplinary methods that bring together molecular biology, pharmaceutics, polymer science, and bioconjugate chemistry.

Controlled drug delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. While these

advantages can be significant, the potential disadvantages cannot be ignored like the possible toxicity or non-biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and the higher cost of controlledrelease systems compared with traditional pharmaceutical formulations. The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize. The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional drug delivery systems, the drug level in the blood follows the in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective.

Terminology or Definition of Control Release Drug Delivery System

The United States Pharmacopoeia (USP) defines1 the modified-release (MR) dosage form as "the one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms". One class of MR dosage form is an extended-release (ER) dosage form and is defined as the one that allows at least a 2- fold reduction in dosing frequency or significant increase in patient compliance or therapeutic performance when compared with that presented as a conventional dosage form (a solution or a prompt drug-releasing dosage form). The terms "controlled release (CR)", "prolonged release", "sustained or slow release (SR)" and "long-acting (LA)" have been used synonymously with "extended release". Controlled drug delivery is one which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time.

Sustained Drug Release.

Sustained release allows delivery of a specific drug at a programmed rate that leads to drug delivery for a prolonged period of time.

Prolonged-release products release the active ingredients slowly and work for a longer time. A prolonged-release drug delivers a dose of a medication over an extended period of time. The prolonged release or sustained release systems, which only prolong therapeutic blood or tissue levels of the drug for an extended period of time, cannot be considered as controlled release systems by this definition. They are distinguished from rate controlled drug delivery systems, which are able to specify the release rate and duration in vivo precisely, on the basis of simple in vitro tests. The difference between controlled release and sustained release, Controlled drug delivery- which delivers the drug at a pre-determined rate for a specified period of time. Controlled release is perfectly zero order release that is the drug release over time irrespective of concentration. Sustain release dosage form- is defined as the type of dosage form in which a portion i.e. (initial dose) of the drug is released immediately, in order to achieve desired therapeutic response more promptly, and the remaining (maintenance dose) is then released slowly there by achieving a therapeutic level which is prolonged, but not maintained constant. Sustained release implies slow release of the drug over a time period. It may or may not be controlled release. Drug targeting, on the other hand, can be considered as a form of controlled release in that it exercises spatial control of drug release within the body.

Rationale

The basic rationale of a controlled release drug delivery system is to optimize the biopharmaceutics, pharmacokinetics, and pharmacodynamics properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of disease condition in the shortest possible time by using smallest quantity of drug, administered by most suitable route. The immediate release drug delivery system lacks some features like dose maintenance, controlled release rate and site targeting. An ideal drug delivery system should deliver the drug at a rate dictated by the need of body over a specified period of treatment.

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels as shown in Figure 1.

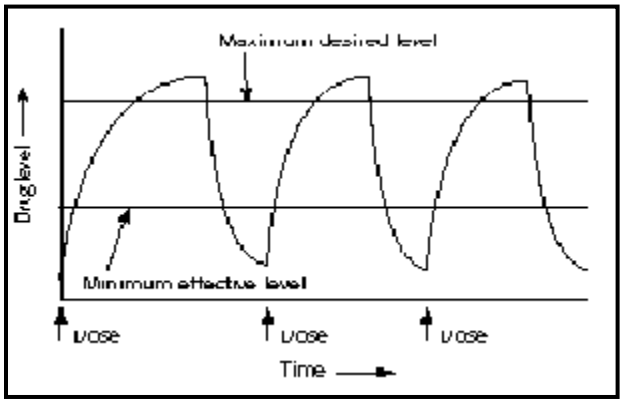


Figure 1: Drug levels in the blood with Conventional drug delivery systems

Advantages of Controlled Drug Delivery System

1. Avoid patient compliance problems.
2. Employ less total drug.
3. Minimize or eliminate local rate effects.
4. Minimize or eliminate systemic side effects.
5. Obtain less potentiation or reduction in drug activity with chronic use.
6. Minimize drug accumulation with chronic dosing.
7. Improve efficiency in treatment
8. Cure or control condition more promptly.
9. Improve control of condition, i.e., reduce fluctuation in drug level.
10. Improve bioavailability of some drugs.
11. Make use of special effects, e.g. sustained-release aspirin for morning relief of arthritis by dosing before bedtime
12. Economy.

