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NOVEL DRUG DELIVERY SYSTEM – RECENT APPROACHES TOWARDS DRUG DEVELOPMENT

Ekjot Kaur[1*], Saloni Narula[2] and Mahesh Kumar Kataria[1]

[1]Department of Pharmaceutics, Seth G.L. Bihani S.D. College of Technical Education, Gagan Path, Sri Ganganagar (Raj.) 335001, India.

[2]Department of Pharmaceutics, Om Sterling Global University, Hisar, Haryana, 125001, India.

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ABSTRACT

A drug delivery process is the method for the administration of any pharmaceutical compound to achieve maximum therapeutic effect in humans and animals. It may be defined as a system comprising of Drug formulation, Medical device or dosage form /technology which carries the drug inside the body. A drug carrier is any substrate used in the process of drug delivery which servesto improve the selectivity, effectiveness and safety of drug administration. Drug Carriers are primarily used to control the release into systemic circulation. A wide variety of drug carrier systems have been developed and studied, each of which has unique advantages and disadvantages. The popular drug carriers include liposomes, microspheres, nanoparticles etc.

Corresponding author
Ekjot Kaur
M. Pharm (Pharmaceutics) 4th Semester,
Research Scholar, Department of Pharmaceutics,
Seth G.L. Bihani S.D. College of Technical Education,
Gagan Path, Sri Ganganagar (Raj.) 335001, India.
ekjot.khurana@gmail.com

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INTRODUCTION

A drug delivery process is the method for the administration of any pharmaceutical compound to achieve maximum therapeutic effect in humans and animals. It may be defined as a system comprising of Drug formulation, Medical device or dosage form /technology which carries the drug inside the body. A drug carrier is any substrate used in the process of drug delivery which servesto improve the selectivity, effectiveness and safety of drug administration. Drug Carriers are primarily used to control the release into systemic circulation. A wide variety of drug carrier systems have been developed and studied, each of which has unique advantages and disadvantages. The popular drug carriers include liposomes, microspheres, nanoparticles etc.

Carrier-Based Drug Delivery Pathways: The following four major steps are included in carrier based drug delivery system;

(i) Encapsulation of drug into carrier or adsorption of a drug onto a carrier.
(ii) Delivery of the drug by carrier construct to the desired location within the human body.
(iii) Uptake of the construct by a cell membrane.
(iv) Release of the drug from the carrier.

The review article dealt with the introduction, production, advantage and disadvantage, evaluation and applications of different drug carriers.

TYPES OF DRUG CARRIER USED IN NOVEL DRUG DELIVERY SYSTEM

NANOPARTICLES

Nanoparticles are defined as particulate dispersions or solid particles with a size range of 10-1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix **(Bhatia S., 2016).** The major goals in designing nanoparticles are to control particle size, surface properties and release of active pharmaceutical ingredient in order to achieve the site specific action of the drug at the therapeutically optimal rate and dose regimen.

Types of nanoparticle:

Nanocrystals/nanosuspensions are crystals of poorly water soluble drug in nanosize which when dispersed in water produce nanosuspension. Nanoemulsion/microemulsion are clear, dispersed systems comprising of two immiscible liquids wherein the dispersed phase droplets are of nanosize but differ from each other. Nanocapsules are oil containing nanocapsule differ from o/w nanoemulsion in providing a barrier made from polymers between the core and the surrounding environment.

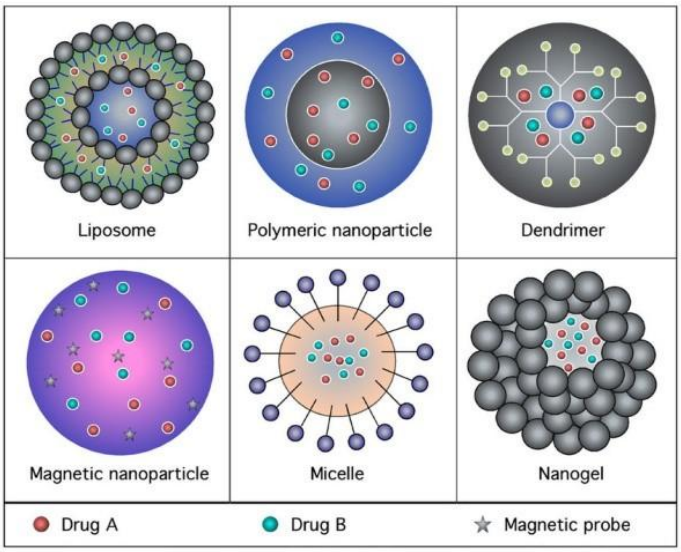

Figure 1 Different Type of Nanoparticles.

