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Review Article

Understanding Drug Delivery System for Safe Dispensing and Good Therapeutic Efficacy: A Review

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Abstract

Pharmacology is the study of drugs, or chemical compounds, that act by interacting with different living things, such as cells, tissues, and even whole organisms, to achieve a desired result. A drug must enter the body and be distributed in some way that allows it to reach its site of action for it to be effective. The technique or approach used to provide pharmaceutical drugs to achieve therapeutic effect in people or animals is known as drug delivery. The creation of new materials or carrier systems for efficient therapeutic medication administration is a large area of study in the field of drug delivery. These systems are crucial in the treatment of many diseases. A novel drug's molecule requires expensive and time-consuming development. The employment of numerous methods, including dosage titration, individualising drug therapy, and therapeutic drug monitoring, improves the safety efficacy ratios of older medications. When it comes to delivering drugs to specific bodily regions, traditional methods of drug administration face several obstacles. To enhance the therapeutic delivery of medications, increasing research and development activities have been implemented, along with many investment opportunities. This article discusses the past background and conventional drug delivery methods. It also includes the update on some of the existing drug delivery technologies for oral controlled release, oral disintegrating dosage forms, and nano drug delivery system.

Keywords: Drug Delivery System; Therapeutics; Oral Controlled Release; Nanoparticles

Abbreviations

DDS: Drug Delivery System; FDDS: Fast-dissolving drug delivery system; FDT: Fast dissolving tablets; FDM: Fused deposition modelling; MN: Microneedle; MEC: Minimal effective concentration; MTC: Minimal toxic concentration; ODT: Oral disintegrating dosage

Introduction

Drug delivery systems (DDS) are used to transport pharmaceutical drugs in the body as needed to achieve the desired therapeutic effect. These systems are often made to: (i) increase the solubility of active constituents in liquid and their chemical stability, (ii) enhance pharmacological effectiveness, and (iii) minimize adverse effects [1]. Since the introduction of the first sustained release formulation of Dexedrine in the 1950s, modern drug delivery methods have experienced constant advancement [2]. Any drug delivery system's objective is to deliver and maintain therapeutic drug concentrations at the targeted biological site. Drug delivery strategies were modified to handle the difficulties that arose when treatment modalities grew to incorporate nucleic acids, peptides, proteins, and antibodies in addition to small molecules.

When it comes to delivering drugs to specific bodily regions, traditional methods of drug administration face several obstacles. Since the development of medical application systems, numerous drugs are being provided through a variety of traditional drug delivery dosage forms to treat a variety of diseases [3]. These dosage forms include solutions, lotions, mixtures, creams, pastes, ointments, powders, suppositories, suspensions, injectables, pills, immediate release capsules and tablets, and so on. Some of these traditional dose forms are still used today as the main medication delivery dosage products. These might not always support the best treatment outcomes, though. A revolutionary drug delivery method can significantly enhance the safety, effectiveness, and patient compliance of already available medicine in addition to the existing ones.

The technique through which a medicine is administered can have a big impact on its effectiveness. To allow for the successful and safe application of all pharmaceuticals to patients, appropriate DDS must be developed. This article intends to emphasize the importance of various drug delivery techniques and highlights on the latest advancement in the field.

Evolution, conceptualization

Since the emergence of medical application systems, a variety of medications are being used to treat a variety of diseases through the use of conventional drug delivery dosage forms, such as solutions, lotions, mixtures, creams, pastes, ointments, powders, suppositories, suspensions, injectables, pills, immediate release capsules and tablets, etc. [3]. Some of these traditional dose forms are still used today as the main medication delivery dosage products. These could not always make room for the best treatment outcomes. A revolutionary drug delivery method can significantly enhance the safety, effectiveness, and patient compliance of already available medicine in addition to the existing ones. In this context, the need to effectively administer medications to patients while minimising adverse effects has prompted several pharmaceutical firms to work on the creation of innovative drug delivery systems. Examples of more recent technologies with significantly increased therapeutic potential include aerosols, fast-dissolving dose forms, liposomes, taste-masking systems, transdermal patches, and oral controlled release systems [2].

