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Review Article

Recent Technological Advances in Novel Drug Delivery Systems

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Abstract

The novel drug delivery system (DDS) plays an important role in improving the therapeutic effect of drugs and reducing the toxicity, which is one of the most important fields in pharmaceutics. Oral and injectable administrations represent the most common mode of administering drugs today. However, they are unable to meet many advanced therapeutic needs including targeting, broad applicability to macromolecules and on-demand activation. These limitations have given rise to substantial research focused on the development of novel DDS. In this review some categories of DDS including immediate release drug delivery system, long-acting drug delivery system, insoluble drug delivery system, biopharmaceutical delivery system and targeting drug delivery system are highlighted. The immediate release drug delivery can be absorbed in a few minutes and produce a rapid response, mainly involve disintegrating tablets and nasal sprays, which are urgently needed in the treatment of acute diseases, such as asthma and epilepsy. In order to solve the problem that drug has a short half-life and an obvious peak-valley phenomenon existing in the plasma concentration, long-acting drug delivery systems such as pulsatile drug delivery system (PDDS), transdermal delivery system and sustained parenteral drug delivery were developed which allows the drug to have a slow, sustained or even intelligent release process, maintain a stable plasma concentration, prolong drug action time, reduce drug toxicity and improve patient compliance. Biopharmaceutical delivery system was developed to ensure the stability and activity of biological drugs such as polypeptides and protein drugs as well as gene drugs. It is difficult for pharmaceutical development of water-insoluble drugs, so a variety of methods were developed to improve the solubility and bioavailability of water-insoluble drugs. In view of develop targeting delivery systems, here are three main strategies involving passive targeting, active targeting and magnetic field-based targeting, which can reduce the toxic and side effects of drugs and improve the bioavailability of drugs.

Keywords: Novel drug delivery systems; orally disintegrating tablets; nasal spray; pulsatile drug delivery system; transdermal drug delivery system; sustained parenteral drug delivery system; insoluble drug delivery system; biopharmaceutical delivery system; targeting drug delivery system.

Introduction

The novel drug delivery systems apply multidisciplinary means to deliver the drug to the target site effectively, so as to regulate the pharmacokinetics, pharmacodynamics, toxicity, immunogenicity and biology of the drug. According to the characteristics of the drug, it is divided into three aspects, including immediate release drug delivery system, the long-acting drug delivery system and the efficient drug delivery system. In recent years, with the rapid development of polymer science and modern medicine, pharmacy, biology, and engineering, the concept of intelligent medical care has been proposed and widely recognized by the community, so the development of novel drug delivery system is rather important, which is also the core of pharmaceutical preparations research. Various types of novel drug delivery systems have been developed; this promotes the development of the global medical industry. The research of novel drug delivery systems has also become focused and difficult region. Compared with traditional formulations, the novel drug delivery systems can protect from drug degradation, promote drug penetration through biological barriers and improve its bioavailability, control the release of drugs to maintain a stable plasma concentration, and increase drug concentration in the target area, thereby enhancing the therapeutic effect, reducing the systemic distribution of drugs and adverse reactions. The novel drug delivery systems have great significance in promoting the development and improvement of new drugs. There are so many researches that people can customize and design drugs based on therapeutic effects, including small molecules and biological drugs, but few new drugs are applied in clinical practice. The main reason is that a lot of the latest small molecule chemical entities, so they have the features of poor solubility or poor membrane permeability, leading to low bioavailability. Biological drugs such as proteins, peptides and nucleic acids have poor stability in vitro and in vivo, other influencing factors such as safety, scalability, preparation costs all increase the prepared difficulty. Therefore, the development of novel drug delivery systems has a promising field in the future.

Immediate release drug delivery system

In this paper, orally disintegrating tablets and nasal spray are discussed as follows:

Orally disintegrating tablets (ODTs)

ODTs are new solid single-unit oral dosage forms that can disintegrate or dissolve in the saliva and then be swallowed without the aid of additional water. The disintegration time should be sufficiently rapid so that the patients feel the need or compulsion to chew, and complete the medication process only need a few swallowing action, thus compared with the conventional formulation, ODT have many benefits, on the one hand, it will enhance patient compliance and acceptance related to both feasibility and convenience of dosage administration , on the another hand, it not only has a high bioavailability and a faster effect , but also can reduce the intestinal residue which reduce adverse reactions and avoid the first pass effect. Compared with conventional tablets, orally disintegrating tablets can increase the contact time between the drug substance and the oral mucosal tissue, in addition, the absorption of the local mucosal mucosa tissue and the preganglionic region will also increased. Oromucosal and pregastric absorption can potentially produce a rapid response, partial avoidance of first-pass effects and gastrointestinal irritation . The orally disintegrating tablets are mainly

suitable for the following situation:

(1) Medication for pediatric and geriatric populations who have difficulty swallowing large tablets and people who are not convenient to take water in the field.

