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Advance in Delivery System & their Pharmacological Implications

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Abstract:
Drug delivery is the administration of a pharmaceutical substance to have a medicinal effect on either people or animals. The nasal and pulmonary routes of drug administration are gaining relevance in human disease therapy. Especially for peptide and protein therapies, these methods give excellent substitutes for parenteral medication administration. Many drug delivery means have been developed for this and are now under investigation for nose and pulmonary distribution. Others are microspheres, gels, liposomes, and prodrugs, cyclodextrins, proliposomes. Among the exacting criteria these delivery systems need are suitability for biological systems, targeting particular sites or cell types in the lung, specific medication release, and degradation within an acceptable timeframe; durability against the forces applied during aerosolization; and the ability to be converted into an aerosol— all qualities which nanoparticles produced from biodegradable polymers seem to have potential to meet.

Keywords: Drug Delivery, Pharmaceutical Substance, Therapeutic Effect, Nasal Routes, Pulmonary Routes, Medication Administration, Peptide Therapies, Protein Therapies, Parenteral Administration, Liposomes, Microspheres, Aerosol, Biocompatibility, Targeting, Nanoparticles

INTRODUCTION

Creating new medical treatments is both costly and time-consuming. Attempts have been made to improve the safety-efficacy ratio of "old" drugs using several approaches including dose titration, therapeutic drug monitoring, and personalizing drug therapy. Additionally, other highly attractive strategies being researched include targeted delivery, slow delivery, and controlled rates of drug administration. It is noteworthy that researchers in India have produced a considerable body of work and numerous publications from the USA and Europe[1]. The discovery of novel drugs is founded on natural molecules with various chemical foundations. Natural product discovery based on medicines has recently seen a change towards developing lead compounds readily accessible synthetically mimicking the chemistry of their organic correlates. Natural products have outstanding chemical variety, biological and chemical properties with macromolecular specificity, and reduced toxicity. They therefore provide promise for the advancement of new medicines[2].

LIPOSOMAL DRUG DELIVERY SYSTEM

Usually, drug delivery systems will increase the potency of anticancer chemicals and/or lower their toxicity. By using the "enhanced permeability and retention" effect, long-circulating macromolecular carriers like liposomes might choose to permeate from tumor blood vessels[3]. Liposomal daunorubicin

and pegylated liposomal doxorubicin are examples of liposomal anthracyclines that exhibit significantly extended circulation owing to their highly effective drug encapsulation, yielding considerable anticancer effects with minimized cardiotoxicity. Whether used alone or alongside other chemotherapeutic agents, pegylated liposomal doxorubicin has shown prominent effectiveness in treating breast cancer. Additional liposome structures are being developed for the delivery of various medications. True molecular targeting is set to be a characteristic of the upcoming generation of delivery systems; ligand-directed constructs, like immunoliposomes, merge biological components capable of recognizing tumors with delivery mechanisms[4].

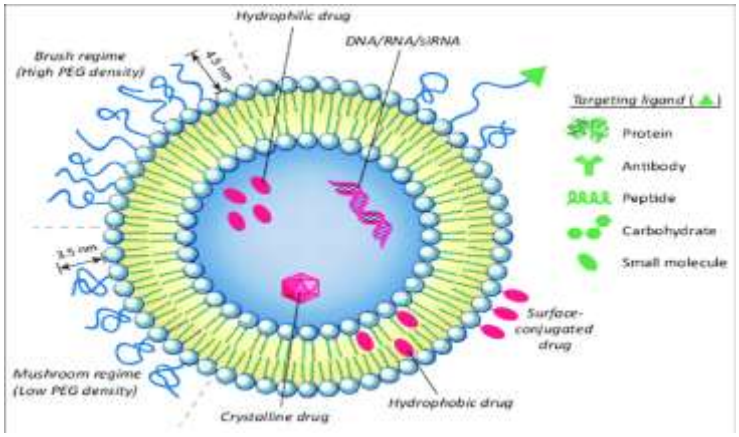

Figure 1: Liposomal Cell[30]

Presently licensed liposomal drug delivery systems offer a stable formulation, better pharmacokinetics, and some "passive" or "physiological" targeting of tumor tissue, as noted before [5]. Still, these carriers do not target tumor cells exclusively. Unlike reactive carriers like positively charged liposomes, changes that shield liposomes from undesirable binding with plasma proteins and cell membranes also stop interaction with cancer cells. Liposomes act instead as a medicine-loaded warehouse lingering in the tumor stroma after they penetrate the tumor tissue. En the end, phagocytes and/or enzymes target liposomes, hence permitting the drug to be released for further diffusing to tumours. Next generation of drug carriers are those that directly molecularly target cancer cells via ligand-mediated or antibody-mediated contacts[6].

