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Review Article

An Overview of Conventional, Controlled, Targeted and Nanotechnology-Based Approaches in Drug Delivery System

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ABSTRACT

Drug delivery systems (DDS) are formulations or technological platforms designed to deliver active pharmaceutical ingredients at an appropriate rate, to an appropriate site, and for a predetermined duration in order to improve therapeutic efficacy, safety, and patient compliance. Conventional dosage forms remain widely used, but they may provide limited control over the rate, duration, and site of drug release. This review provides an overview of conventional and advanced drug delivery approaches, including sustained and controlled release systems, transdermal delivery, mucoadhesive systems, targeted delivery, colon-targeted delivery, pulmonary delivery, and nanocarrier-based platforms. The review discusses the principles, major advantages, limitations, and applications of these systems and highlights the role of modern polymers, lipids, nanocarriers, and responsive biomaterials. The manuscript also considers challenges associated with formulation design, biological variability, safety, characterization, and clinical translation. Overall, advances in drug delivery technology have expanded the ability to control drug release and improve therapeutic outcomes, although careful formulation design and scientific evaluation remain essential.

INTRODUCTION

A drug delivery system is a system that delivers the active pharmaceutical ingredient to the desired site at a proper rate and a predetermined time that improves therapeutic safety, efficacy, and patient compliance [1].

The aim of a drug delivery system is to make a drug delivery more efficient. The active pharmaceutical ingredients are the main component in any formulation. And the other substances in the formulation are called excipients to increase the drug efficacy [2].

The administration and effectiveness of pharmaceutical molecules, such as antibodies, peptides, vaccines,

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medications, and enzymes, are increased by drug delivery systems (DDS). Nowadays, the most preferred ways to administer medications are oral pills and injections[3].

Historical background:

Before the development of modern modified-release technologies, conventional dosage forms generally provided relatively rapid drug release and limited control over release kinetics. The first sustained release formulation that could regulate drug release kinetics and attain 12-hour efficacy was introduced by Smith Klein Beecham in 1952[4].

Drug delivery development shows consistent efforts to improve drug targeting, action duration, and patient convenience with technological advancements. Oral and injectable methods were the main ways that medicines were initially administered, and problems with patient and medication non-compliance typically occur with this form of delivery. The 1970s saw the development of biomedical engineering and the application of endovascular embolization. This permitted the use of occlusive drugs with greater efficiency and targeting by the intervention radiologists with a variety of ailments through the selective administration of the drug with less intervention techniques [5].

TYPES;

1.Sustained release Drug Delivery System 2.Controlled Drug Delivery System 3.Transdermal Drug Delivery System

4.Mucoadhesive Drug Delivery System 5.Targeted Drug Delivery System 6.Conventional Drug Delivery System 7.Parenteral Drug Delivery System 8.Pulmonary Drug Delivery System

1] Sustained Release Drug Delivery System

Sustained release drug delivery systems enhance a medication's therapeutic action by altering drug release over an extended period. This approach improves patient compliance and pharmacological efficacy by maintaining stable blood levels of the medication. Unlike conventional dosage forms that require multiple doses per day, sustained release tablets are typically taken once or twice daily to achieve the desired therapeutic effect[9].

SRDDS Principle: In conventional dosage forms, active chemicals are instantly released into an absorption pool. The kinetics involve the absorption rate constant (k_a) and elimination rate constant (k_e)[10].

Classification of Modified/Sustained-Release Systems:

I.Diffusion-Controlled Systems

II.Dissolution-Controlled Systems

III.Diffusion–Dissolution-Controlled Systems

IV.Ion-Exchange Resin Systems

V.Gastro-Retentive and pH-Dependent Systems

V.Osmotically Controlled System [12,13,14]

Advantages of SRDDS:

Decreased Dose Frequency: Fewer doses required.

Increased Adherence: Better patient compliance.

Reduced Blood Level Variation: Stable drug concentrations.

Lower Overall Medication Use: Compared to traditional methods.

Reduced Drug Buildup: Prevents accumulation over time.

Reduced Toxicity: Minimizes local and systemic side effects.

Stabilized Medical Conditions: Consistent drug levels.

Cost-Effective: Economical for patients and providers.

Drawbacks of SRDDS:

Delayed Drug Effect: Slower onset of action.

Risk of Dose Dumping: Inadequate formulation can lead to sudden release.

First Pass Metabolism: Can affect drug efficacy.

Less Precise Dose Modification: Difficult to adjust doses in specific cases.

Higher Cost per Unit Dose: More expensive than traditional doses.

Poor In Vitro-In Vivo Correlation: Challenges in predicting performance.