Disadvantages of Controlled Drug Delivery System

1. Decreased systemic availability in comparison to conventional dosage forms.
2. Poor *in vitro - in vivo* correlation.
3. Possibility of dose dumping due to food, physiologic or formulation variables, chewing or grinding of oral formulations by the patient
4. Increased risk of toxicity
5. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
6. Higher cost of formulation

Approaches to design controlled release formulations

1. Dissolution controlled release
   - Encapsulation Dissolution control
   - Seed or granule coated

- Micro encapsulation
- Matrix Dissolution control

2. Diffusion controlled release
   - Reservoir type devices
   - Matrix type devices
3. Diffusion and Dissolution controlled systems
4. Ion exchange resins
5. Osmotically controlled release

Mechanistic Aspects for Oral Controlled Release Drug Delivery Formulation

Dissolution controlled release: Dissolution is defined as solid substance solubilized in a given solvent. It is a rate determining step when liquid is diffusing from solid. Several theories explain dissolution: Diffusion layer theory, Surface renewal theory, Limited solvation theory. Noyes Whitney Equation:

$dc/dt = kD.A (Cs – C)$

$dc/dt = D/h A. (Cs – C)$

dc/dt = Dissolution rate, k= Dissolution rate constant (1st order),

D = Diffusion coefficient/diffusivity,

Cs = Saturation/maximum drug solubility,

C =Conc. Of drug in bulk solution,

Cs-C=concentration gradient,

h =Thickness of diffusion layer. Two common formulation system rely on dissolution to determine release rate of drugs are:

Encapsulated dissolution system (ii) Matrix dissolution system

Encapsulated dissolution system

This is also known as Coating dissolution-controlled system. Dissolution rate of coat depends upon stability & thickness of coating. It masks color, odor, taste and minimize GI irritation. Controlled release products by decreasing the dissolution rate of drugs which are highly water soluble can be formulated by preparing appropriate salt or derivatives, by coating the drug with a slowly dissolving material, or by incorporating the drug into a slowly dissolving carrier. Examples: Ornade spansules, Chlortrimeto Repetabs.

Matrix dissolution system

It is also known as monolithic dissolution controlled system. In this dissolution IS controlled by: Altering porosity of tablet, decreasing its wet ability, dissolving at slower rate. It follows first order drug release. The drug release can be determined by dissolution rate of polymer. Examples: Demeaned extencaps, Dimetapp extentabs.

Diffusion controlled system

It is a major process for absorption in which no energy required. In this drug molecules diffuse from a region of higher concentration to lower concentration until equilibrium is attained and it is directly proportional to the concentration gradient across the membrane. In this system release rate is determined by its diffusion through a water-insoluble polymer.

There are two types of diffusion devices:

- Reservoir diffusion system
- Matrix diffusion system

Recent developments in novel drug delivery systems:

1. Phytosome
2. Liposome

3. Nanoparticles
4. Emulsions
5. Microsphere
6. Ethosome
7. Solid lipid nanopartical
8. Niosomes
9. Proniosomes
10. Transdermal Drug Delivery System
11. Dendrimers
12. Liquid Crystals
13. Hydrogels [9]

Phytosome:

Phytosomes are lipid compatible molecular complex which are composed of "phyto" which means plant and "some" meaning cell-like. Complexing the polyphenolic phytoconstituents in the molar ratio with phosphatidyl choline results in a new herbal drug delivery system, known as "Phytosome". Phytosomes are advanced forms of herbal products that are better absorbed, utilized to produce better results than those produced by conventional herbal extracts. Phytosomes show better pharmacokinetic and therapeutic profiles than conventional herbal extracts.

Advantages of phytosome:

1. Phytosome increases the absorption of active constituents, so its dose size required is small.
2. There is appreciable drug entrapment and improvement in the solubility of bile to herbal constituents, and it can target the liver.
3. In Phytosome, chemical bonds are formed between phosphatidylcholine molecules, so it shows good stability.
4. Phytosome improves the percutaneous absorption of herbal phytoconstituents.

Liposomes:

Tiny pouches made of lipids, or fat molecules surrounding a water core widely used for clinical cancer treatment. Several different kinds of liposomes are widely employed against infectious diseases and can deliver certain vaccines. During cancer treatment they encapsule drugs, shielding healthy cells from their toxicity, and prevent their concentration in vulnerable tissues such as those of patient kidneys and liver. Liposomes can also reduce or eliminate certain common side effects of cancer treatment such as nausea and hair loss.