Polymeric-nanoparticle/nanosphere consists of drug dispersed in an amorphous form within a polymer matrix. Polymers suitable for the preparation of biodegradable nanoparticles include cellulose derivatives, poly alkyl cyano acrylates), poly methylidene malonate, polyorthoesters, polyanhydrieds and polyesters etc. Solid-lipid nanoparticles (SLN) melt emulsified nanoparticle based on lipids (or waxes) are solid at room temperature and generally prepared by hot high pressure homogenization.

Nanoparticles Production Processes

1) Dispersion based processes

a) Wet milling
b) High pressure homogenization
c) Emulsification technology

*2) **Precipitation based processes***

a) Spray freezing into liquid (SFL)
b) Evaporation precipitation into aqueous solution(EPAS)
c) Rapid expansion from a liquefied –gas solution (RESS)
d) Preparation with a compressed fluid antisolvent (PCA)

Applications:

In drugs and medications:

- Superparamagnetic iron oxide nanoparticles are used in MRI contrast enhancement, immunoassay etc.
- Biodegradable nanoparticles are used as effective drug delivery devices.
- Semiconductor and metallic nanoparticles are shown to have antineoplastic effect which are used to inhibit tumor growth and can be used in cancer diagnosis.

In manufacturing and materials:

Metal nanoparticles such as noble metals which includes Au and Ag are useful in chemical sensors and biosensors.

In the environment:

Nanoparticles have their applications in green chemistry or pollution prevention, remediation of materials that are contaminated with hazardous substances. **(Khan Ibrahim et.al 2019)**

EVALUATION OF NANOPARTICLE:

- Particle Size
- Surface Charge
- Surface Hydrophobicity
- Drug Release

LIPOSOMES

Liposome (meaning lipid body) are spherical microscopic vesicles composed of one or more concentric lipid bilayer, separated by water or aqueous buffer compartments with a diameter ranging from 25 to 10000nm. They are commonly composed of one or more amphiphilic phospholipid bilayer membrane that can entrap both hydrophilic and hydrophobic drugs. Hydrophilic drugs are trapped in the aqueous center of liposomes while hydrophobic drugs are trapped in the liposome wall made up of phospholipid membrane . Biological membrane contain two type of phopholipid i.e. phosphodiglycerides and sphingolipid. **(Ali Javed et.al 2013)**

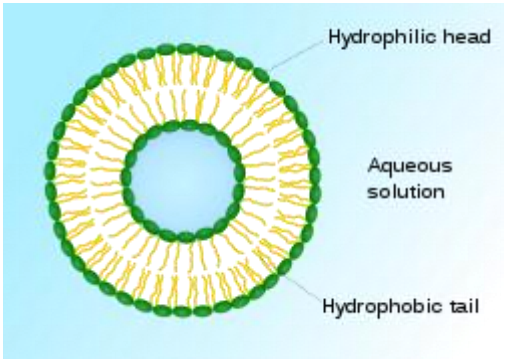

Figure:

Types of Liposomes

Depending upon their size and structure liposomes classified as-:

1. **MLV (Multi Lamellar Vesicles):** These liposomes are made of series of concentric bilayer (5-20 bilayer) of lipid enclosing a small internal volume. They have a diameter of more than 5000 nm.
2. **OLV (Oligo Lamellar Vesicles):** These are made of 2 to 5 bilayer of lipids surrounding a large internal volume. They have a diameter of 100-1000 nm.
3. **MVV (Multi Vesicular Vesicles):** These have multi compartment structure and have diameter more than 1000 nm. They are also known as vesosomes—meaning "*vesicles-inside-vesicles"*.
4. **ULV (Uni Lamellar Vesicles):** These are made of single bilayer of lipids.