Mechanism of SRDDS:



Drug molecules move from high to low concentrations in gastrointestinal fluids via diffusion. Factors like diffusion coefficient, concentration gradient, diffusion channel, and surface area influence this process. Two approaches are used:

Insoluble Matrix: Stomach fluid enters, dissolves the drug, and releases it through diffusion.

Polymer Coating: Drug particles are coated with a polymer, allowing gradual diffusion to maintain steady levels[23,24].

2. Controlled Drug Delivery System:

This system delivers medication at a set rate for a specific duration, targeting the action site effectively. It uses polymers to incorporate drugs, proteins, or bioactive substances for controlled release[25,26,27,28].

Advantages:

Enhanced Patient Compliance: Easier use.

Stable Drug Levels: Reduced fluctuations.

Larger Safety Margin: For potent drugs.

Lower Dosage Requirements: Minimal doses.

Increased Bioavailability: Better absorption.

Reduced Side Effects: Fewer systemic/local reactions[29].

Disadvantages:

Reduced Blood Circulation: Less drug reaches bloodstream.

Inconsistent Results: Variability in lab outcomes.

Dose Dumping Risk: Sudden release potential.

Irreversible Dosing: Cannot be stopped once given.

High Production Cost: Expensive to produce[30]

Mechanism:

The release rate is controlled by drug penetration through a membrane wall and diffusion through a polymer matrix[30].

3. Transdermal Drug Delivery System (TDDS):

TDDS, commonly known as patches, deliver medication through the skin for systemic effects. This method considers the skin's morphological and physicochemical characteristics, offering advantages over oral

delivery by enhancing patient compliance and avoiding first-pass metabolism[31].

Benefits:

I. Avoids First-Pass Metabolism: Direct absorption into the bloodstream.

II. Lower Plasma Concentration: Fewer side effects.

III. Suitable for Short Half-Life Drugs: Reduces plasma level variations.

IV. Easy Removal: Allows for quick discontinuation in case of toxicity. V. Improved Compliance: Reduces dosing frequency.

VI. Continuous Infusion: Provides prolonged drug delivery[33].

Limitations:

I. No Universal Dose Limit: Depends on drug potency, skin permeability, and other factors.

II. Physicochemical Requirements: Drugs must penetrate the stratum corneum.

Potential Skin Irritation: Risk of dermatitis from medication or excipients.

Variable Skin Barrier: Differences in permeability based on location and individual[34].

Types of TDDS :

First Generation:

Commonly used patches for small lipophilic drugs.

Methods: Metered sprays, gels, topical formulations.

Examples: Estradiol spray, testosterone gels[35].

Second Generation:

Enhances skin permeability for broader drug delivery.

Techniques: Chemical enhancers, iontophoresis, non-cavitation ultrasound.

Focus: Increase delivery, protect deeper tissues[35,36].

Third Generation:

Targets the stratum corneum for efficient delivery.

Methods: Novel enhancers, electroporation, microneedles, thermal ablation.

Effective for macromolecules like proteins and vaccines[37].



Ideal Drug Characteristics:

Low dosage (<20 mg/day)

Molecular weight <400 Dalton

Half-life <10 hours

Skin permeability coefficient $>0.5 \times 10^{-3}$ cm/h

Lipophilicity: Log P between 1.0 and 4.0

Low oral bioavailability, low therapeutic index, melting point <200°C, pH 5.0–9.0[38,39].

Chemical enhancers for TDDS (passive delivery)

Drugs should have low molecular weight (MW) (less than 1 kDa), an affinity for hydrophilic and lipophilic phases, a short half-life, and little skin irritation in order to improve transdermal administration and therapeutic efficacy. Drug penetration into the skin is influenced by a variety of factors, including species differences, skin age and site, skin temperature, skin condition, application area, exposure length, skin moisture content, pretreatment techniques, and physical properties of the penetrant.

Recent research has examined various transdermal drug delivery technology, from the chemical enhancers that improve drug solubility or diffusion across the skin to new, creative methods that expand on this idea.[41].

All things considered, the low bioavailability of many oral medications, the discomfort and difficulty of injections, and the restricted controlled release choices of both present strong prospects for transdermal drug administration. Third-generation physical enhancers (such as ultrasound, thermal ablation, and microneedles) may allow transdermal delivery of macromolecules and vaccines, while second-generation chemical enhancers and iontophoresis are extending delivery capabilities for small molecules, building on the successes of first-generation transdermal patches

Polymers use in TDDS

Polymers is backbone of a transdermal medication. Transdermal delivery systems are made as multilayered polymeric matrix with a drug reservoir or drug-polymer matrix positioned between two polymeric layers: an inner polymeric layer that serves as an adhesive and/or rate-controlling membrane, and an outer impermeous backing layer that stops drug loss through the

backing surface[42]. Example : 1] Hydroxypropyl methyl cellulose

2]methyl acrylate, ethyl acrylate, and propyl acrylate Isopropyl acrylate ,n-Butyl acrylate , Hexyl acrylate Heptyl acrylate, dodecyl acrylate Acrylate hexadecylate