They are form of vesicles that consist either of many, few or just one phospholipid bilayers. The polar character of liposomal core enables polar drug molecules to be encapsulated. Amphiphilic and lipophilic molecules are solubilized within phospholipid bilayer according to their affinity towards phospholipids.

Advantages of liposomes:

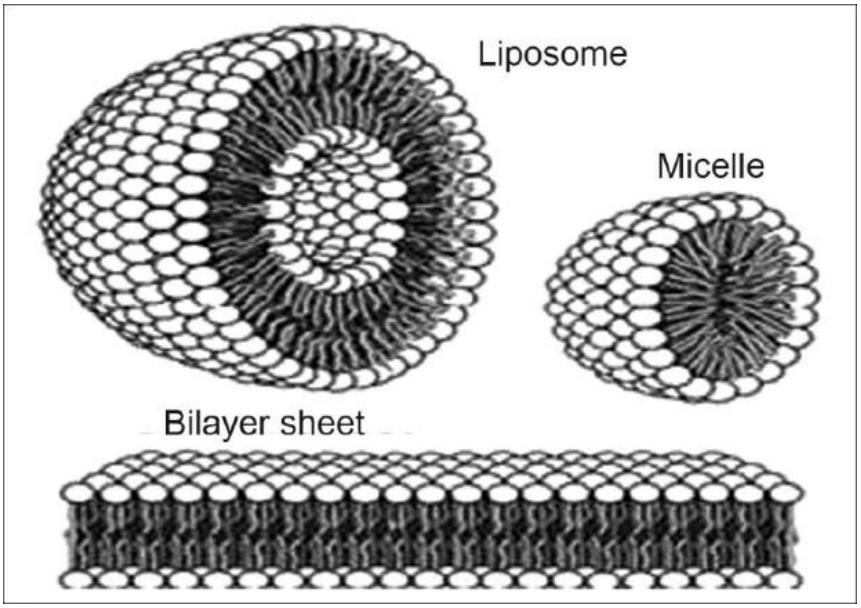
1. The high biocompatibility.
2. The easiness of preparation.
3. The chemical versatility that allows the loading of hydrophilic, amphiphilic, and lipophilic compounds.

The simple modulation of their pharmacokinetic properties by changing the chemical composition of the bilayer components.

Use of Liposomes:

Another major and important advancement in the novel drug delivery systems is the use of liposomes for carrying the drugs to the site of action. Liposomes in both modified and unmodified forms are able to change the course of pharmacokinetic parameters of the drugs. These are widely used in delivering the cytotoxic agents to the tumour tissue and preventing side effects like myelosuppression. These are also used in targeting through receptor-mediated

endocytosis. Modified liposomes also have huge applications in targeting various drugs to the organs like heart, liver, kidney, lungs and bones.



Nanoparticles

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. 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 peroralroute.

Advantages of herbal nanoparticle delivery system

1. Nanoparticulate system delivers the herbal formulation directly to the site of action.
2. Increased efficacy and therapeutic index.
3. Increased stability via encapsulation.
4. Improved pharmacokinetic effect.
5. Producible with various sizes, compound surface properties.

Emulsions:

Emulsion is a biphasic system in which one phase is intimately disperse in the other phase in the form of minute droplets in ranging in diameter from 0.1μm to 100 μm. In emulsion, one phase is always water or aqueous phase, and the other phase is oily liquid, i.e. non aqueous. Among them, the microemulsion is also called nanoemulsion, and the sub-micro-emulsion is called liquid emulsion. Microemulsion is a clear, thermodyanamically stable, frequently in combination with a co-surfactant.

Advantages of emulsion-based formulations:

1. It can release the drug for a long time because it is packed in the inner phase and makes direct.
2. Contact with the body and other tissues.
3. As a result of the lipophilic drugs being made into o/w/o emulsion, the droplets of oil are phagocytosised by macrophages and increase its concentration in liver, spleen and kidney.

4. As the emulsion contains herbal formulation, it will increase the stability of hydrolyzed formulated material and improve the penetrability of drug into skin and mucous.
5. The new type, viz., Elemenum emulsion, is used as an anti-cancer drug and causes no harm to the heart and liver.