i. **SUV** (Small Unilamellar Vesicles) of size 20 to 40 nm.
ii. **MUV** (Medium Unilamellar Vesicles) of size 40-80 nm.
iii. **LUV** (Large Unilamellar Vesicles) of size 100-1000 nm. **(Brahmankar D.M., 2016)**

Liposomes production processes

1) Passive loading techniques

i. Mechanical dispersion method

a. Sonication method
b. Micro emulsification
c. Hand shaken MLVs
d. Non shaking vesicles
e. Membrane extension

ii. Solvent dispersion method

a. Ethanol injection method
b. Reverse phase evaporation vesicles
c. Water in organic phase
d. Ether injection

iii. Detergent solubilization

a. Dialysis
b. Dilution

2) Active loading technique

Applications of liposome

1) ***Liposome as drug/protein delivery vehicles:***

- Controlled and sustained drug release
- Enhanced drug solubilization
- Altered pharmacokinetics and biodistribution
- Enzyme replacement therapy and biodistribution
- Enzyme replacement therapy and lysosomal storage disorders

2) Liposome in antimicrobial, antifungal and antiviral therapy:

- Liposmal drugs
- Liposomal biological response modifiers

3) Liposome in tumour therapy:

- Carrier of small cytotoxic molecules
- Vehicle for macromolecules as cytokines or genes

4) Liposome in gene delivery:

- Gene and antisense therapy
- Genetic (DNA) vaccination

5) ***Liposome in immunology:***

- Immunoadjuvant
- Immunomodulator
- Immunodiagnosis

6) Liposome as radiopharmaceutical and radio diagnostic carriers

7) Liposome in cosmetics and dermatology. (**Kaur Loveleenpreet et.al.)**

EVALUATION OF LIPOSOME:

- Visual Appearance
- Determination of Liposomal Size Distribution
- Liposome Stability
- Entrapped Volume
- Surface Charge

MICROSPHERES

Microspheres are the spherical are the spherical particles, with diameters in the micrometer ranges (1µm to1000 µm). Microspheres are also known as microparticles. **(Shivani et.al.2015).**

Microspheres with bioadhesive properties exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site to produces better therapeutic action.

Magnetic Microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4µm) but are sufficiently susceptible (ferromagnetic) to be captured in microvessels and dragged into the adjacent tissues by magnetic field of 0.50.8 tesla.

Floating Microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period without affecting gastric emptying rate. The drug is released slowly at the desired rate.

Radioactive Microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. They are injected to the arteries that lead to tumour of interest to deliver the drug at target site. The different kinds of radioactive microspheres are α emitters, β emitters and γ emitters. **(Ali Javed et.al 2013)**

Polymeric Microspheres are those which contain biodegradable polymers which prolongs the residence time when contact with mucous membrane due to high degree of swelling property with aqueous medium, results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. Synthetic polymeric microspheres are those which are made up of synthetic polymers and are used as used as bulking agent, fillers, embolic particles, drug delivery vehicles etc

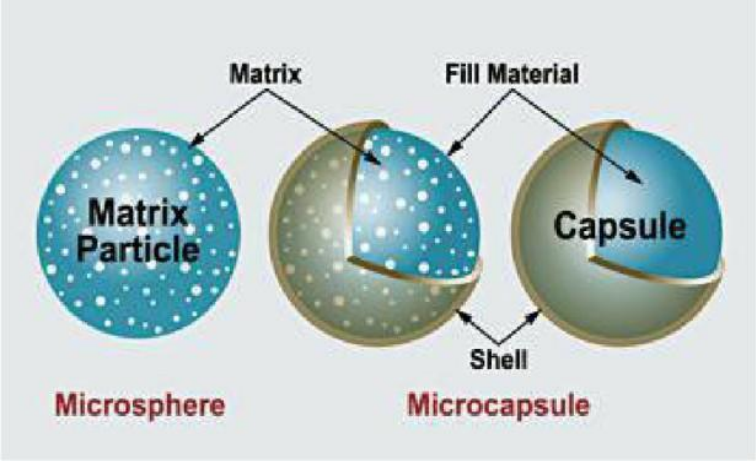

Figure 2 Microspheres and Microcapsules.