4.Mucoadhesive Drug Delivery Systems

: Mucoadhesive drug delivery systems are those that target a medicine to a specific area of the body for extended periods of time by utilizing the bioadhesion of certain polymers. An interfacial phenomena known as "bioadhesion" occurs when two materials, one of which is biological in nature, are kept together by interfacial forces. The attachment, which resembles the adhesion between a biological membrane and a polymer, can occur between a biological substrate and an artificial material. The word "mucoadhesion" refers to a polymer that is adhered to the mucous layer of a gastrointestinal tract (GI tract) mucosal membrane. The GI tract, urogenital tract, airways, ear, nose, and eye are among the areas of the body covered by the mucosal layer line. The mucoadhesive medication delivery system contained the following because these are possible locations for any bioadhesive system to be taken.

I. The buccal medication delivery method

II. Oral medication administration method

III. Drug delivery via the vagina

IV Drug delivery systems for the rectal, nasal, and ocular systems [43].

. Routes, mechanism, and possible function of mucus : Many possible therapeutic benefits result from the ability to hold pharmacologically active substances on any mucosal epithelia, such as the mouth, nose, eyes, rectum, or vagina, for prolonged periods of time. A layer of mucus covers each of these epithelial layers. The most promising systems will be tested for physiological effects in healthy volunteers and indications of mucoadhesive activity. A medication must first diffuse through a layer of mucus and any related unstirred water layer of the GI tract in order to be absorbed across mucosal epithelia [43].

Advantage Of mucoadhesive drug delivery system



I It is simple to administer drugs and to stop their effects.

II.. Enables the medication to be localized or retained in the designated oral cavity region for a prolonged amount of time.

III. Avoid first pass metabolism in the liver.

IV..It is convenient to deliver drugs with low bioavailability because to significant first pass metabolism.

V..Since the manner of absorption is passive, no energy is needed.

VI. Drug administration to patients who are unconscious is simple.

VI. Saliva's water content can guarantee medication disintegration

VII.Certain drugs that are easily broken down in acidic environment can be administered appropriately.

VIII.Absence of noticeable goblet cells that secrete mucus [44].

Limitations of mucoadhesive delivery system:

i).It is frequently challenging to deliver drugs in large doses.

ii)The patient may ingest the forgotten medication.

iii)Drinking and eating may be prohibited until the drug's release is complete iv)Drugs that are unstable at the pH of the buccal environment should not be taken this way.

v)Drugs that irritate the mucosa, taste bitter or unpleasant, or have an unpleasant odor cannot be administered using this method. vi)The amount of surface area accessible for absorption is small [45].

Mechanism of mucoadhesion:

The process by which many macromolecules adhere to a mucosal membrane's surface is still poorly understood. Mucoadhesive must extend across the substrate in order to initiate contact, expand the surface area of contact, and cause macromolecular chains to diffuse within the mucus membrane. Since both forces are applied during the adhesion, attraction forces must outweigh repulsion forces for a bioadhesion to be successful. The nature of the dosage form and the methods

used to give it can help with each step of the bioadhesion process. For instance, the substrate may adsorb a partially hydrated polymer due to surface water's attraction[46].

The following qualities characterize an ideal polymer in Mucoadhesive drug delivery system .

I.The polymer must be non-toxic, non-irritating, non-degradable, and nonabsorbable from the gastrointestinal system. cells.

II .Ideally, establish a robust non-covalent connection with the mucin covering surfaces of epithelial cells.

III .It should have some site specificity and stick to wet tissue fast.

IV..During storage or the dosage form's shelf life, the polymer shouldn't break down.

V.The polymer's price shouldn't be so high that it becomes difficult to market the manufactured dosage form. Example; benzene/acrylic acid Cellulose hydroxyethyl Alginate sodium Gum Gelatin Gum guar Heat-modified starch [47].

Types:

1] Buccal drug delivery system

The most popular and favored method of medicine delivery is oral administration. Compared to most other drug delivery methods, it has a number of benefits, such as being painless, patient-friendly, easy to self-medicate, and allowing for a flexible and controlled dose schedule. The first pass effect, gastrointestinal enzymatic degradation, and the delay between the time of administration and absorption are some of the major drawbacks of the oral route, despite the fact that it is the preferred method for administering medications.