NANO BASED DRUG DELIVERY SYSTEMS

The use of nanostructures and nanophases across many scientific disciplines shows that nanotechnology might connect the biological and physical sciences. Particularly fascinating in nanomedicine and nano-based drug distribution mechanisms are these small part [7]. In the spheres of advanced medicine and drug formulations, effective controlled release and dispersal of medications depends on nanotechnology. Materials have dimensions between 1 and 100 nm. Their influence on the cutting-edge of nanomedicine, which comprises microarray analysis, optical sensors, microfluidics, tissue engineering, and drug delivery, helps to deliver drugs [8].

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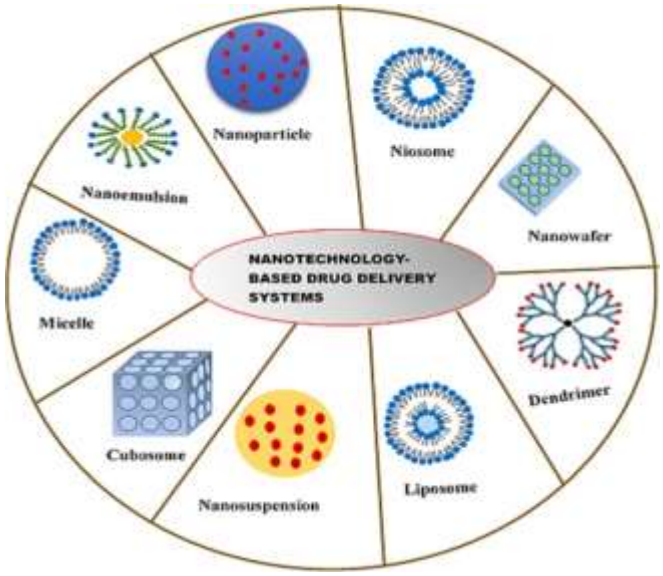

Figure 2: Nanotechnology- Based Drug Delivery System[31]

Principles of drug design strategies based on nanotechnology:

Figure 3: Example of Natural Compounds Extracted from Higher Plant[32]

Nanomedicine represents the medical field that employs nanotechnology discoveries to stop and combat illnesses through nanomaterial-based approaches which include absorbable nanoparticles and nano robots that serve multiple diagnostic, delivery, sensor, and activating functions inside living organisms[11]. Drugs with very low solubility face several challenges regarding biopharmaceutical delivery, including inadequate bioaccessibility after oral consumption, diminished ability to penetrate the outer membrane, heightened necessity for intravenous delivery, and adverse effects that can manifest before the typical vaccination protocol. Nonetheless, the implementation of nanotechnology strategies in the drug delivery system could potentially alleviate all of these limitations[12]. Nanoscale drug development stands as the most advanced technology within nanoparticle applications because

researchers have extensively studied and developed its possible advantages that include transforming properties such as solubility along with drug release rates and diffusivity and bioavailability and immunogenicity. Such research may enable drug developers to create new administration methods combined with reduced toxicities and side effects and better distribution patterns and prolonged drug survival times[13]. The engineered drug delivery systems exist as two types to fulfill their dosage requirements either through spatial-directed delivery with controlled release mechanics or targeted area delivery. Building blocks in self-assembly processes naturally form well-defined patterns along with predetermined structures[14].

Drugs are delivered by nanostructures in two ways: passively and self-delivered. In the former, the hydrophobic effect is primarily used to incorporate pharmaceuticals into the interior cavity of the structure. The low content of the drug, which is contained in a hydrophobic environment, allows the nanostructure materials to target specific areas and release the desired amount of the drug[15].