A drug formulation, such as a tablet, capsule, ointment, or solution, is referred to as a "drug delivery system." When a formulation includes a technology built in to manage the drug release kinetics over time, it is referred to as having a "controlled release drug delivery system" or a "controlled drug delivery system." Contrary to traditional formulations, which mostly or completely release the loaded drug(s) instantly and uncontrolled, controlled release drug delivery methods allow for regulatory drug release. Therefore, "immediate release" or IR formulations are the common names for traditional formulations [4]. Maintaining a comparatively consistent drug concentration in the blood throughout time (i.e., the same) was another definition of the term "controlled." But it proved challenging to maintain a steady medication concentration, particularly for oral controlled release formulations.

Smith Kline and French created the first controlled release formulation in 1952 For a 12-hour dosage of dextroamphetamine (Dexedrine). From that moment until the end of the 1970s, the fundamental knowledge of controlled drug delivery was developed, including the many drug release mechanisms based on ion exchange, diffusion, osmosis, and dissolution. Numerous twice-daily and once-daily oral delivery systems were created using the technology created during the first generation [5]. Transdermal patches that release medication once daily and once weekly were also created using the same drug release processes.

It was believed that zero-order release kinetics systems would maintain a constant medication concentration in the blood. First, a constant drug concentration in the blood cannot be maintained with zero-order release and this is obvious for oral delivery systems. Many other drug delivery systems were created during the second generation. The advent of delivery systems that are activated by changes in environmental variables like pH, temperature, or glucose levels led to the development of so-called "smart" polymers and hydrogels. To distribute peptides and proteins over a month, solid implants, *in situ* gel-forming implants, and biodegradable microparticles were all employed [6].

Importance of understanding drug delivery system

Despite substantial progress in the design and development of new drugs, many of them still have undesirable side effects because they interact with areas of the body other than the ones they are intended to address. Occasionally, adverse effects might happen based on the drug, the administration method, and our body's reaction. Unfavourable side effects might result from the accumulation of high blood plasma drug concentration brought on by the frequent administration of traditional DDS. Therefore, efforts must be taken to ensure that the reduction in the number and frequency of doses required to maintain the desirable therapeutic responses results in greater patient compliance [7]. The kind and intensity of these adverse effects might differ widely from person to person. The drug's effectiveness can be significantly impacted by the way it is administered.

To ensure that all medications are administered to patients safely and effectively, appropriate DDS must be developed for each medication. DDSs regulate both the drug's adverse effects and its therapeutic effects, as well as its rate of release and rate of absorption. Ideal DDSs make sure the active medicine is accessible at the site of action in accordance with the patient's needs during the prescribed period of time. The therapeutic window, or the range between minimal effective concentration (MEC) and minimal toxic concentration (MTC), should be maintained for the medication concentration at the target site [8].

Different methods of drug delivery system

The site at which the medicine is administered, such as oral or intravenous, is typically used to classify a medication administration route. The route of administration of pharmaceuticals is determined not only by convenience, but also by the drug's properties and pharmacokinetics. Most of the drugs can be administered by different routes. Selection of routes for drug administration is determined by drug and patient related factors [9]. (Figure 1).

Figure 1

Local routes

- **Topical:** For local action, the drug is applied to the skin or mucous membrane at various sites such as oral cavity, GI tract, rectum and anal canal, bronchi, skin, eye, ear and nose.
- Administration of the drug into deep tissues by injection, e.g., administration of triamcinolone directly into the joint space in rheumatoid arthritis.
- **Intra - arterial route:** Used during diagnostic studies such as coronary angiography and for the administration of some anticancer drugs. e.g., for treatment of malignancy involving limbs.

Systemic routes

In systemic route the drug directly enters the systemic circulation or blood and produce systemic effects.