Due to its simplicity of administration, the buccal area of the mouth cavity is a desirable site for medication delivery. The process of administering the intended medication through the buccal mucosal membrane that lines the oral cavity is known as buccal drug delivery. This method works well for both transmucosal (systemic effect) and mucosal (local effect) medication delivery. While the second example involves drug absorption across the mucosal barrier to reach the systemic circulation, the first scenario aims to achieve a site specific release of the medication on the mucosa.



Toxicity or unwanted side effects may be greatly decreased because the medication amount of buccal formulations can be much lower than that of tablets and capsules [48].

2] Oral medication drug delivery

The most common method of treating both local and systemic gastrointestinal disorders is oral administration.

The GIT's various components—the mouth cavity, esophagus, stomach, small intestine, and colon—are crucial for both food digestion and medication absorption.

Drug absorption may also be change by other anatomical features, such as the mouth cavity's small surface area, the stomach mucin-bicarbonate barrier, and enteric enzymes. Significant attempts have been made to address these problems, primarily through better understanding of the physiological characteristics of both healthy and ill person [49].

5.Targeted drug delivery system ;

Overview Ehrlich's 1906 "magic bullet" theory is the source of the targeted drug delivery system concept. Identifying the appropriate objective for a particular disease state. Identifying a suitable bioactive that effectively addresses the specific illness. Locating an appropriate carrier that will deliver the medication to the intended location while maintaining its stability and avoiding any immunologic or nonspecific reactions. There are numerous cutting-edge methods available for various organs and tissues to get beyond these restriction superior to the traditional methods. These methods are typically intended to improve the therapeutic response of traditional medications and to get beyond traditional drawbacks such inadequate drug particle dispersion, restricted solubility, and particle aggregation. They can lengthen the drug's residence period at the absorption site since they are biocompatible, non-toxic, non-interactive, and unhazardous. Additionally, the application of permeability enhancers can boost the concentration of medicines at the intended region. Photodynamic and photothermal therapy are two examples of specialized cancer treatments. When a particular wavelength of light is present, a medication known as photosensitizer is used in photodynamic

treatment to produce oxygen that kills surrounding cells[50].

Significance Of targeted Drug Delivery system;

A method known as "targeted drug delivery" delivers a particular quantity of medication to a damaged organ over an extended period of time. Because targeted DDS overcomes the constraints of conventional DDS, it is more popular than the traditional approach. In contrast to targeted DDS, the conventional method delivers poor drug solubility together with increased instability, poor drug absorption, less $t_{1/2}$, and a large volume of distribution. The therapeutic index of pharmacodynamically traditional DDS is narrow. In targeted DDS, particular bioactives are sent to a predetermined infected organ or set of cells via a carrier mechanism[51].

Categories :

Drug targeting is another name for targeted drug delivery. To transport the bioactives to the targeted tissues, cells, or organs, two targeting strategies are available.

1. Active Targeting
- 2.Passive Targeting

This kind of targeting relies on blood circulation, and it is founded on the ligand-receptor targeting. Only when two chemicals are close to one another (i.e., less than 0.5 nm) may a ligand and a receptor react. The ligand is unique to the receptors that are overexpressed on the target or injured cell surface [52]

There are three kinds of active targeting:

First-order targeting:

Limited drug-carrier complex dissemination to the previously chosen target site, organ, or tissue (e.g., lymphatic tissue, brain ventricles, eyes, peritoneal cavity, etc.)

Delivery of a drug-carrier complex to a particular target region, such the liver's Kupffer cells, is known as second-order targeting.

Delivery precisely to the intracellular region via endocytosis or a receiver-based ligand-mediated process is known as third-order targeting[53,54]

Drug Targeting Components •



The goal the cells, tissues, or organs that need to be treated. The particular drug moiety is called API. • **Delivery or Drug Carrier Vehicles** The active pharmaceutical ingredients are moved from the site of administration to the intended site by carriers. Carrier-mediated drug delivery involves two different mechanisms: either the drug is released very slowly over a long period of time, or it is released in bulk at the targeted spot as a result of certain pH, heat, or light initiating changes. Additionally, these vectors can improve the pharmacokinetic characteristics of medicinal compounds, such as permeability and solubility. Additionally, the medication moiety is encapsulated in this carrier's core[55].

Passive targeting;

The buildup of active pharmaceutical ingredients (API) at the targeted site, primarily in the leaky vasculature, is known as passive targeting. Certain features, such as charge (+/-) or polarity, as well as some physical attributes, like as size, mass, zeta potential, etc., modify passive targeting. The medication does not require a ligand to bind to the particular target site in this targeting. To achieve sufficient drug accumulation at the target site, a long residence time in blood circulation is all that is required[56,57]

Colon Targeted Drug Delivery System

It is a systemic techniques are designed to transport protein and peptide medications to the colon, while local treatments are possible for conditions including ulcerative colitis, Crohn's disease, amoebiasis, colon cancer, etc.