Microsphere:

Microsphere comprises of small spherical particles, with diameters in the micrometer range, typically 1 μm to 1000 μm (1 mm). Microspheres are sometimes referred to as micro-particles. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Microspheres are classified as biodegradable or non-biodegradable. Biodegradable microspheres include albumin microspheres, modified starch microspheres, gelatin microspheres, polypropylene dextranmicrospheres, polylactic acid microspheres, etc. According to the current literature reports on non-biodegradable microspheres, polylactic acid is the only polymer approved to be used by people, and it is used as a controlled-release agent. Solid and hollow microspheres vary widely in density and therefore are used for different applications.

Ethosomes:

Ethosomes are developed by mixture of phospholipids and high concentration of ethanol. This carrier can penetrate through the skin deeply lead to improve drug delivery into deeper layer of skin and in blood circulation. These formulations are useful for topical delivery of alkaloids in form of gel and cream for patients comfort. They show increase in their permeability through the skin by fluidizing the lipid domain of the skin. Unstable nature and poor skin penetration are limits for Ethanosomes tropical delivery. The Ethosomes was developed and examined for their ability the topical absorption of Tetrandine through dermal delivery, and the relation of formulations to the pharmacological activity of Tetrandrine loaded in the formulation was also accessed. Result of the drug levels in rat plasma showed that when Tetrandrineloded Ethosomes were topically administered in rats the drug level was low to be detected in rat plasmaIn conclusion, Ethosomes were demonstrated to be promising carrier for improving topical delivery of Tentrandrine via skin.

Advantages of ethosomal drug delivery:

1. Ethosomes enhance transdermal permeation of drug through skin.
2. Ethosomes are a platform for the delivery of large amounts of diverse groups of drugs.
3. Ethosomaldrud is administered in semisolid form resulting in improvement in patients compliance.

Solid lipid nanoparticles:

(SLNs) are a new pharmaceutical delivery system or pharmaceutical formulation.

The conventional approaches such as use of permeation enhancers, surface modification, prodrug synthesis, complex formation and colloidal lipid carrier based strategies have been developed for the delivery of drugs to intestinal lymphatics. In addition, polymeric nanoparticles, self-emulsifying delivery systems, liposomes, microemulsions, micellar solutions and recently solid lipid nanoparticles *(SLN)* have been exploited as probable possibilities as carriers for oral intestinal lymphatic delivery.

A solid lipid nanoparticle is typically spherical with an average diameter between 10 and 1000 nanometers. Solid lipid nanoparticles possess a solid lipid core matrix that can solubilize lipophilic molecules. The lipid core is stabilized by surfactants (emulsifiers). The term lipid is used here in a broader sense and includes triglycerides (e.g. tristearin), diglycerides (e.g.glycerolbahenate), monoglycerides (e.g. glycerol monostearate), fatty acids (e.g. stearic acid), steroids (e.g. cholesterol), and waxes (e.g. cetyl palmitate). All classes of emulsifiers (with respect to charge and molecular weight) have been used to stabilize the lipid dispersion. It has been found that the combination of emulsifiers might prevent particle agglomeration more efficiently.

Niosomes:

Niosomes are multilamellar vesicles formed from non-ionic surfactants of the alkyl or dialkyl polyglycerol ether class and cholesterol. Earlier studies, in association with L'Oreal have shown that, in general, niosomes have properties as potential drug carriers similar to liposomes. Niosomes are different from liposomes in that they offer certain advantages over liposomes.

Proniosomes:

Proniosomes gel system is step forward to niosome, which can be utilized for various applications in delivery of actives at desire site. Proniosomal gels are the formulations, which on in situ hydration with water from the skin are converted into niosomes.

Dendrimers:

Dendrimers are precisely defined, synthetic nanoparticles that are approximately 5–10 nm in diameter. They are made up of layers of polymer surrounding a control core. The dendrimers surface contains many different sites to which drugs may be attach and also attachment sites for materials such as PEG which can be used to modified the way of dendrimer which interacts with body. PEG can be attached to dendrimer to 'disguise' it and prevent the body's defense mechanism for detecting it, there by slowing the process of break down. This fascinating particle holds significant promise for cancer treatment. Its many branches allow other molecules to easily attach to its surface. Researchers have fashioned dendrimers into sophisticated anticancer machines carrying five chemical tools–a molecule designed to bind to cancer cells, a second that fluorescence upon locating genetic mutations, a third to assist in imaging tumor shape using x–rays, a fourth carrying drugs released on demand, and a fifth that would send a signal when cancerous cells are finally dead. The creators of these dendrimers had successful tests with cancer cells in culture and plan to try them in living animals soon.

Liquid Crystals:

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

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.

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