Methods for the preparations of microspheres:-

- Spray drying and spray congealing
- Solvent evaporation technique
- Wet inversion technique
- Hot melt technique
- Single emulsion technique
- Double emulsion technique
- Polymerization methods
- Phase separation technique

EVALUATION OF MICROSPHERE:

- Particle size and shape
- Electron spectroscopy for chemical analysis
- Attenuated total reflectance Fourier Trans-Infrared Spectroscopy
- Capture efficiency
- Thermal analysis
- Swelling index

FAST DISSOLVING DOSAGE FORMS

United States Food and Drug Administration (USFDA) defined fast dissolving tablets (FDT) as a "solid dosage form containing a medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue". The tablet disintegrates into smaller granules or melts in the mouth from a hard solid structure to a gel like structure, allowing easy swallowing by the patients. **(Garg Ashishet.al.2013)**

Ideal Properties of FDT

- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.

Methods for the preparation of FDT(Masih Ashish et.al. 2017)

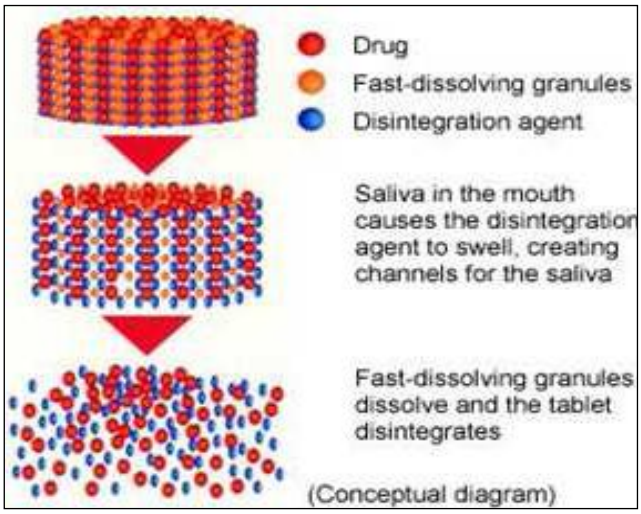

Figure 3 Concept of Fast Dissolving Tablets.

EVALUATION PARAMETERS:-

- Weight variation
- Hardness
- Friability test
- Disintegration test
- In vitro dissolution study
- Taste or mouth feel
- Stability study
- Uniformity of dispersion

MONOCLONAL ANTIBODY

Monoclonal antibody is a form ofimmune therapy that uses monoclonal antibodies (mAb) to bind nonspecifically to certain cells or proteins. The objective is that this treatment will stimulate thepatient's immune system to attack those cells. Alternatively, in radio immunotherapy a radioactive dose localizes a target cell line, delivering lethal chemical doses. More recently antibodies have been used to bind to molecules involvedin T-cell regulation to remove inhibitory pathways that blockT-cell responses. This is known as immune checkpoint therapy. **(Justin k.h.Liu)**

Monoclonal Antibody was produced by fusion of a B cell, sensitized with an antigen, and myeloma cell in presence of poly ethylene glycol (PEG) in 1975 by Köhler and Milstein. An antibody secreting B cell becomes cancerous after fusion.
Köhler and Milstein found a way to combine the unlimited growth potential of myeloma cells with the predetermined antibody specificity of normal immune spleen cells. The technique is called somatic cell hybridization/hybridoma technique.

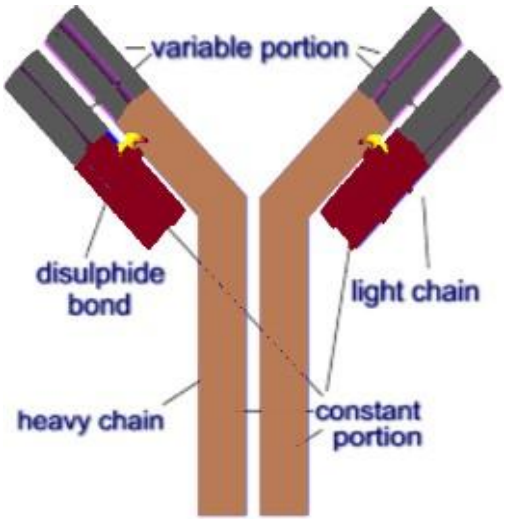

Figure 4 Antibody structure.

