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A Self-Assembled and Synergistically Method of Novel Carrier System: An Update Review

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Lalit Rana*[1], Vivek [1], Anu Kaushik[2], Utsav Gupta[3]

[1]Associate Professor – IIMT College of Pharmacy, Greater Noida India.

[2]Associate Professor – HIMT College of Pharmacy, Greater Noida India.

[3]School of Medical and Allied Science Galgotias University Greater Noida India.

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ABSTRACT

The existing method to deliver the drugs may reduce the efficacy of the drug to a great extent to increase the drug efficacy and compatibility a new type of drug delivery system was introduced which has the ideal characters like low toxicity, high bioavailability, person compatibility, low side effects. This drug delivery method was possible due to the advancement in the technological world and also due to the modification in the existing one. Also, the discovery of new bio-compactable material contributed greatly to this new drug delivery method. This method is called a novel drug delivery system under which various techniques like liposome, nanoparticles, resealed erythrocytes, microspores, and transdermal drug delivery systems are present. Also, the incorporation of the herbal drug in novel drug delivery increases the self-life and efficacy of the drug. Recent advancements in technology helped to make such non-remote guided chips which work on body hormone system these chips are called as microchips. This review focuses on the conventional and recent advancements in novel drug delivery systems.

1. INTRODUCTION:

The controlled-release technology is a premeditated mechanism to release the drug's active compound steadily over the specified period. since every drug has the side effect, toxicity problem, less bioavailability, less sustainability, therefore, it is not feasible to develop a new drug for every existing disease, therefore, research is done to modify the existing drug in such a way so that it can give maximum effect in minimum dose with the minimum side effect. [1] Those drugs with zero side effects, 100% bioavailability at any time, have optimal compliance i.e. easy to administer and low-cost production are called ideal drugs but in reality, it is almost impossible to make such a drug with these kinds of features. But at least an approach can be made to produce an ideal drug. [2]

The controlled release technology is a premeditated mechanism to release the drug's active compound steadily over a specific period. The main aim of this technique is to provide sustain release of drug in the body which increase the bioavailability of the drug. Encapsulated cells, oral soft gels, impregnated lozenges are some examples of controlled release technology. [1]

Drug delivery system can be classified into: -Conventional drug delivery system involves the drug to be formulated as tablet, capsules or injection so that easy administration can be there.

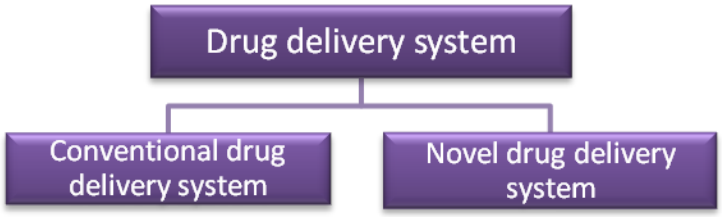


Figure No. 1: Classification of drug delivery system

This method is widely used to deliver the drugs however there are some drawbacks like no sustained release, side effects, toxic effects and can't be easily retrieved [3]. So, to overcome these drawbacks a new method of drug delivery was discovered that is a novel drug delivery system. In this system, we try to make an ideal vehicle or drug which possesses all the ideal characters. Although this process is in development but is a promising and more advantageous route of administration over the widely accepted conventional route.

1.1 Conventional drug delivery system

Conventional drug delivery is a method by which a drug is delivered inside the body by various routes of administration. This method is used by many pharmaceutical companies to cure a variety of diseases. Most of the formulations of this method are in the form of tablets, capsules, solutions, or injections. Since there are various routes to administer the drug and also there is a variety of formulation these two factors contribute to the development of some major drawback like limited bioavailability, toxicity.[3]

Classification of conventional routes of administration:

A) Oral route: One of the oldest routes of administration of drug inside the body. The formulations used in the oral route are generally tablets, capsules, some suspensions, or solutions. It is cheap, easy to administer, painless, and noninvasive in addition the medicine need not be sterile.

This route has some drawbacks like when the drug is taken orally it goes through GIT where every location have different pH so the drug has to stable in varying pH, also the drug is absorbed and distributed in the whole body i.e. not target specific and therefore take time to show the effect, the drug also goes through the first-pass metabolism which results in loss of drug from the body i.e. low bioavailability.

Sublingual tablet preparations disintegrate hastily and the petite amount of saliva present is typically sufficient for attaining disintegration of the dosage form coupled with enhanced dissolution and improved bioavailability. The sublingual drug delivery route is alternative and improved in contrast to oral drug delivery because sublingually administered dosage forms bypass the first-pass metabolism. A swift onset of pharmacological response is often desired for several drugs, particularly those which are used in the treatment of acute disorders, for example, glyceryl trinitrate (GTN), desamino-oxytocin, etc.[4]

B) Parental route: In the parental route the drug is administered through injections by this means the drug enters into the systemic circulation and also bypasses the first-pass metabolism which mostly occurs in the liver. The bioavailability is relatively high in this method compared to any other conventional route because of this it can be used in case of emergencies.

The major drawback of this route is the formulation should be sterile and this increases the cost of production, it is a painful route of administration, and muscle damage can be there, also a skilled person is necessary to administer the drug.

Depending on the site, and muscle in which injection is injected the parental route can be broadly classified into four categories.

Classification of parental route:

Subcutaneous: In this route, the drug is injected in such a way that the drug gets deposited in the subcutaneous tissue layer from where it slowly gets into the systemic circulation. Only a small amount of drug is delivered through this route and therefore an unskilled person can also administer the drug since the injection is not much deep in the muscle. Because of these factors, the subcutaneous route is modified as follows:

1) Dermojet: A high-velocity jet of drug solution is made to pass from a micro-fine orifice using a gun-like implement instead of needles. The drug pass penetrates the superficial layer and gets deposited in the subcutaneous layer. It is a painless process and beneficial in the case of mass inoculations.

2) Pellet implantation: As the name indicates in this route the drug is in the form of a solid pellet which is implanted with the help of trochar and cannula. As a result, the drug is released in a sustained manner for weeks or month[4]. The pellet implants find their use as a contraceptive and in the treatment of symptoms associated with androgen deficiency.[5-6]

3) Sialistic and biodegradable implants: In this method, crystalline drugs are used which are packed in suitable material tubes and capsules. These are then implanted under the skin over course of time the drug gets released in the blood and maintains a constant level i.e. sustain release of the drug is achieved. The non-biodegradable implants are removed but not the biodegradable implants. Norplant is given by this method.