POLYMERS FOR DRUG DELIVERY SYSTEMS

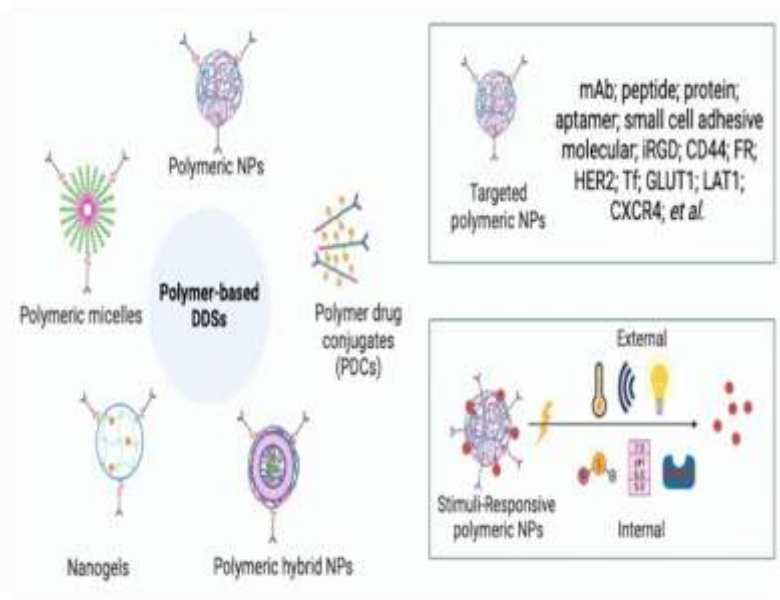

Figure 4: Polymer Based Drug Delivery System[33]

The advancement of drug delivery technology has been significantly supported by polymers, which provide cyclic dosing, customizable release of both hydrophilic and hydrophobic drugs, and controlled release of therapeutic agents in steady doses over prolonged periods. Partially because of the progress made by chemical engineers, the field has grown considerably since its initial days of using readily available materials. Current advancements in drug delivery are now founded on the rational design of polymers tailored for specific cargo and designed to perform specific biological functions. We go over the physiological obstacles to medication administration and emphasise the basic drug delivery methods and their mathematical underpinnings. We go over the history and uses of polymer treatments, including polymer-protein and polymer-drug conjugates, as well as stimuli-responsive polymer systems. To highlight areas of research pushing the boundaries of drug delivery, the most recent advancements in polymers that can recognise molecules or guide intracellular distribution are reviewed[16].

NANOPARTICULATE SYSTEMS FOR BRAIN DELIVERY OF DRUGS

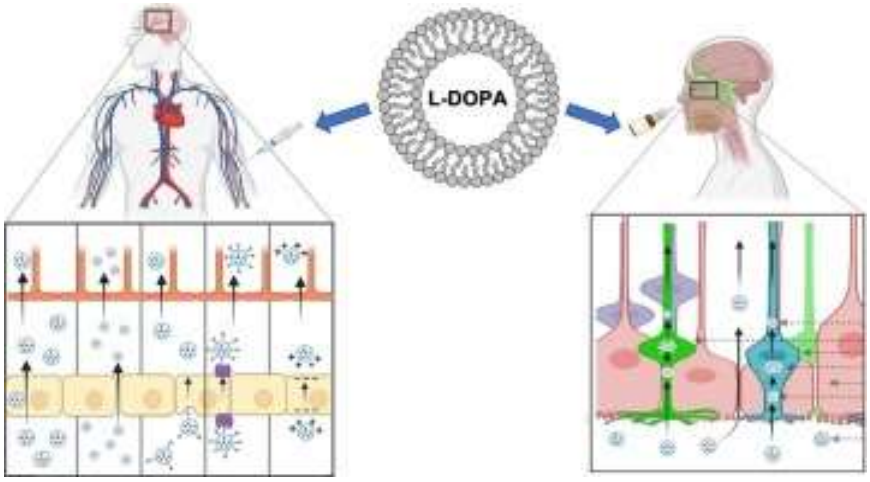

Figure 5: Nano-Particulate Systems for Brain Delivery of Drugs[34]

Antibiotics, antineoplastics, and many medications that act on the central nervous system (CNS), particularly neuropeptides, face an impassable barrier in the blood–brain barrier (BBB). This barrier, which is essentially the main contact between the blood and the brain, is created at the level of the cerebral capillaries' endothelial cells. Additionally, the arachnoid membrane and the ependymal cells that encircle the brain's circumventricular organs provide a barrier function[17]. It plays a crucial role in controlling the stability of the brain's internal environment. To provide a stable environment where the brain's integrative neuronal activities can occur as best they can, the composition of the extracellular fluid is regulated within exact bounds, mainly independent of the composition of the blood in circulation[18].