Drug targeting for the colon must ensure that it does not break down in the stomach or small intestine. Only when it gets to the colon site should it release and break down[58,59]

Proteolytic enzyme activity in the colon mucosa is lower than that of the small intestine, which prevents drug degradation hydrolysis in the duodenum and jejunum and releases the drug in the colon site for better absorption and systemic bioavailability. These factors make protein and peptide drugs advantageous in the case of a systemic approach for colon targeting[60] medicines used in targeted the colon.

- 1] Local: 5-fluorouracil (5-FU): cystic fibrosis, colorectal cancer, pancreatic.
- 2] systemic :steroids, and non-steroidal anti-inflammatory drugs (N-SAIDs) are the desired site API issues to be addressed: Gastric irritation to stop oral peptide medications from undergoing first-pass metabolism Tinidazole, mercaptopurine, sulfasalazine.
- 3] topical: hydrocortisone, and IB: (irritable bowel illness)[61].

Approach for colon targeting drug delivery system

1] PH sensitive colon targeted :Colon Targeting with pH-Sensitive Polymer Coating Since the pH of the colon is higher than that of the GIT, it can be used to target any colon part. Due to its superior mucoadhesiveness and pH- dependent medication release, Eudragit is the most promising synthetic polymer to address colonic illness[62].

2. Liposomal drug delivery that is sensitive to pH Compared to normal tissues, some diseased tissues such as tumors, inflammatory, and infected tissue have a more acidic environment. This is explained by the fact that some trapped viruses contaminate cells, which causes the endosomal lumen of the virus- infected cells to acidify. Despite being stable at physiological pH, pH-sensitive liposomes break down in acidic environments, their aqueous content. Many compounds, including fusogenic peptides enclosed in the lipid bilayer, pH-sensitive lipids, and those on the surface of liposomes, can reduce the reactivity to acidic pH. The liposomes attach to cell surface receptors and are ingested via endocytosis.

[63,64].

Levels of Drug Targeting; Targeted drug delivery can be accomplished through the use of carrier systems, which rely on taking advantage of both the intrinsic pathway or pathways that these carriers follow and the bio-protection that they can provide to medications while they are in the body. The several methods of delivering the medication to the intended location can be broadly categorized as follows:

1. The use of passive targeting
2. Targeting in reverse



3. Active targeting, including physical and ligand-mediated targeting
4. Two-way targeting
5. Targeting twice
6. Targeting combinations.

Passive Targeting;

Systems that target the systemic circulation are typically referred to as “passive” delivery systems (i.e., targeting happens as a result of the body’s natural reaction to the physicochemical properties of the drug or drug-carrier system). It is a kind of passive process that makes use of the carrier system’s natural biodistribution (attributed to inherent qualities), which leads to its eventual accumulation in the body’s organ compartment.

Inverse targeting

Inverse targeting is mostly based on successful attempts to evade the reticuloendothelial system’s (RES) passive uptake of colloidal carriers. This effectively causes the carrier’s biodistribution trend to reverse, which is why the method is known as inverse targeting.

Dual Targeting: This traditional method of drug targeting uses carrier molecules, which work in concert with the loaded active drug's antiviral effects due to their inherent antiviral properties. Drug conjugates with a strengthened activity profile against viral replication can be made using this method. The ability to tackle the virus reproduction process at several stages eliminates the potential for the generation of resistant viral strains, which is a significant advantage.

Double Targeting: For the drug delivery system, drug targeting can be paired with passive and active targeting. Drug distribution is controlled both spatially and temporally. Prior to the invention of drug targeting, the temporal control of drug delivery was developed in terms of controlling drug release.

Combination Targeting: These targeting systems have molecularly specific carriers, polymers, and homing devices that may allow for a direct approach to the target region. Proteins and peptides can be modified using synthetic polymers like poly (ethylene glycol) or natural polymers like polysaccharides to change their

physical properties and target particular organs, tissues, or compartments within the vasculature. In order to accomplish site-specific active targeting of encapsulated contents, additional vectorization of these modified proteins and peptides into vesicular or micro-particulate carriers may exploit the inherent (via homing devices) features of the carrier[67,68].