Intramuscular: In this method, the drug is injected into the skeleton muscle such as- deltoid, triceps, gluteus maximus, rectus femoris, etc. these muscles do not have well supplied sensory nerves but are richly supplied with a vascular system which helps in the fast absorption of aqueous drugs in the blood and also is a less painful process. Since deep

penetration is needed therefore self-injection can't be administered. Depot preparations are given through this method.

Intravenous: when the drug is injected into the veins so that it can avoid the first-pass metabolism and can show fast therapeutic effect in the body. The drug can be given through as lump form or can infuse slowly in superficial veins over an hour. Since the innermost layers of veins are insensitive it is easy to deliver highly irritant drugs through this route. But i.v route has its disadvantage like it can cause necrosis of nearby tissues, only aqueous preparation can be given by this way, air embolism is also a risk in this route, in addition, it lacks targeted drug delivery which leads to the exposure of drug with the vital organs such as heart, brain, liver, etc.

Intradermal: In this route, the drug is injected under the skin resulting in a formation of a bleb or scarring/multiple punctures. This route is suited for limited drugs only as drug action is very slow in route. [4]

1.2 Novel drug delivery system

A novel drug delivery system is an advanced strategy to deliver the drug inside the body. The main aim of a novel drug delivery system is to overcome the limitations of conventional forms of drug delivery.

The followings are the limitations of the conventional drug delivery system.

1) Instability of drug

2) Less solubility

3) Because drug get distributed in all parts of the body its therapeutic activity decreases.

4) Not target specific

5) Some drug in the biological environment get converted into a different compound.

6) Most of the drug are get deposited in lipid membranes.

7) Because of first-pass metabolism the drug half-life get reduced.

8) No sustained release of drug.[7]

Classification of novel drug delivery system

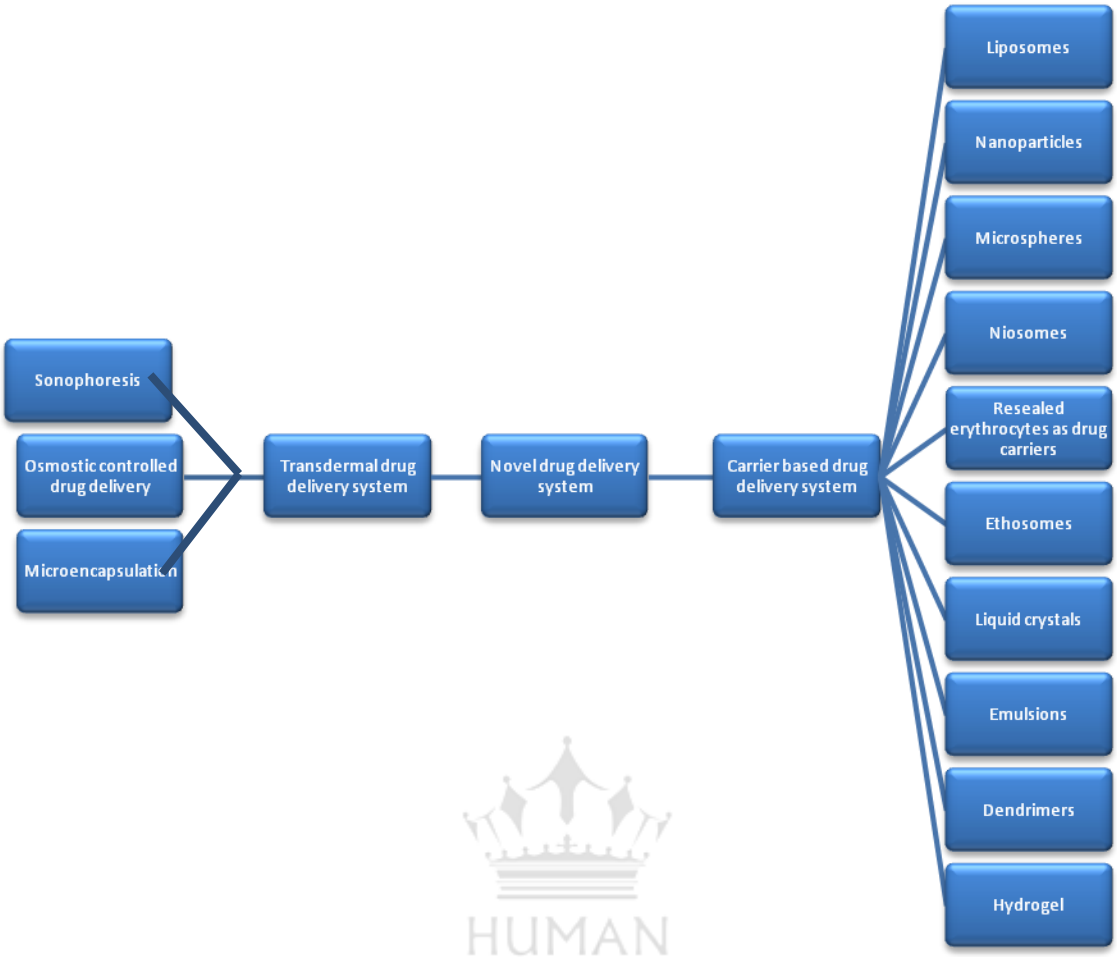


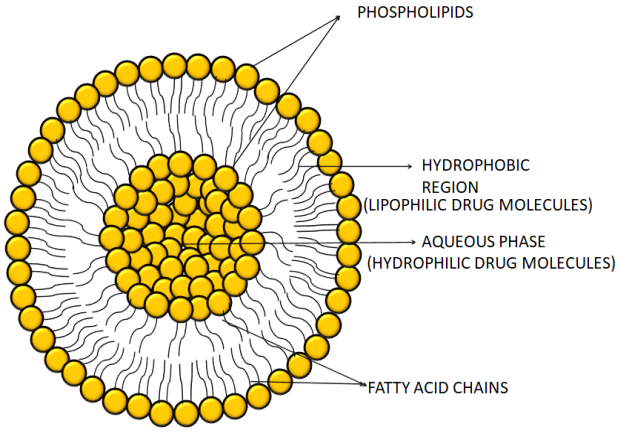
Figure No. 2: Classification of novel drug delivery systems and their further sub-classes.