The ability of drugs to passively diffuse across brain endothelial cells depends on their molecular weight and lipophilicity. Nevertheless, many medications with favourable lipophilicity that ordinarily should allow for simple transport across these cells are quickly reabsorbed into the bloodstream by very efficient efflux pumps[18]. Among these pump systems are P-glycoprotein (Pgp), also known as multidrug resistance protein (mdr), and multiple organic anion transporter (MOAT).

LEVO-DOPA DELIVERY SYSTEMS

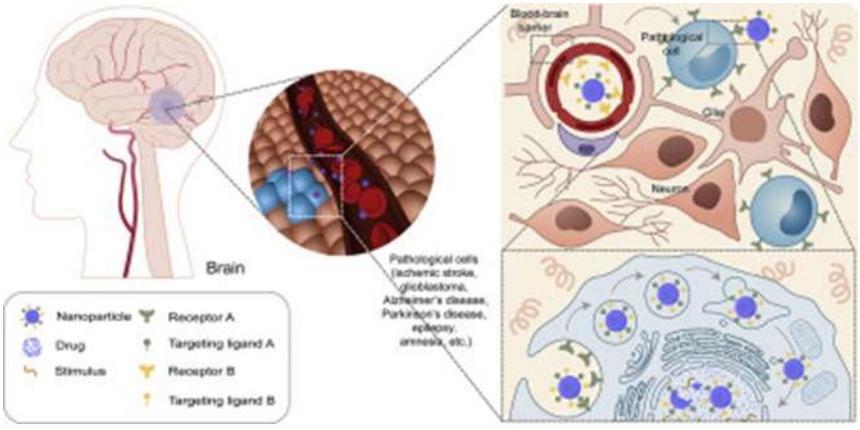

Figure 6: Levo-Dopa Delivery System[35]

Even though Parkinson's disease (PD) has been recognized for nearly 200 years, managing and treating the condition remains quite challenging due to the gradual degeneration of dopaminergic nigral neurons, the motor difficulties that patients experience as the disease advances, and the constraints of

pharmacological treatment. Levodopa (l-DOPA), selegiline, amantadine, bromocriptine, entacapone, pramipexole dihydrochloride, and more recently istradefylline and rasagiline are among the therapeutic agents that have been employed to address Parkinson's disease. Despite being the oldest agent, l-DOPA continues to be the most effective. Nearly all PD patients need l-DOPA since it is less costly, easier to give, and better tolerated. However, metabolism, resulting limited bioavailability, and unpredictable changes in its plasma levels severely impair the effectiveness of l-DOPA in advanced Parkinson's disease. Immediate-release formulations, liquid formulations, dispersible tablets, controlled-release formulations, dual-release formulations, microspheres, infusion, and transdermal delivery are various drug delivery methods that have been utilized for l-DOPA administration. This study discusses the l-DOPA-loaded drug delivery systems that have been created over the past thirty years[19].

TUMOR DELIVERY OF MACROMOLECULAR DRUGS BASED ON THE EPR EFFECT

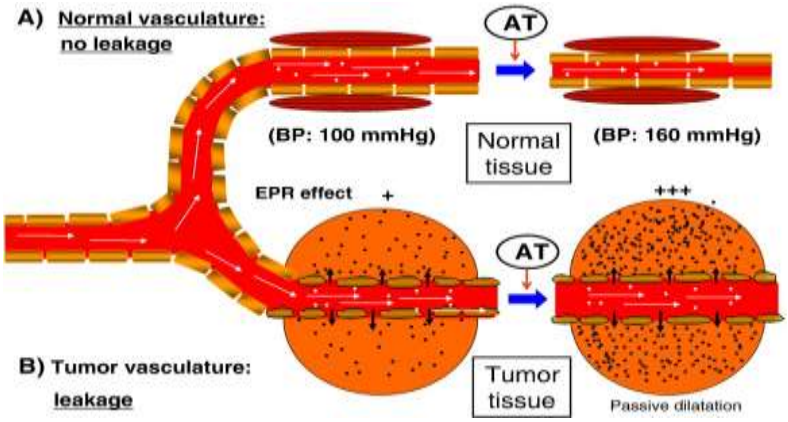

Figure 7: Tumor Delivery Of Macromolecular Drugs Based On The Epr Effect[36]