6. Conventional drug delivery system;

Conventional Drug Delivery Systems 1. Oral Administration of medication has long been a pharmaceutical practice, providing a practical and patient-friendly method of drug delivery. The oral route is widely used in healthcare due to its non-invasiveness, simplicity of administration, and high patient acceptance. Oral drug distribution offers various advantages in the field of pharmacological administration. Firstly, it is well known for its high level of patient compliance, as the approach is non-invasive and easy for patients to administer themselves. The acceptance of oral drugs is prevalent among both patients and healthcare providers, adding to its standing as a favored mode of delivery[69,70]

7. Parenteral Delivery :

A vital route for delivering drugs directly into the bloodstream is parenteral drug delivery, which includes intravenous (IV), intramuscular (IM), and subcutaneous injection. Parenteral administration, which is distinguished by its quick beginning of action and exact control over drug dosage, is essential in emergency situations and therapeutic interventions that need to be effective right away. The three most popular and extensively researched injection routes for administering medications are IV, IM, and SC delivery. The choice of route is influenced by factors such as patient preference, safety, efficacy, and cost-effectiveness. Each route has pros and cons of its own [71]

8. Pulmonary Drug Delivery System.

The ability of the lung to absorb medications for either local deposition or systemic administration has made pulmonary drug delivery an appealing target and a subject of great scientific and biological interest in the field of health care research. The formation of airway lining fluid and the control of airway tone are important functions of respiratory epithelial cells. In this regard,



the potential of a pulmonary route as a non-invasive administration for systemic and local delivery of therapeutic agents has drawn increasing attention due to its high permeability, large absorptive surface area and good blood supply [72,73]

The majority of medications and other macromolecules have been demonstrated to be absorbed by the distal lung's alveolar epithelium. The relatively low enzymatic activity, quick drug absorption, and ability to overcome first-pass metabolism are further benefits over oral uses. It has previously been observed that administering medication via the pulmonary route can effectively treat certain systemic diseases as well as local respiratory ailments. This covers the topical management of pulmonary hypertension, local infectious illnesses, asthma, and the systemic administration of oxytocin, insulin, and human growth hormones. This is now the case for several biotherapeutics that are currently administered intravenously, such as insulin, growth hormones, and glucagon, all of which might potentially be administered to people through inhalation if inhalation were more effective[72,73].

Methods and Mechanisms of Pulmonary Drug Administration : In the past ten years, both humans and animals have shown systemic absorption of a wide variety of medicinal drugs following pulmonary administration. There are two main ways to take the medication through the pulmonary route: intranasal administration, which has anatomical limitations such as a smaller airway lumen, and oral inhalative administration. Because oral inhalation allows for the delivery of very small particles with a concentration loss of only 20% as opposed to 85% by nasal route, much better results can be anticipated [74]

A tiny amount of medication solution or dispersion is injected into the lungs during instillation using a specialized syringe. This offers a quick and measurable way to administer medication to the lungs. A relatively small absorptive region is used to accomplish the localized drug deposition. Therefore, the medication distribution is not uniform and the instillation technique is more simpler and less expensive. [75].

However, intratracheal instillation is not a physiological route for administration, therefore the findings of these experiments might not apply to human aerosol

applications. In contrast, the aerosol approach used in the inhalation procedure allows for more penetration and more uniform distribution. Nevertheless, this approach is more expensive and challenging to measure the precise amount in the lungs. Three mechanism gravitational sedimentation, inertial impaction, and expensive are primarily responsible for the drug's deposition in the pulmonary airway following aerosol administration. If the drug particle size is relatively larger, deposition happens through the first two mechanisms: either sedimentation is caused by gravity, or inertial impaction is caused by hyperventilation[75]

Device For delivery

The effectiveness of the pulmonary administration system is significantly influenced by the delivery device. The creation of sophisticated technologies has improved significantly in recent years. But compared to powder formulations, devices are far less investigated. An essential component of the formulation design is the choice of drug delivery system for the lungs. The chosen device must be able to produce and transport particles or droplets with a precise aerodynamic diameter if the medication is intended to be administered to a particular area of the lungs. Nebulizers, metered-dose inhalers, and dry powder nebulizers are the most often utilized respiratory delivery devices[76, 77].

Nebulizers

Asthma and other respiratory conditions have been treated with nebulizers for many years. Nebulizers can be classified as either jet or ultrasonic. The Bernoulli principle is used by the jet nebulizer to create an area of low pressure at the output of the adjacent liquid feed tube as compressed gas (air or oxygen) flows through a small opening. As a result, the medication solution is pulled up from the fluid reservoir and broken up into gas stream droplets. The ultrasonic nebulizer creates a liquid fountain in the nebulizer chamber by vibrating a piezoelectric crystal at a high frequency (about 1-3 MHz); the smaller the droplets produced, the higher the frequency[78].

With minimal patient coordination or expertise, constant output jet nebulizers can aerosolize the majority of medication solutions and deliver high dosages. In addition to being time-consuming, treatments with



these nebulizers are ineffective and result in significant drug waste (50% loss with continuously operating nebulizers). These disposable nebulizers are cheap, but the compressors that supply the oxygen or air are not. Nebulization never gets the majority of the recommended medication into the lungs. Most of the medication is either discharged into the atmosphere upon expiration or kept inside the nebulizer (known as dead volume). Just 10% of the dosage administered by the nebulizer is typically deposited in the lungs[78].