Carrier-based drug delivery system

In this type of drug delivery, the carrier is the main component that is responsible to carry the drug inside the body and release the drug in sustains way without giving any toxic effect. To achieve this goal carriers like liquid crystals, nanoparticles, micelles, dendrimers, and many other carriers are used. The size of these particles lies between 10-400nm. [8]

1.2.1. Liposomes: - liposomes are bi-layer vesicles consisting of an aqueous layer which is enclosed by two bi-layer lipid membrane. The lipid layer is generally made from both natural and synthetic substances. The drug is incorporated in the aqueous layer so that the drug can pass through the cell membrane without any difficulty.

Liposomes are easy to make, have high bioavailability and give the flexibility to change their composition so that hydrophilic, amphiphilic and lipophilic can be incorporated [8-9]. As a result, liposomes find their uses as an adjuvant to elucidate immune response, as antiviral and antibacterial therapy, in anticancer therapy they were found to less toxic, they can be used to transport drug targeted to lungs, due to the ability of liposomes to accumulate in liver and spleen it was used to treat neonatal jaundice in animal model.[10-14]



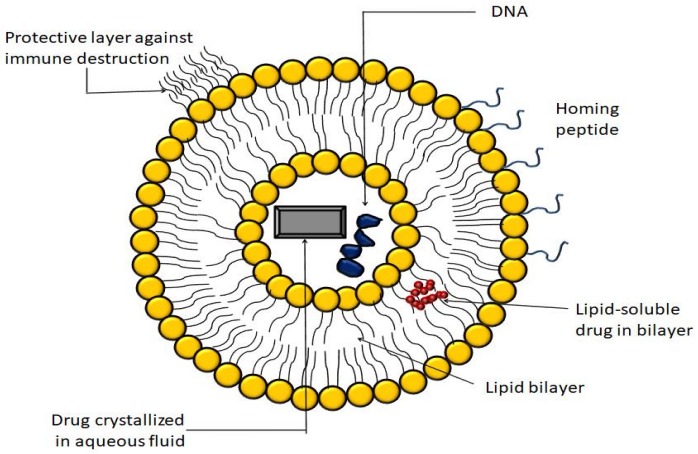


Figure No. 3: structure of liposome Figure No. 4: Drug delivery via liposome

1.2.2. Niosomes: -Niosomes are made when non-ionic surfactants like span 60, alkyl, or dialkyl glycerol ether are mixed with cholesterol. Both niosomes and liposomes are equally active but niosomes are preferred because they are biodegradable, highly stable, are biocompatible, and have a non-immunogenic effect[8-9]. As a result, niosomes finds its application in the formation of more effective antibacterial drug, also it is used in topical formulations.[15-16]

1.2.3. Proniosomes:- They are a much more advanced form than the niosomes. Their gels are actually in situ hydrated with water from the skin and convert into niosomes. They are more stable during the storage and sterilization process and are easy to transfer and distribute[9].

1.2.4. Nanoparticles: - Nanoparticles are in solid-state and can be crystalline or amorphous. Particles size range from 10-1000nm, the drugs are encapsulated, adsorbed, or entrapped hence is protected from physical or chemical degradation. In recent years, the discovery of biodegradable polymers as nanoparticle carriers led to the development of their application in gene therapy, controlled drug release, targeting specific organ/tissue, as the carrier to deliver protein or gene through peroral route[8]. Nanoparticles are a potent candidate for

thromboresistant uses, in the case of chemotherapy of drugs like -doxorubicin and dasatinib in cancer also increase cell sensitivity.[17-18]

Classification of nanoparticles-

a) **Nanotubes:** These are made up of carbon atoms and look like hollow cylinders which can later be mold a test tube-like structure. They can be filled and sealed and can prove itself as an important drug delivery carrier.

b) **Nanowires:** They are made up of glowing silica which is wrapped around a single strand of human hair. They look delicate and are five times smaller than the virus. Nanowires early application found in the detection of breast and ovarian malignancies[8]. Through the studies, it was observed that when drugs were tagged with nanowire their efficacy increased, and during the experiment, it was observed that functional recovery of the spinal cord in rats occurred.[19]

c) **Nano cantilever:** Cantilever is beamed of light which is anchored at one end. A nano cantilever serves as a sensor ideal enough to detect the extremely small molecules in the biological fluid.[8]

d) **Nanoshells:** They are gold-covered hollow silica spheres and on their surface antibodies are attached which make these shells to target cells like cancer cells. In the future, these nanoshells can be filled with drugs.[8]

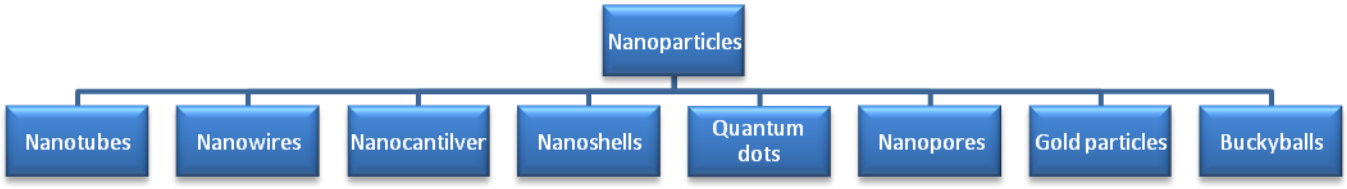


Figure No. 5: Classification of nanoparticles

e) **Quantum dots:** They are minuscule semiconductor particles that act as signposts for specific cells or molecules inside the body. This ability arises because of the emission of the radiation of a different wavelength which mainly depends on the type of cadmium used in their core. For example cadmium sulfide for ultraviolet to blue, cadmium selinide for most of the visible spectrum.

f) **Nanopores:** Nanopores are nanoparticles that have pores small enough so that DNA molecules can pass through them. Only one strand at a time can pass through the pores which makes them highly efficient and precise in DNA sequencing because of this reason it finds its use in cancer treatment and research. The nanopores can be engineered on the surface of drug capsules in such a way that they are slightly larger than medicines chemical structure we can control the rate of drug diffusion in the body.

g) **Gold nanoparticles**: In transmission electron microscope image gold particles are used as they have a solid core. In northwestern universities, researchers are using gold nanoparticles to make an ultra-sensitive device to detect DNA and protein markers that are linked with different forms of cancer.

h) **Bucky balls**: They are formed from buckminsterfullerene which is made up of 60 carbon atoms. They are very stable because of their hollow cage-like structure and unusual chemistry they can withstand high temperatures.