Since cancer mortality is still on the rise, breakthroughs in nanotechnology have made it possible to target drugs to tumour tissues efficiently while avoiding all of the drawbacks of traditional chemotherapy. The importance of polymeric drug-delivery systems in oncology has risen significantly over the past decade. The creation of drug-loaded nanoparticles for cancer treatment has concentrated on poly(lactic-co-glycolic acid) (PLGA), a polymer that is commonly utilized for producing "nanoparticles" because of its biocompatibility, extensive track record in biomedical applications, and demonstrated capacity to release drugs in a sustained manner.These PLGA nanoparticles have also been utilised to create nanomedicine proteins and peptides, nanovaccines, a drug-and gene-delivery system for cancer treatment, nanoantigens, and growth factors.

Tumor delivery of proteins and peptides

Numerous proteins and peptides, particularly anticancer medications, possess biological functions that render them potent and therapeutic. Thanks to advancements in solid-phase peptide synthesis, recombinant DNA, and hybridoma technology, clinical-grade peptides and proteins can be generated in limitless quantities. However, their rapid removal from circulation—primarily due to renal filtration, rapid enzymatic breakdown, and uptake by the mononuclear[20].

Tumor delivery of macromolecules

Drugs can occasionally be attached to polymers that are insufficiently sized to impede renal elimination but can adhere to naturally present long-circulating blood plasma elements, like serum albumin or lipoproteins, to extend circulation time. These polymers consist of poly(styrene-co-maleic acid

anhydride) (SMA). It has been shown that the conjugation of proteins and peptides with a polymer of this type as small as 1. 5 kDa can enhance[20].

Tumor delivery of nanoparticles

Long-circulating pharmaceutical nanocarriers, such as liposomes, micelles, or polymeric nanoparticles, have often been used for drug delivery into tumors via passive accumulation. These nanocarriers are able to gather in various diseased areas with impaired vasculature due to the EPR effect. The kinetics of long-circulating liposomes and other nanocarriers are log-linear, not saturable, independent of dosage, and show improved bioavailability[20].

Tumor delivery of DNA and related products

As a component of extensively circulating macromolecular or nanoparticular systems, DNA and related products can also be introduced into tumours through the EPR effect. This is particularly the case when passive EPR-mediated targeting is paired with an additional ligand-mediated targeting to promote intracellular delivery[21].

NANOTECH APPROACHES TO DRUG DELIVERY

Over the last decade, nanotechnology has profoundly influenced the advancement of delivery systems for small molecules, proteins, and DNA. This has led to the formation of entirely new and possibly unanticipated fields. Cutting-edge drug delivery techniques are an essential tool for the pharmaceutical sector to expand its drug markets. The technology can solve problems with existing medications, such prolonging the shelf life[22].

FLOATING DRUG DELIVERY SYSTEMS

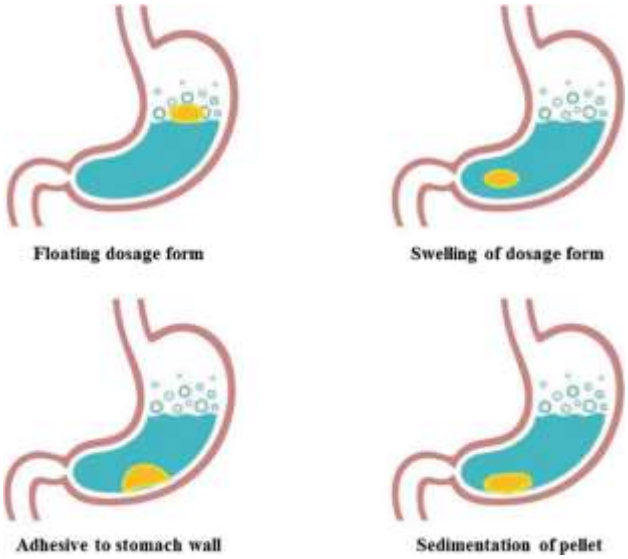

Figure 8: Floating Drug Delivery system[37]