Metered-dose Inhaler

Metered-dose inhalers (MDIs) As the first portable outpatient inhalation device and currently the most used aerosol delivery device, the MDI was a ground-breaking technology that solved the issues with the hand-bulb nebulizer. Through a nozzle at a high speed (> 30 m/s), the MDI releases a medication aerosol propelled by propellants such as chlorofluorocarbons (CFC) and, more recently, hydrofluoroalkanes (HFAs). Only a little portion of the medication dose is delivered to the lung by MDIs. Only 10–20% of the dosage is usually deposited in the lungs. About 50–80% of the medication aerosol impacts the oropharyngeal region due to the spray's high velocity and big particle size. Another is hand-mouth discoordination[79]

The overall lung dosage deposition and penetration into the peripheral airways decrease as IFR rises. Because the aerosol is more easily deposited by inertial impaction in the conducting airway and oropharyngeal regions, rapid inhalations (>60 l min⁻¹) result in a decreased peripheral deposition. Slow inhalation of aerosols increases their gravitational sedimentation deposition in the lung's periphery[80,81].

Inhalers of dry powder

The coordination issues with the MDI were intended to be resolved by DPIs. The need to get rid of MDIs that include CFCs has sparked renewed interest in this delivery mechanism. There are many different types of DPI devices available on the market, including reservoir-type (bulk powder) systems multiple unit doses sealed in blisters on a strip that passes through the inhaler and single-dose devices loaded by the patient [82].

Varying DPIs have varying lung deposition. About 20–25% of the medication is kept inside the device, while the lungs get 12–40% of the released dose[83].

Ineffective disaggregation of the fine drug particles from coarser carrier lactose particles or drug pellets is the cause of poor drug deposition with DPIs. Drug disaggregation and, thus, the effectiveness of pulmonary drug administration with DPIs are known to be impacted by slow IFR, high humidity, and sudden, significant temperature changes [82]. Fast inhalation improves medication distribution to the lungs with the majority of DPIs. [83].

Inhaled drug formulations :

For an inhalable treatment to be effective, drug formulation is crucial. In addition to being pharmacologically active, a medication must be effectively administered into the lungs, reach the proper site of action, and stay there until the intended pharmacological effect takes place. For maximum systemic bioavailability, a medication intended to treat a systemic illness, such as insulin for diabetes, must be deposited in the lung peripheral. Long-term medication residence in the lungs may be necessary for gene therapy or antibiotic treatment in cystic fibrosis in order to achieve the best possible therapeutic outcome. Consequently, a formulation that avoids the clearance processes and stays in the lungs for the appropriate amount of time[84].

Therefore, a formulation that avoids the lung's clearance processes and stays in the lungs for the required amount of time may be required. This section will concentrate on dry powder formulation research, which has been expanding recently. In order to create dry powders for inhalation, different excipients, such as lipids and polymers, or carrier systems, such as lactose, must be micronized utilizing jet milling, precipitation, freeze-drying, or spray-drying. Depending on the medicinal agent being developed, each one has particular benefits and drawbacks[85].

Nanocarrier used in drug delivery ;

Drug delivery systems employing nanocarriers The National Nanotechnology Initiative (NNI) defines nanoparticles as structures with at least one dimension that ranges in size from 1 to 100 nm. Nonetheless, particles up to several hundred nanometers in size are



frequently denoted by the prefix "nano." Because they are more readily absorbed by cells than bigger molecules, nanocarriers with optimal physicochemical and biological properties can be effectively employed as delivery systems for currently known bioactive chemicals. Nanocarriers that have been explored as drug delivery methods include liposomes, solid lipid nanoparticles, dendrimers, polymers, silicon or carbon materials, and magnetic nanoparticles[86].

A medication can either be encapsulated in the nanocarrier or adsorbed or covalently linked to its surface. The benefit of covalent bonding over other attachment methods is that it allows for exact control over the quantity of therapeutic substance given by controlling the number of drug molecules attached to the nanocarrier. Both active and passive techniques can be used to target specific cells with nanocarriers. The first method depends on a drug's attraction; the nanocarriers bind to the afflicted location using low molecular ligands, such as folic acids or peptides, or recognition ligands that are affixed to the surface of conjugate antibodies. Manipulating physical stimuli is another way to accomplish the active method[87].