Buckyballs in the future may be used as a potent drug delivery carrier in cancer therapy or other treatments. In combination with antibodies, they can inhibit HIV and can fight allergy but it is quite difficult to use it in targeted drug delivery systems also they show high tissue accumulation.[8]

1.2.5. Microspheres: - microspheres are free-flowing powder particles whose size is in micrometers ranging from 1µm to 1000µm. They are made from synthetic polymer and natural polymer. The synthetic polymer can be classified into biodegradable and non-biodegradable polymers. In non-biodegradable polymer, the carrier may remain and accumulate inside the body after releasing the drug which can cause toxicity and adverse effects. Polylactic acid, epoxy polymer, and polymethyl methacrylate are few examples of non-biodegradablepolymer.[8-9]

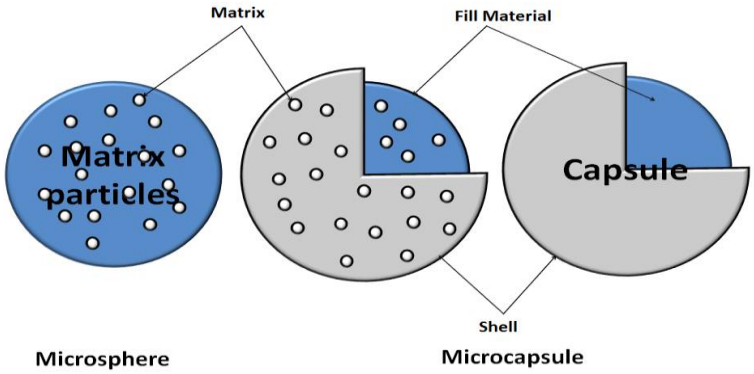


Figure No. 6: Structure of microsphere and microcapsule

The biodegradable polymers do not accumulate inside the body and can be easily excreted out. Lactides, glycolides, and their polymer, poly anhydrides are some biodegradable polymer.[8]

Natural polymers are derived from nature for example albumin, gelatin, agarose, starch, and some natural polymer can be modified like poly starch, polydextran.[8]

Advantages:

1) microspheres can be administered orally or through injections, they can be modified so that control release of drug can take place, target specificity of the drug is also increased.

2) The drugs do not degrade easily and are release on the outer surface which results in long-acting effect.[9]

1.2.6. Resealed erythrocytes as drug carriers: Resealed Erythrocytes are biocompatible, biodegradable, high bioavailability, and can be linked with numerous active drug substances. Resealed erythrocyte has numerous benefits over the other drug delivery administration mechanism which makes it advanced than another mechanism. Carrier erythrocytes are constructed by collecting a blood sample from the organism of interest and sorting out erythrocytes from plasma. By using a variety of methods, the cells are wrecked and the drug is ensnared into the erythrocytes, at last, they are resealed and the resulting carriers are then called "resealed erythrocytes". Resealed erythrocytes, as a drug delivery system, has excellent capacity to enhance the therapeutic index and patient compliance. It has immense potential to attain site-specific drug delivery with the least wastage of drugs and it also extends the

release of the drug. So many drugs like aspirin and steroids which have many side effects can be reduced by resealed erythrocyte drug delivery mechanism.[8]

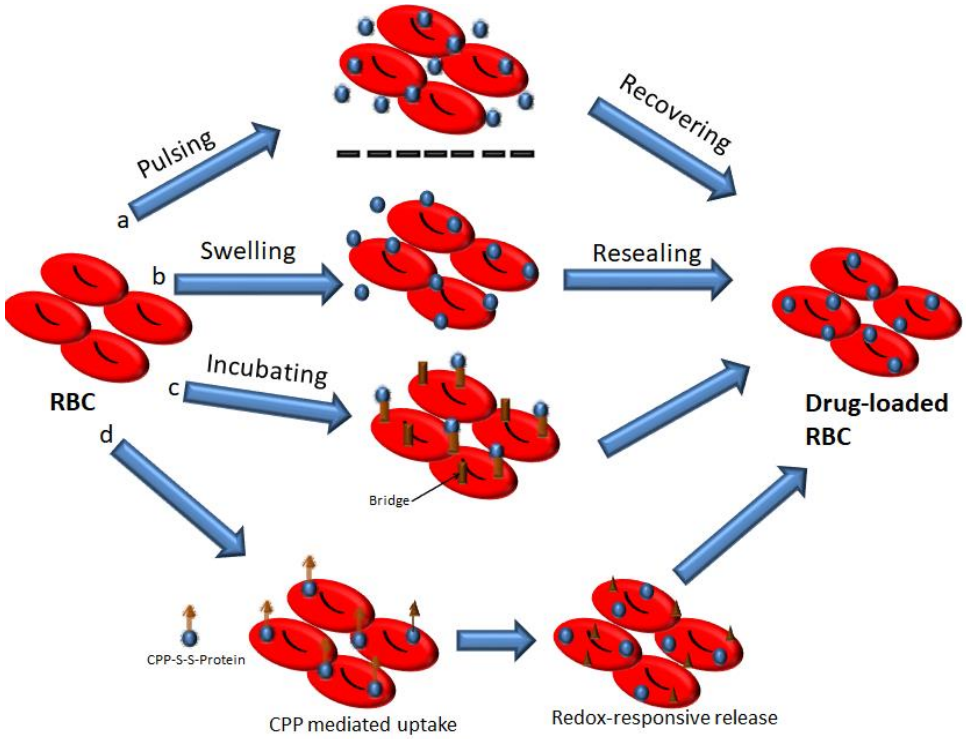


Figure No. 7: Procedure for drug incorporation in erythrocytes.