Enteral route

- **Oral**: It is the most common, cost-effective, and acceptable route for drug administration. Dosage forms include tablet, capsule, syrup, mixture, etc. When an agent is taken orally, the higher the first-pass effect, the less the agent will enter the systemic circulation.
- **Sublingual**: The drug is placed under the tongue. The medication is absorbed directly into the systemic circulation through the buccal mucosal membrane. When it's placed beneath the tongue, it disintegrates and is absorbed in the mouth. [10]
- **Buccal Route**: The drug is kept in the buccal cavity where it disintegrates, and absorption occurs in the mouth. Compared to sublingual tissue, which has a highly permeable mucosa with rapid access to the underlying capillaries, buccal tissue is less permeable and has a slower drug absorption. A minor disadvantage of the buccal route of administration is that holding a drug in place for an extended period could be quite uncomfortable. Other side effects come from the drug's systemic activity once it's been absorbed (Figure 3).
- **Rectal**: Drugs can be administered in either solid or liquid form.
    - **Suppository:** It can be used for local (topical) effect as well as systemic effect, e.g., indomethacin for rheumatoid arthritis.
    - **Enema:** Retention enema can be used for local effect as well as systemic effect. The drug is absorbed through rectal mucous membrane and produces systemic effect, e.g. diazepam for status epilepticus in children.

Figure 2

Figure 3

Drugs and excipients that are well absorbed after oral administration are also readily absorbed via the rectum, resulting in systemic exposure and the risk of systemic side effects being identical.

Parenteral route

In parenteral route of drug administration, the drug does not pass through the gastrointestinal tract, and it directly enters the circulation. It can further be classified into two:

- **Injections:** Drugs are administered with the use of injections e.g., Intravascular, intramuscular, subcutaneous, intra-articular, transdermal.
- **Inhalation:** Volatile liquids and gases are given by inhalation for systemic effects, e.g., general anaesthetics. An inhaled medication is delivered rapidly across the large surface area of the respiratory tract epithelium.

Types of drug carriers used to design drug dosage form.

Oral transmucosal dosage forms

Several new dosage forms, including solutions, tablets/lozenges, chewing gum, solution sprays, laminated systems and patches, hydrogels, adhesive films, hollow fibres, and microspheres, have been developed to improve oral transmucosal drug administration [9].

- **Solid forms:** Patients can easily employ this technique of delivery. In the oral cavity, the solid formulations disintegrate. The drugs are released into the mucosa and exposed to the whole mucosa as well as the upper third of the esophageal mucosa. The lozenge or tablet is generally dissolved within 30 minutes, depending on the size and composition, limiting the total quantity of drug that can be delivered. Absorption and bioavailability of solid dosage forms vary significantly between and within individuals. [11] (Figure 4).
- **Gum**: Chewing gum is a novel method of oral transmucosal drug delivery that can be used for systemic drug delivery. The advantages over other oral mucosal drug delivery methods, includes the capacity to control drug release over time and the potential to increase drug release and retention time variability. It is a convenient method of drug delivery. Furthermore, an individual may be able to manage drug consumption by simply adjusting the rate chewing, or by completely removing the gum [12].
- **Patches:** Transmucosal delivery patches have distinguishing features, such as rapid onset of drug delivery, sustained drug release, and a fast drop in serum drug concentration after the patch is removed. Most patches provide you a longer time to release the drug or manufactured as solvent cast mucoadhesive polymer discs to and through the buccal mucosa. [13] (Figure 5).
- **Solution, suspension, and gel-forming liquids**: Viscous liquids have been researched primarily for their ability to coat the mucosa for protective coating or as a medium for drug delivery in the treatment of local disorders such as motility dysfunction and fungal infections.
- **Multiparticulates, microparticles, and nanoparticles**: When compared to monolithic matrix tablets, oral delivery methods based on multiparticulates, microparticles, and nanoparticles frequently work better. These little immobilized carriers demonstrate an extended gastrointestinal residence duration by diffusing into the mucous gel layer due to their small size.
- **Sprays**: One of the possible alternatives to solid dosage forms is an aerosol spray, which can carry the medicine into the salivary fluid or onto the mucosal surface, making it readily available for absorption. As the spray delivers the dose in fine particulates or droplets, the lag time for the drug to be available for the site of the absorption is reduced.
- **Lozenges:** Lozenges are an example of solid-form delivery, and many drugs are available for this route of administration, including nitro-glycerine, fentanyl and prochlorperazine. Although taste can present a barrier to compliance, this is a simple form for patients to use. The lozenge dissolves and coats the oral cavity and top one-third of the oesophagus.
- **Chocolate based drug delivery system**: Pediatric administration frequently involves a medicated chocolate formulation that boosts the patient's willingness to ingest the drug. A chocolate basis is used to make medicated chocolate, and the medicine is then added to the ready-made base. The appearance, moisture content, viscosity, blooming test, drug content estimation, and *in vitro* drug release of the medicated chocolate may all be assessed. Additionally, chocolate has benefits including a rapid onset of effect, a decrease in the manufacturing and scale of the medication dose, and an increase in the drug loading capacity. Because certain medications have a bitter taste, oral delivery of bitter medications causes patient

noncompliance, particularly in youngsters. It is advisable to develop a dose form that is most palatable to paediatric children in order to get over this restriction. Since youngsters find chocolate to be particularly tasty and popular, a chocolate drug delivery method was developed [14].