Medical nanocarriers must be nontoxic (harmless to a particular biological system) and biocompatible (able to integrate with a biological system without evoking an immune response or any harmful effects). The hydrodynamic size, shape, quantity, surface chemistry, administration route, immune system reaction (particularly a route of uptake by macrophages and granulocytes), and residence time in the bloodstream all have a significant impact on the undesirable consequences of nanoparticles. Toxicological research is required for every new DDS formulation because it might be challenging to estimate the toxicity of nanoparticles due to several reasons. Nonetheless, some generalizations about their size may be made: smaller particles have a larger surface area[88]. Drug delivery systems based on nanotechnology ;

In order to deliver the bioactive chemical, a perfect nanoparticulate drug delivery system should both penetrate target cells and preferentially aggregate in the required organ or tissue [89]. It has been suggested that certain ligands or cell-penetrating peptides could mediate intracellular transport, whereas passive or

antibody-mediated active targeting could accomplish organ or tissue accumulation [90,91]. Drug delivery aims to increase efficacy, safety, and/or patient comfort by implementing prolonged (or delayed) and/or regulated drug release. Therefore, in order to improve the therapeutic index of antimicrobials in the intracellular environment, drug delivery devices have been proposed for passively targeting infected cells of the mononuclear phagocytic system[91]

While reducing the negative effects associated with the antibiotic's systemic uses..These systems offer numerous benefits for drug delivery, primarily concentrating on increased drug safety and efficacy, such as targeted drug delivery, enhanced bioavailability, prolonged drug or gene effect in target tissue, and enhanced stability of therapeutic agents against chemical/enzymatic degradation [92].All of these benefits arise from the delivery devices' nanoscale size. As a result, it is believed that DDS with improved targeting properties has great promise for boosting treatment effectiveness and efficiency while reducing adverse effects [93].

Current applications and systems for medication delivery

The effective development of drug delivery systems based on organic, inorganic, and hybrid nanoparticles as drug carriers for active targeting—particularly in chemotherapy—has advanced significantly in recent years. Improved characteristics of modern drug delivery systems (DDS) include reduced particle size, enhanced permeability, enhanced solubility, efficacy, precise site targeting, stability, toxicity, and prolonged delivery. Compared to traditional dose forms, they can greatly enhance the performance of medicinal agents [94].

Recent drug delivery systems are acknowledged as the most recent advancements and creative comprehension of the pharmacokinetic and pharmacodynamic behavior of medicines in the building of an ideal drug administration system.

These DDS can carry material to the site of action and maintain drug concentrations in the therapeutic range for extended periods of time since they are transporters. The innovation's commercial and therapeutic success is closely linked to the delivery mechanism's adoption.



Involving patients early in the development process, identifying any issues, and making sure they get the most out of the gadget are all necessary to achieve this. Enhancing delivery methods that lower toxicity and boost effectiveness[95].

Future Direction :

In recent years, drug delivery and nanomedicine have drawn a lot of attention in both research and experimentation in several clinical trials, making them a very fascinating field of study in modern science. The new drug delivery system has a lot of potential despite the setbacks that have prevented these delivery systems from being used in clinical settings. However, in order to help achieve the efficiency we need to find results from bench to bedside, collaboration across academic theory, laboratory experimentation, medical knowledge, pharmaceuticals, and excellent research is needed. According to Vargason et al., cell treatments have the potential to significantly improve drug delivery systems' bio-acceptability problems and produce an effective single dose[96].

In actuality, cell treatments break down innate biological boundaries, produce reactions that seem natural inside the system, and provide a seemingly persistent source of complicated biologics. Inorganic mesoporous nanoparticles, microfluids, and molecular imprinting polymers have all been proposed by Adepu deli[97]. as potential solutions to some of the problems associated with drug delivery. Khalid et al. state that using priming agents that can affect the biological environment in which they are administered—particularly those that can alter the form and function of tissues in a way that makes the administered drug favorable without endangering the patient is one way to increase the efficacy of drug delivery[98].

In the field of biomaterials, cell-based drug systems should also be taken into consideration. This refers to the use of cells in conjunction with nanobiomaterials because cells are a natural part of the human body. This is a novel approach that is still theoretical but seems to be the most inventive; it promotes drug delivery with the goal of achieving the maximum drug delivery pattern. The effectiveness of these contemporary medication delivery methods and the difficulties associated

with their use still require extensive research and clinical testing[99].

CONCLUSION :

Drug delivery mechanisms have evolved from conventional dosage forms to sophisticated controlled, sustained, targeted, transdermal, mucoadhesive, pulmonary and nanotechnology-based systems. These approaches allow better control of drug release, improve drug bioavailability, enhance site-specific delivery, reduce dosing frequency and may improve therapeutic efficacy, safety and patient compliance. The rise of nanocarriers and targeted delivery systems has paved new ways to deliver drugs to a particular tissue and maintain therapeutic drug levels for long durations.

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