Erythrocytes as a carrier are used in the following ways:-

For target-specific action- In this, the member of an erythrocyte is used. This is achieved by rupturing the cell into a hypotonic solution and after that initiating the drug into the cell and then resealing them into spherical form. These erythrocytes are also termed red cell ghosts.

To sustain drug release- the life of an erythrocyte is up to 120 days by entrapping the drug into the erythrocytes and releasing them in the bloodstream leads to the sustained release of drug in the body which in result give sustain action. The encapsulation of drugs within erythrocytes can be done by various methods.[20]

Desire properties of resealed erythrocytes as drug carriers-

1) Controlled and sustained release of the drug.

2) Should have shape and size which do not hinder their flow from the capillaries.

3) Drug leakage should be minimum and should have a low toxic effect.

4) Should have the ability to carry a wide spectrum of the drug.[21-22]

Advantages:-

1. Erythrocytes are the body's self-made product and can be degraded in nature.

2. Isolation and encapsulation of erythrocytes are easy and a large volume of drug can be entrapped in it.

3. Chemical alteration of entrapped the drug is not necessary. As in some drug delivery system, the covalent bonding between the drug and carrier hinder the action of the parent drug.

4. They are not targeted by the immune system.[22-23]

Drawbacks: -

1) Dose dumping or clumping can be there.

2) Their potential as a carrier is limited for non-phagocyte target tissue. [8]

3) The physiology of erythrocyte can be changed by loaded molecules.[31]

4) Since they have biological origin the encapsulation of drug maybe not uniform because of inherent variations.[29]

In vivo application of resealed erythrocytes:-

1) Slow drug release- it can be used as a moving deport station for the delivery of antineoplastic, antibiotics, vitamins, steroids, and cardiovascular drugs.[24-25]

2) Drug targeting- resealed erythrocytes act as a targeting tool because of the surface modification. Which is then used to target the organs of the mononuclear phagocytes system/ reticuloendothelial system (RES) as macrophages can identify the change in the membrane.[20-26]

3) Treatment of parasitic organs- the property of resealed erythrocytes to aggregate in the RES organs is an advantageous point while delivering the anti-parasitic agents. As some

parasites which develop in the RES organs can be successfully monitored by this method. Animal models for anti-malarial, anti-leishmanial, and anti-amoebic drugs showed positive results.[29]

4) Removal of toxic agents – to remove the toxic substance from the body resealed erythrocytes can be used. Cannon et al. reported that the inhibition of cyanide intoxication with murine as a carrier in erythrocytes.[29]

5) Enzyme therapy- resealed erythrocytes can be used to treat metabolic disorders related to deficiency or missing enzymes. Such as in Gaucher's disease, hyperargininaemia, hyperuicaemia.[27]

6) Removal of RES iron- due to excessive transfusion in thalassemic patients the iron gets deposited in the RES organs as aged RBCs get destroyed in RES organs to treat this overloaded Desferrioxamine-loaded erythrocytes have been used.[20-28]

7) Targeting Non-RES- the application of resealed erythrocytes outside the RES organs includes:

a) Entrapping paramagnetic substance along with drug

b) Entrapping the photosensitive material

c) Use of ultrasound waves. [29]

Ethosomes: - when phospholipids and a high concentration of ethanol are mixed ethosomes are formed. They show high skin permeability and therefore is mainly used as topical drug delivery carrier. It works by fluidizing the lipid domain of the skin which results in high permeability of drug in the deeper layer of skin and also in blood circulation. But ethosomes have unstable nature which makes their storage difficult. It was developed to deliver tetrandrine through a tropical method which may reduce the side effects and increase patient compliances. Via ethosomes as a drug carrier we can deliver a wide range of drugs, also since this formulation is in semisolid form when administered the patient compliance is increased.

In conclusion, ethosomes is a potent drug carrier for delivering the drug through tropical route[9].

Liquid crystals: - They exhibit the properties of both liquid and solid-state and are formed via layering the polar and non-polar solvents in a definite proportion and indifferent geometry. The drug is dissolved or entrapped in this solvent layers[9].

Emulsions: - Emulsion is a biphasic liquid dosage form in which one phase is the continuous phase and the other is the disperse phase which is distributed in the form of small droplets whose size range from 0.1µm to 100µm. The common emulsion is made by mixing the aqueous and non-aqueous components with some surfactant.

A microemulsion or Nanoemulsion is a type of emulsion in which the droplet size range is in nanometer. It is clear and thermodynamically more stable.

Advantages of emulsion as a drug carrier-

1) Since the drug is packed in the inner phase it takes time to release the drug hence prolongs action.

2) In the case of lipophilic drug which is delivered by O/W/O emulsion, the oil layer is degraded by macrophages which results in increase concentration in the spleen, liver, and kidney.

3) Elemenumemulsion is a new emulsion type that is used as an anti-cancer drug and does not produce any toxic effect on the heart and liver[9].

Hydrogels: - hydrogels have a 3-dimensional structure and are hydrophilic. Their polymeric networks can imbibe a large amount of water and biological fluids in their structure. Hydrogels are used as drug reservoirs to regulate the drug release, or also used for the sustained release of the drug or as swelling-controlled release devices [9].

Recent Trend in Hydrogel Based Targeted Drug Delivery

1. Supramolecular Hydrogels

The supramolecular hydrogel system is constituted of intermolecular non-covalent interactions that have two or more molecular components detained together. The non-covalent crosslinking is an extremely recent and attractive aspect of hydrogels because it helps in targetting the problems of limited drug loading potential and drug incorporation for use only as implantables which might be the mere option with a covalently cross-linked

arrangement. Apart from providing the right physical constancy for the hydrogels, they achieve drug loading and gelation concurrently in an aqueous environment devoid of the need for a covalent cross-linking. Modern development has been developed with supramolecular hydrogels using self-assembled inclusion complexes between cyclodextrins and bio-degradable block copolymers which offer the constant and restricted release of macromolecular drugs [30].