Figure 4

Figure 5

Fast dissolving drug delivery system

In late 1970, the fast-dissolving drug delivery system (FDDS) was introduced as an alternative to conventional tablets, capsules, and syrups. Oral fast dissolving films can be defined as "A thin flexible, non-friable polymeric film having dispersed active pharmaceutical ingredient which is intended to be placed on the tongue for rapid disintegration and dissolution in the saliva prior to swallowing for delivery into gastrointestinal tract" [15].

Fast dissolving tablets (FDT) or films are designed to improve patient compliance and acceptance. Because of their physical condition, institutionalized psychiatric patients, as well as hospitalized or bedridden patients suffering from a variety of disorders such as stroke, thyroid disorder, Parkinson's disease, and other neurological disorders, have difficulty swallowing and require fast dissolving tablets. FDT can help with some of these problems: the rapid disintegration of tablet into a solution containing the medicine allows people who have trouble swallowing or pain to have a more patient-friendly experience. In terms of shape, size, and thickness, fast dissolving films are quite comparable to the ultra-thin strip of a postage stamp. Fast dissolving film can be easily placed on tongue or any other oral mucosal sites of the patient. It is instantaneously moistened by saliva and rapidly hydrates and adheres to the application site. It then swiftly disintegrates and dissolves to release the drug for mucosal absorption, or it can be modified to keep the quick-dissolving feature while allowing for gastrointestinal absorption when ingested [16].

Nano based drug delivery systems.

Because of its potential advantages, such as the ability to modify properties like solubility, drug release profiles, diffusivity, bioavailability, and immunogenicity, drug design at the nanoscale has been extensively studied and is by far the most advanced technology in the field of nanoparticle applications. As a result, it may be possible to improve and produce more convenient administration methods, as well as lower toxicity, fewer side effects, improved biodistribution, and a longer drug life cycle [17]. Engineered drug delivery systems are either targeted to a specific location or are designed to release therapeutic substances in a regulated manner to a specific region [18]. Targeting of drugs is another significant aspect that uses nanomaterials or nano formulations as the drug delivery systems and, is classified into active and passive. In active targeting, moieties, such as antibodies and peptides are coupled with drug delivery system to anchor them to the receptor structures expressed at the target site [19]. In passive targeting, the prepared drug carrier complex circulates through the bloodstream and is driven to the target site by affinity or binding influenced by properties like pH, temperature, molecular site and shape. The main targets in the body are the receptors on cell membranes, lipid components of the cell membrane and antigens or proteins on the cell surfaces [20]. Currently, most nanotechnology-mediated drug delivery system are targeted towards the cancer disease and its cure.

Oral disintegrating dosage forms

A fast-dispersing oral dosage form is a solid dosage form that quickly dissolves or disintegrates in the GI tract and produces a solution or suspension without the need for water [21]. These

are also known as mouth-dissolving tablets and rapid-melt, and rapid-dissolve tablets. The benefits of fast-dispersing oral dose forms are, it can be given to patients who have trouble swallowing for patient compliance and convenience, and whose drug absorption is quicker. These dose forms are most suited for elderly and young patients who struggle to swallow (dysphagia), as well as for patients who are travelling and for whom water may not always be available. Oral disintegrating dosage (ODT) increase the drug's bioavailability, speed up the onset of clinical effects, and pregastric absorption, all of which reduce dosage in comparison to conventional dosage forms and avoid the first pass hepatic metabolism [22,23]. ODTs begin dispensing medications as soon as they are placed in the mouth, and drug absorption begins due to the existence of oral mucosal tissues in the oral cavity, throat, oesophagus, gastric (the stomach), or post gastric (the large and small intestines) segments of the GI tract. The manufacturing process has a direct impact on how well ODTs perform, and the capacity of a dosage form to swiftly dissolve in saliva is one of its most important properties.