Procedure:

Mix spleen cells from a mouse that has been immunized with the desired antigen with myelomacells in presence of PEG. Myeloma cells should lost the ability to synthesize hypoxanthine-guanine- phosphoribosyltransferase (HGPRT) and the ability to synthesize any antibody molecules of their own. The fused mixture is then grown in Hypoxanthine Aminopterine Thymidine (HAT) medium. (**Kohler G.1975)** Further the produced MABs are characterized by Antibody & antibody conjugates, Suppresser deletion therapy, Site specific modification, Antibody- enzyme conjugates and Antibody as receptor surrogates for mediating cell-cell interaction. **(Patel Hetal M., 2005-06)**

Applications of Monoclonal Antibody

There are various applications as following-:

Diagnostic Applications:

Monoclonal antibodies have revolutionized the laboratory diagnosis of various diseases. For this purpose, MAbs may be employed as diagnostic reagents for biochemical analysis or as tools fordiagnostic imaging of diseases.

- **MAbs in Biochemical Analysis:**

Diagnostic tests based on the use of MAbs as reagents are routinely used in radioimmunoassay (RIA) and enzyme-linked immunosorbent assays (ELISA) in the laboratory. These assays measure the circulating concentrations of hormones (insulin, human chorionic gonadotropin, growth hormone, progesterone, thyroxine, triiodothyronine, thyroid stimulating hormone, gastrin, renin), and several other tissue and cell products (blood group antigens, blood clotting factors, interferon's, interleukins, histocompatibility antigens, tumor markers). In recent years, a number of diagnostic kits using MAbs have become commercially available. For instance, it is now possible to do the early diagnosis of the following conditions/diseases.

- **Pregnancy**:

Pregnancy by detecting the urinary levels of human chorionic gonadotropin.

- **Cancers**:

Cancers estimation of plasma carcinoembryonic antigen in colorectal cancer, and prostatespecific antigen for prostate cancer.

MAbs in Diagnostic Imaging:

Radiolabeled—MAbs are used in the diagnostic imaging of diseases, and this technique is referred to as immunoscintiography. The radioisotopes commonly used for labeling MAb are iodine—131 and technetium—99. The MAb tagged with radioisotope are injected intravenously into the patients.

These MAbs localize at specific sites (say a tumor) which can be detected by imaging the radioactivity. Inrecent years, single photon emission computed tomography (SPECT) cameras are used to give a more sensitive three dimensional appearance of the spots localized by radiolabeled— MAbs.

Therapeutic Applications:

Monoclonal antibodies have a wide range of therapeutic applications. MAbs are used in the treatment of cancer, transplantation of bone marrow and organs, autoimmune diseases, cardiovascular diseases and infectious diseases.

The therapeutic applications of MAbs are broadly grouped into 2 types:

a) Direct use of MAbs as therapeutic agents: Monoclonal antibodies can be directly used for enhancing the immune function of the host. Direct use of MAbscauses minimal toxicity to the target tissues or the host.

b) MAbs as Targeting Agents in Therapy: Toxins, drugs, radioisotopes etc., can be attached or conjugated to the tissue-specific monoclonal antibodies and carried to target tissues for efficient action. This allows higher concentration of drugs to reach the desired site with minimal toxicity. In this way, MAbs are used for theappropriate delivery of drugs or isotopes.

Protein Purification:

Monoclonal antibodies can be produced for any protein. And the so produced MAb can be conveniently used for the purification of the protein against which it was raised. MAbs columns can be prepared by coupling them to cyanogen bromide activated Sepharose (chromatographic matrix). The immobilized MAbs in this manner arevery useful for the purification of proteins by immunoaffinity method. **(Jha Nandkishore, 2016)**

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