2. DNA-Hydrogels

Hybrid bio-nano materials might be produced using DNA as the fundamental unit. Unsurprisingly two- or three-dimensional structures are produced from DNA molecules. Highly structured networks are created by hybridizing complementary DNA molecules and the consequential hydrogel structures develop upon encounter with an aqueous environment which results in swelling. These materials append to any other type of nucleic acid molecules (such as siRNA, miRNA), and they can also load DNA binding drugs. High solubility, biocompatibility, versatility, and receptiveness are key features of such hydrogels. They can be tagged with appropriate fluorescent molecules for tracking biological research studies *in vitro* [31].

An attractive application of hydrogels has been made with the progression of multi-functional quantum dot (QD) DNA hydrogels. DNA hydrogels are composed of complementary strands of DNA hybridized to form a crosslinked network that bulges in an aqueous environment. Although, for biological research to be more easily and effectively performed their requirement of fluorescent molecule attached to the hydrogel can be a superlative option offering both targeted delivery and imaging. Zhang et al. recently developed a QD-based DNA hydrogel which has highly tunable size, spectral, and delivery properties and is linked to the DNA binding drug doxorubicin The drug targeted cancerous cells and the QD DNA hydrogel improved the potency of the drug *in-vitro*. The single-step assembly of zinc sulfide QD Doxorubicin DNA hydrogels demonstrated elevated tumor accumulation *in vitro*, soaring bio-compatibility, was three times more efficacious than free DOX, and served as an exceptional tool for *in vivo* bio-imaging in monitoring tumor progression over time [31].

3. Bio-Inspired Hydrogels

New types of hydrogels are used for drug delivery purposes are bio-inspired hydrogels. These 3D materials review the biological micro-environment related to the disease condition and

encourage studies on the optimized mechanism of the targeted drug delivery process, the mechanism the therapy behaved *in-vivo*, the way disease progressed, and so on. These are predominantly helpful in cancer therapy because the disease is specifically complex and normally connected with complex cellular and physiological changes that need progressive monitoring. Engineering such microenvironments might be a very positive approach to endorse research and study the diseased state and therapeutic procedure better. The rigidity of the 3D structure used for studying liver cancer is a significant element to regulate molecular diffusivity and malignancy. The flexible unit of the collagen gels was increased by strengthening interconnected collagen fibers with wide-ranging amounts of poly(ethylene glycol) di(succinic acid *N*-hydroxysuccinimidyl ester). The softer gels developed cancer spheroids while the stiffer ones demonstrated decreased malignancy. The model presented enhanced understanding and regulation of the evolving nature of cancerous cells [32].

Fluid for an extended phase of time concerning eye drops was observed. The drug timolol was released in response to lysozyme in the medium and not in PBS. Enzyme cleavable polymers in hydrogels enabled this [32].

4. Multi-Functional and Stimuli-Responsive Hydrogels

Hydrogels are multi-functional and carriers of anti-cancer drugs which are a typical example of the resourcefulness of these delivery vehicles and their amenability to chemical alterations to enhance their therapeutic property. Magnetite nanoparticles that maintained improved intracellular uptake by HeLa cells also had folate ligand on them to facilitate targeted delivery. In addition, the hydrogel polymers were thermally receptive and DOX-loaded. These customized hydrogels presented advantages for instance increased cellular uptake and apoptotic activity *in vitro* [33].

Another stimuli-responsive hydrogel developed very lately made application of biocompatible thermally receptive polymers that aided in the disintegration of cancerous cells. The experiment was performed *in vitro* with an exterior resource of heat and showed successful cell degradation. Those hydrogel particles had RGD (Arginine, Glycine, Aspartate) peptides linked to their surface that could bind to cells [33].

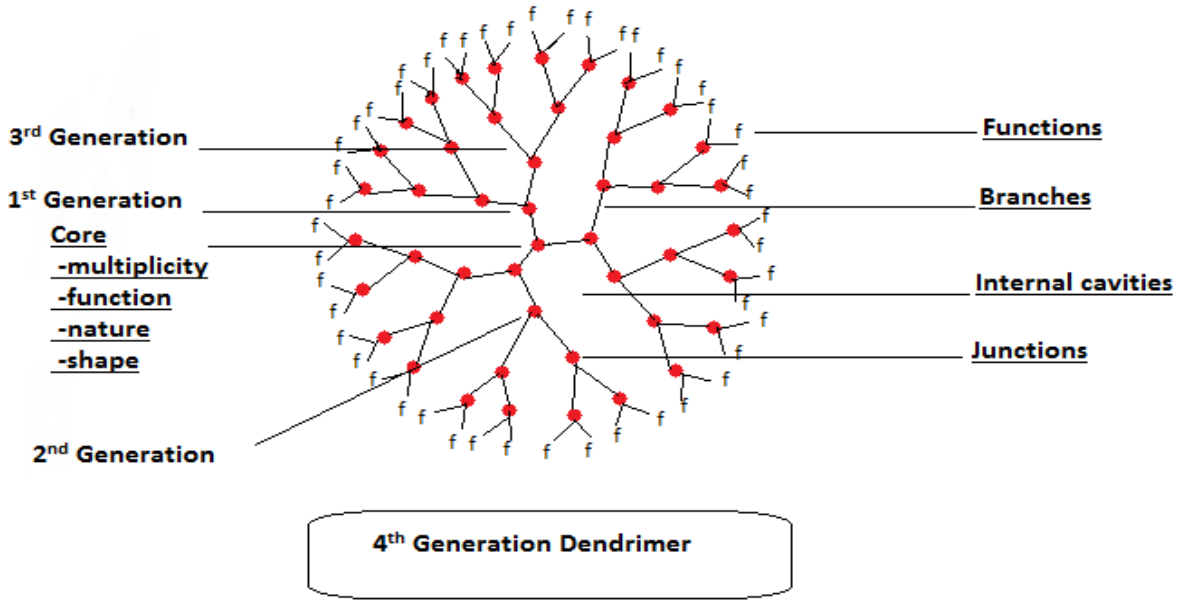


Figure No. 8: **4th Generation Dendrimer**

Dendrimers: - They are micrometer-size, highly branched, and monodisperse macromolecule with symmetrical architecture which provide them stability. They consist of three-unit i.e. central core, branching units, and terminal functional group. The property of nanocavity is determined by the core and internal units which ultimately determine the solubilizing properties.