Emerging techniques for drug delivery

3D printing-based drug delivery technology

3D printing is a layer-by-layer procedure that allows computer ideas to be turned into 3D drug delivery formulations. The most widely used 3D printing technology for the preparation of special drug dosage forms is fused deposition modelling (FDM). Various drug delivery formulations, such as fast or controlled release tablets, time delayed capsules, multilayer capsules, T type intrauterine implant system, personalised percutaneous patch, and drug-eluting stents or implants, have been printed using FDM-based 3D printing technology [24,25].

Microneedle-based transdermal drug delivery technology

The development of transdermal drug delivery systems has been substantially accelerated because of microneedle (MN) technology. The microneedle can breach the stratum corneum barrier of transdermal delivery systems without reaching nerve fibres or blood vessels because of the needles' microscale size. As a result, the MN is painless and simple to use, with the capacity to escape hepatic first pass metabolism and achieve prolonged release. MNs are classified into solid MN, coated MN, dissolving MN and hollow MN according to the shape and use of MNs [26,27].

Nanocrystals

The incorporation of nanocrystals significantly reduces the number of excipients required in the formulation, allowing for ultra-high loading capacity. As a result, nanocrystals are seen as strong contenders for intravenous administration, and some weakly water-soluble drugs have been synthesised as nanocrystals for intravenous administration [28,29].

Future perspective of drug delivery research

In the upcoming 10 to 20 years, it is anticipated that protein- and peptide-based medications would account for more than half of all new medications released into the market; more than 80% of these protein medications will be antibodies. Because they are frequently big molecules that breakdown quickly in the blood stream, these biopharmaceuticals (proteins, peptides, polysaccharides, oligonucleotides, and nucleic acids in the form of DNA) create controlled delivery issues [30]. Additionally, they typically cannot be administered orally and have a limited capacity to cross cell membranes. Such molecules will be more difficult to transport through conventional methods, and injections may be the only delivery method available. The delivery strategies, construction techniques, and potential materials for enhancing the bioavailability, biocompatibility, and therapeutic index of drugs have all made significant development in the last three years. Many currently designed prescription drugs have impoverished physicochemical and pharmacokinetic traits, as well as numerous dosing regimen limits and unwanted side effects in the traditional dose form [31]. New drug delivery technologies and formulations are viable and promising options for improving therapeutic indices and reducing adverse effects. However, because the clinical application should be the main emphasis of our work, it is important to strike a balance between druggability and functional design. Furthermore, decades of experience in drug research and development have shown that without technical innovation, there would be no new pharmaceutical preparations. As biotech businesses now focus on medication delivery, one of the most exciting growth industries is anticipated to be gene therapy. In conclusion, the market for medication delivery systems has come a long way and will continue to expand quickly. Modern drug delivery methods make it easier for drug molecules to be incorporated into novel delivery systems, which has a number of clinical and financial benefits [32]. Within the pharmaceutical sector, it is critical to improve research and development of innovative technologies and drug delivery systems. Unquestionably, a novel technical idea becomes a creative technology that can be used in a medication delivery system after extensive testing, modification, and optimization.

Conclusion

If the drugs have reached their significant outcome-the clinical use-pharmacologists must be involved in the examination of the pharmacokinetics and pharmacodynamics of drug delivery systems. However, there are still a lot of difficulties in this field of medication delivery research, both technologically and economically. Many pharmaceutical firms, research facilities, and regulatory agencies are working to find solutions to these problems. In the last few years, a number of innovative drug delivery methods have significantly improved, and this trend is anticipated to continue in the near future. The need for research on drug delivery systems extends beyond sways to administer new pharmaceutical therapies. It is possible to predict rates, biodegradation, and site-specific targeting. From a financial and global health standpoint, finding new ways to administer injectable medications is a priority from a health-care standpoint. Hence, there are low-cost multiple-dose formulations with improved bioavailability needed. The pain factor associated with drug administration via parenteral routes can be eliminated. Buccal adhesive systems provide a plethora of benefits in terms of accessibility, management, and withdrawal retentively, low enzymatic activity, economy, and high patient compliance.

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