The main objective of the de novo creation of an oral controlled drug delivery system (DDS) should be to enhance and forecast the bioavailability of drugs. Nevertheless, several physiological obstacles impede the development process, such as the highly variable nature of the gastric emptying process and the difficulty in confining and localising the DDS within specific areas of the gastrointestinal (GI) tract. The emptying process may last anywhere from a few minutes to twelve hours, depending on the subject's physiological condition and the design of the pharmacological formulation. Since most drugs

are predominantly absorbed in the upper section of the small intestine, this inconsistency may lead to unpredictable bioavailability and timelines for achieving peak plasma concentrations. Additionally, partial drug release from the DDS can lead to reduced effectiveness of the administered dose due to the relatively short gastric emptying time (GET) in humans, which typically averages 2–3 hours in the primary absorption zone (stomach or upper part of the intestine). Therefore, there are numerous advantages to managing the placement of a DDS in a specific area of the GI system, particularly for drugs with stability challenges or those having an absorption window within the GI tract. All things considered, the DDS's close contact with the absorbing membrane may increase drug absorption and have an impact on its rate. Because of these factors, oral controlled-release (CR) dose formulations with the ability to retain in the stomach have been developed. The present technological progress in FDDS, encompassing patented and clinically accessible products, formulation development strategy, their advantages, and their possibilities for oral controlled drug delivery in the future are discussed in this initial installment of a series of reviews on contemporary gastroretentive systems[23].

SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Figure 9: Sustained Drug Delivery System[38]

Israel Lipowski's 1938 patent is likely the first work in the field of sustained medication administration dosage formulations. The creation of the coated particle method for sustained drug delivery, initially presented in the early 1950s, was probably affected by this experiment, which utilized coated pallets for extended drug release. Since the primary goal of therapy is to attain a stable blood level that is both therapeutically beneficial and non-toxic over an extended duration, a drug should preferably reach the site of action (receptor) rapidly at the ideal concentration, stay there for the required duration, avoid other locations, and be swiftly eliminated from the site when necessary. [24].

The two categories of sustained-release drug delivery systems for managing glaucoma are intraocular (including intraocular implants and microspheres for supraciliary drug administration) and extraocular (including wearable ocular surface devices or multi-use (immediate-release) eye formulations (such as aqueous solutions, gels; ocular inserts, contact lenses, periocular rings, or punctual plugs)[25].

TARGETED DRUG DELIVERY SYSTEM

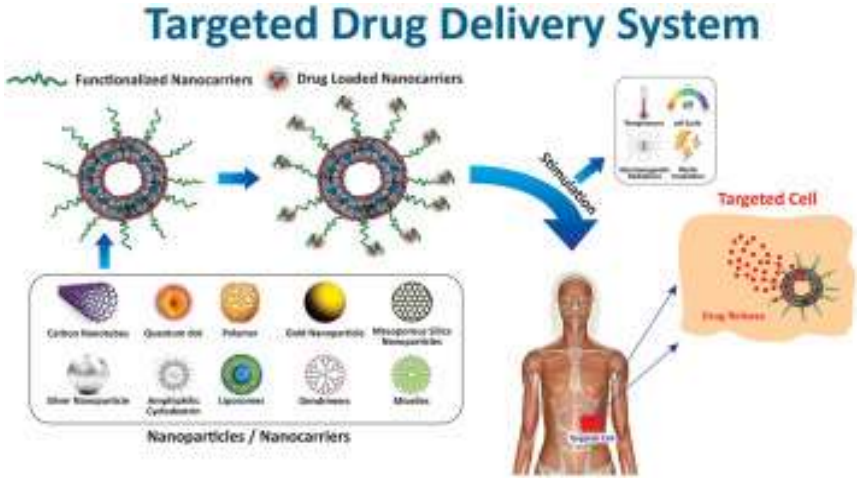

Figure 10: Target Drug Delivery System[39]