To protect the stability of dendrimers from the mononuclear phagocyte system (MPSs) functionalization of dendrimers with polyethylene glycol chains (PGC) is done[8-9].

Transdermal drug delivery system

In the transdermal drug delivery system the drug is delivered through the skin, the skin helps in the sustained release of the drug inside the circulatory system. The drug is self-contained and in the discrete dosage form. This route of drug administration drew scientists attention because it is safe and convenient.

Advantages of transdermal drug delivery system: -

1) Since the drug directly enters the systemic circulation the first-pass metabolism and gastrointestinal irritation is avoided.

2) It is easy to terminate the therapy at any point in time.

3) This route of administration is predictable and also has a long action period as result physiological and pharmacological response is increased.

4) Patient compliance increases due to multiple dosage profile elimination[8].

Methods of transdermal drug delivery system:-

Sonophoresis: - In the sonophoresis ultrasonic energy is used to increase the rate of absorption of skin, dermis, or in the epidermis. This method is localized, convenient, rapid, non-invasive, and used for low molecular weight drugs and also for some macromolecules.

The mechanism of action of sonophoresis is that it combines the thermal, chemical, and mechanical strength to create an alteration in the skin layer so that the drug can penetrate deep inside the skin layer. The desired effect is achieved when ultrasound frequency is in the range of 20 kHz- 16 MHz with intensity up to $3W/cm^2$.[8]

Osmotic controlled drug delivery: - In this method to release the drug in a controlled manner osmotic pressure as a driving force is used. This route of drug delivery can be used for oral as well as for parental administration, the oral administration is known as a gastro-intestinal therapeutic system and the parental one is known as implants[8].

Classification: -

1) Implantable: some common implants are a) the rose and nelson pump, b) higuchi leeper pump, c) higuchi theuwes pump.

2) Oral osmotic pump: it can further classify into 3 categories i.e. a) single chamber, b) multi-chamber and c) specific type.

Advantages: -

1) The release of the drug is independent of intestinal pH, presence of food, or another factor.

2) The rate of release of drugs is high compare to the conventional method.

Since this method is easy to understand we can be predicted and can easily change the features that control the release parameters of the drug.

3) This route of administration shows a zero-order release profile after the initial lag phase.

Disadvantages: -

1) This route is expensive.

2) Film defects will be there if the uniform coating is not there which can cause dose dumping.

3) In case of adverse effects, the retrieval therapy of the drug is not possible[8].

Microencapsulation: - It is a process in which small droplets or particles are coated with a continuous film of polymeric material. The size range of microencapsulation is from 1micrometer to 1000 micrometers in diameter. The method helps us to convert the liquid into solid, changing the colloidal and properties, protection from environmental factors.

In microencapsulation the drug or active agent also called the core is surrounded by a shell this shell is mostly made from organic components and in some cases, lipids or wax are also used. Active agents like living cells, enzymes, agrochemicals, flavors, and pharmaceutical drugs can be delivered through microencapsulation. Through research, it was concluded that the rate of drug release, sustained release, prolong release, or delay in the release can be achieved by altering or using a different type of polymers in the formulation process which can also ensure safety or through new drug entities and by also improving the therapeutic efficacy[8].

Microchip technology

Microchip technology is an implant method in which the release of drugs is controlled by a microchip. The microchip is wirelessly programmed in such a way that the drug is released every day at a particular time hence maintaining the desire drug level in the body.

It is believed that this method can cure the problems that arise due to the deregulation of the endocrine system or in the case of osteoporosis. The early human trials were conducted in 2015 and it was concluded that this device worked without any side effect or other problem[34].

1. Recent studies

An investigation of modern microchip developments, prominent patents, and clinically pertinent applications can enlighten the arrangement of microchips in modern medicine, as well as inspiring areas of advanced research study. In 1998, the US Patent "Microchip Drug Delivery Devices" was honored to Santini Jr. et al., who for the first time delineated the stricture of a multi-reservoir microchip system with a dynamic release system. In 1999, Santini Jr. et al. debuted the initial electrochemically activated drug administration microchip. In their contrivance, release from individually dosed reservoirs is activated by providing an electric potential between the cathode and the anode—a thin gold membrane casing the particular reservoir to be arranged. A widespread number of additional advancements, especially including (but not limited to) refined fabrication methods, microchip flexibility for ophthalmic use, and improved diversity, mechanism of operation, and information of wireless data and power transfer, have so far been discovered and patented by the researchers.[35-43]

Based on these studies, primarily in vitro release studies dogged whether microchip technology could attain the controlled release of a selected therapeutic compound, with standard pulses of drug release into the experimental system. Numerous molecular masses of PLGA copolymer (PLGA 4.4, 11, 28, or 64) were elected as the reservoir membrane substance of option, with a 50 : 50 ratio of lactic acid and glycolic acid. As observed with a ^{3}H-heparin discharge under, a regular stepwise release of the drug was experienced—correlating with every microchip reservoir membrane degrading and opening [23]. analogous results were accomplished with ^{14}C-dextran, ^{125}I-HGH, and an amalgamation of dextran and heparin. These observations offered confirmation that controllable and pulsatile drug release from microchips was possible in vitro, catalyzing in-vivo experimental model systems. A 2007 research study observed that the canine pharmacokinetic profiles of leuprolide—a polypeptide therapeutic pointed out for prostate cancer and endometriosis treatment—when administered in vivo via microchip sources in contrast to subcutaneous injection. The recent research concluded that the pharmacokinetics of the two delivery methods were undeniably comparable, hitherto the microchip mechanism presented better control on serum drug concentration. fascinatingly, the fibrous capsule that formed around the implant was found to be insignificantly affecting the pharmacokinetic parameters of the drug—a noteworthy consideration for human in vivo application, where bio-adhesion to alien material (encouraging to altered performance, infection, etc.) is well recognized.[36-38]

2. Future applications

The prevalent purpose of microchip technology tends to be transformative to the modern healthcare structure. Therapeutic development will be enhanced, billions of dollars worth of unnecessary expenses will be avoided, and the quality treatment of patient populations will elevate.

Although human research including microchips is limited to treating a small number of particular diseases, modifications will allow diversification of this technology into a larger range of therapeutic areas. Drugs with dose delivery systems, which are considered difficult or undesirable in other administration ways, could take place by a passive mechanism. Medications for diseases such as diabetes and hypertension where dose titrations are essential could be transformed to develop automated therapy regimens that are harmless and more effective. When used in combination with implants, this controlled-release technology will decline the chances of alien body reactions and rejection, as a result decreasing the chances of inflammation and pain, permitting the body to heal faster after surgery. Applications of microchips might be diversified to create artificial glands. Regulations of hormones in the body related to dysfunctional glands could assist in controlling current disease states and preventing the development of other hormone prompted disorders.

Microchip delivery mechanism will help in the treatments for diseases which has a lower rate of compliance (mental disorders, few cancer therapeutics, long-term antibiotics, etc.) or which have abusing potential. An extension of inpatient acquiescence will save money in healthcare expenditures every year due to the reductions in hospital stays, doctor visits, and lack of prescription follow. Drug abuse might be better standardized for patients who are under II and III classified treatments. Patients with addiction before implantation might be weaned off of their treatment until they are given the anticipated set of reimbursement.

With the advancement in microchip technology, as well as trials representing pulsatile release, steady drug pharmacokinetics, and effectiveness and efficacy in treating disease conditions, applied microchip research is on the rise. Further research is necessary to establish clinical procedures in which a drug needs local release, pulsatile control, and reduced compliance burden. As the anode membrane is ablated electro-thermally, the fortune of the degraded byproducts on drug release, compatibility, and toxicity additional in vivo research.

The development of an elevated-level market model to predict the future sales for a company that exploits microchip technology starts with a quantification of the size of the patient population and current statistics concerning medication options. From these outcrops, estimates of translation rates, pricing, and raw peak sales can be calculated. Raw peak sales were calculated for the year 2035, which would be reasonable if preclinical trials were currently underway. This estimate was used for the sake of modeling potential sales since no date is known for the start of research into its application in the diabetes field. Though the technology already has evidence supporting its efficacy, its modeled early stage in development and a large number of competitors in the insulin market yield both a low probability of success and a low market share. With these numbers handicapping the sales projections, Company X would still be near $1 billion in peak sales, giving the application of microchip technology in the field of diabetes a blockbuster status[35].

Herbal drug incorporation with the novel delivery method

Herbal drugs are the formulation that is made from one or more than one herb. The herbs can be processed or natural and are in specific quantity to give the beneficial desire effect. To make the drugs from herbs that are from plants various methods are employed such as distillation, fermentation, extraction, purification, and concentration. Herbal drugs consist of many active constituents and have a complex structure as a whole every active constituent has a synergistic effect and so the therapeutic effect is increased with fewer side effect[9].

The incorporation of herbal drugs with novel delivery methods reduces the side effect, toxic effects and since the herbal drug production cost is low their incorporation will lead to cheap medication availability in the market. Also, novel drugs can be modified to be target-specific and to release drugs for a long time the degradation or repeated administration of herbal drugs won't be there. The herbal drugs can be incorporated by many methods like liposome, noisome, microencapsulation, nanoparticles, transdermal methods, liquid crystals, hydrogels, dendrimers, and many others which we discussed above along with that there is one more method that is via phytosome[9].

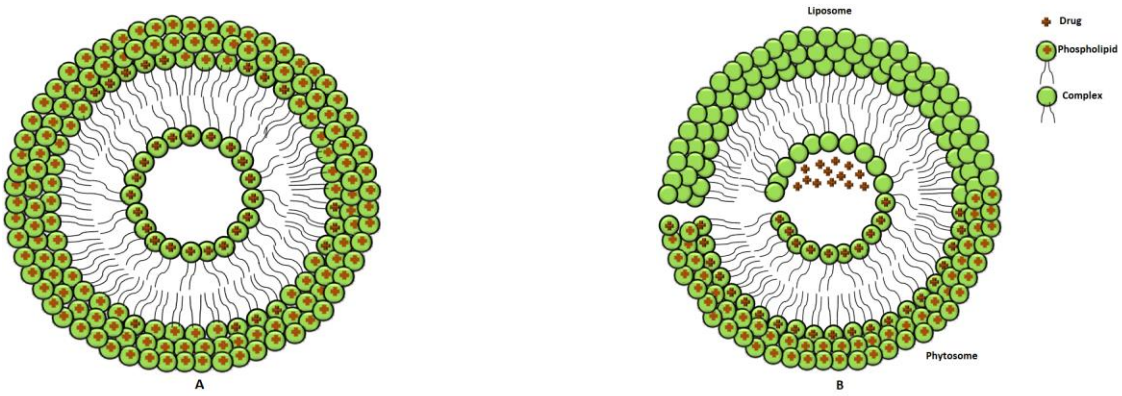


Figure No. 9: (A) Structure of phytosome (B) Difference between liposome and phytosome.

Phytosome: - As the name suggests phytosome is made up of two constituents "phyto" which means plant and "some" which means cells. It is prepared by complexing the molar ratio of polyphenol which is a phyto constituent with phosphatidylcholine. It is a lipid compatible molecule and an advanced form of herbal drug which shows better absorption, pharmacokinetic effect and has a good therapeutic profile than the conventional method.

Advantages –

1) Better stability since the chemical bonds are formed between the phosphatidylcholine molecules.

2) Enhance percutaneous adsorption due to its lipid nature.

3) A good amount of drug can be entrapped in phytosome and can have good solubility in bile along with that it can target the liver.

4) A low dose is required as it increases the absorption of herbal active constituents[9].

CONCLUSION:

Novel drug delivery is a new advancement with a better result than the existing drug delivery system. As in this we can achieve the low toxicity, high bioavailability, and sustain release of drug and can also increase the shelf-life of the drug. The incorporation of herbal drugs with novel drug delivery systems is one of the best drug delivery systems as herbal drugs have an inbuilt low toxic effect and have a wide variety of compounds that ultimately give the synergetic effect in the body. Also, the regulation of drug dose with the help of micro-chips

gives freedom from remembering the dose time and caring the drug as it is an implant that releases drug at regular intervals of time and works in sync with the body endocrine system.

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