The procedure of administering medication to a patient in such a way that it elevates the concentration of the drug in certain parts of the body relative to others is referred to as targeted drug delivery. The aim of targeted drug delivery is to decrease the relative concentration of the drug in other tissues while enhancing the concentration of the drug in the targeted tissues. This lessens adverse effects while increasing the product's effectiveness. A medication molecule finds it extremely challenging to make its way through an organism's intricate cellular network. As the name implies, the goal of targeted medication delivery is to help the drug molecule get to the preferred location. This method's intrinsic benefit has been the decrease in medication dosage and adverse effects[26].

Targeted agents fall into a number of types, and each has unique but connected purposes. There are many potential combinations as a result of this variety of categories. As fields like molecular biology, cell biology, and materials science have advanced, the targeted agents have developed quickly, making them a research hotspot for pharmaceutics and pharmacy professionals worldwide. In western medicine, targeted agents have been thoroughly researched and used in clinical settings. Currently, analogous items are available in the United States, Europe, and other industrialised nations. However, basic research is still being conducted in the field of traditional Chinese medicine (TCM)[27].

INTRAUTERINE DRUG DELIVERY SYSTEM

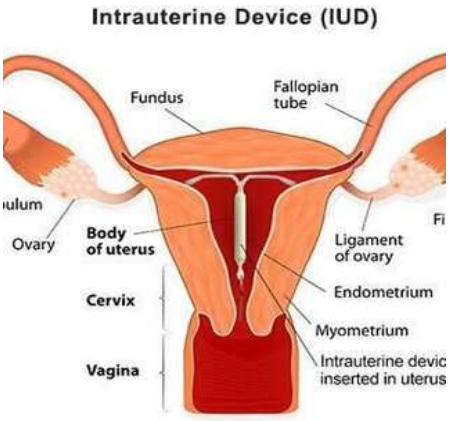

Figure 11: Intrauterine Drug Delivery System[40]

In the US, 3 million unintended pregnancies occur annually, of which half are electively terminated. Lack of utilisation seems to be the main culprit, not a lack of effectiveness in the solutions that are available. Although oral contraceptive pills (OCPs) are the most often prescribed reversible contraceptive drug in the US, only 22% of women in their reproductive years take them, and 32–50% stop using them within the first year. Adverse effects and the need for daily administration are among the reasons for stopping. Astute practitioners and controlled drug delivery development teams have long sought to create a long-term contraception with a manageable side effect profile. One extremely successful instance of innovative drug delivery in the context of contraception is the creation and introduction of the levonorgestrel intrauterine system (LNG IUS, Mirena®). The non-contraceptive advantages of this technology will encourage its adoption outside of the contraceptive population in addition to its core application[28].

To evaluate a novel "frameless" intrauterine drug delivery system, the FibroPlantTM levonorgestrel intrauterine system, which dispenses 14 μg of levonorgestrel daily, for its contraceptive efficacy, user acceptability, side effects, and adverse reactions. Investigating how the new intrauterine device influenced menstrual blood loss was a secondary objective. This pilot study was ongoing, open-label, and non-comparative. The lead author performed fifty-four contraceptive insertions in reproductive women aged sixteen to fifty-one. To address severe bleeding and offer contraception, 18 of these women received the FibroPlant levonorgestrel intrauterine system. Twelve of these women experienced heavy menstrual flow alongside medium-to-large uterine fibroids. The follow-up phase of the trial extended from six to sixteen months[29].

CONCLUSION

Pharmacological therapies have been transformed by developments in drug delivery methods, which have greatly enhanced patient compliance and therapeutic results. Key issues like low bioavailability, systemic adverse effects, and dose frequency have been addressed by innovations like targeted delivery systems, controlled-release formulations, and nanotechnology-based delivery. These innovative methods allow medications to be delivered precisely to targeted locations, increasing effectiveness while reducing side effects. Furthermore, the combination of digital monitoring systems, smart materials, and biologics has enormous potential for personalised medicine, opening the door to therapies catered to the unique needs of each patient. To overcome current constraints and fully utilise these technologies, more multidisciplinary research and cooperation are necessary to ensure wider accessibility and application across a range of medical issues.

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