(2) The first-aid drugs which can be absorbed by oromucosal tissues or drugs to be promptly effective, such as nitroglycerin, nifedipine, salbutamol sulfate, etc;

(3) Medication for patients who have difficulty in swallowing, including patients who are bedridden, mentally retarded, nauseous, and those suffering from nervous or anatomical disorders of the larynx or esophagus, or patients on reduced liquid intake diets also cannot swallow conventional tablets.

(4) Medication for patients who are uncooperative or not active, such as antidepressants rizatriptan benzoate and zolmitriptan etc;

(5)The drugs which are supposed to prolong the contact times between the drug substance and oromucosal tissues or reduce gastrointestinal irritation, such as aspirin, ibuprofen and so on.

Technologies for manufacturing orally disintegrating tablets include the freeze-drying method , solid solution technology , spray drying process and powder direct compression method . Meantime, To meet these requirements, researchers have developed a variety of patent technologies, such as Orasolv®, Durasolv®, Wowtab®, Flashtab®, Zydis®, Flashdose®, Oraquick®, Lyoc®, Advatab®, Frosta®, Quick-Disc® and Nanomelt® etc. Nowadays, the orally disintegrating tablets of the market surge in the recent years, it opened up a new dosage form for the emergency treatment, especially for the drugs which are unstable or irritating to the gastrointestinal tract. At present, high blood pressure, vomiting, pain, epilepsy and other treatment all can choose the rapid onset of oral disintegration tablets. There are some examples of products listed in (Table1).

Table 1: Clinical available orally disintegrating tablets

Active drug	Indication	Company	Time-to-market
Oratatine	Allergic rhinitis	Schering-plough	1993
Piroxicam	Rheumatoid arthritis	Pfizer Inc.	1993
Famotidine	Enterelcosis,gastrohelcosis	Merck	1998
Rizatriptan Monobenzoate	Migraine	Merck	1998
Ondansetron	Chemotherapy and radiotherapy caused Nausea and vomiting	Glaxo Wellcome	2000
Olanzapine	Schizophrenia,bipolar depression	Lilly	2000
Rofen	Pain, Fever, Inflammation	Reckitt Benckiser	-
Carbidopa/levodopa	Parkinson's disease	Schwarz Pharma	2002
Clonazepam	Epilepsy	Solvay Pharmaceutical	2003
Baclofen	Muscle relaxant, Antispastic	Schwarz Pharma Inc.	2003
Mirtazapine	Major depressive disorder	Merck & Co.	2003
Risperidone	Bipolar disorder	Janssen Pharma	2003
Clozapine	Treatment-resistant schizophrenia	AzurPharma	2004
Selegiline	Adjunct therapy in parkinson's disease	Valeant Pharmaceuticals	2005
Loperamide hydrochloride	Diarrhea	Janssen	2008
Enalapril maleate	Hypertension	Qingdao Guohai	2013
Nimesulide	Chronic arthritis	NCPC	2013
Glimepiride	Diabetes	Wuhan Weihao	2013
Nisoldipine	Primary hypertension	Jiangxi Herbisky	2014
Nisoldipine	Bronchial asthma	Chongqing Conquer	2015

Nasal spray

Nasal spray is one of the forms of nasal drug delivery and mainly refers to play a systemic treatment through the nasal mucosa absorption. Nasal spray is usually divided into solutions, suspensions and emulsions, which is composed of active ingredients and excipients including osmotic pressure regulator, suspending agent, viscosity modifier and preservatives, etc. Nasal drug delivery has been widely concerned as a promising technique. The nasal route improves patient compliance Compared with parenteral routes, making self-medication possible. The nasal cavity has a relatively large absorption surface area and the high vascularity of the nasal mucosa make sure that absorbed compounds are distributed promptly. Drugs can be absorbed into blood vessels directly into the systemic circulation, circumventing gastrointestinal first pass metabolism . It can offer lower doses, more rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity, low side effects, and the capacity of delivering directly to the brain , the avoidance of sterilization in nasal preparations and thus save costs. The current requirements for nasal drug delivery include three key elements: reliability, safety and effectiveness. In view of the rapid onset of nasal spray advantage, the

US FDA approved the Naloxone nasal spray for the treatment of opioid poisoning on 18 November 2015 through a fast-track channel, making it the world's first non-injection of naloxone preparations. Nasal spray injection is often used to treat rhinitis or allergy related indications and other local symptoms as a new non-injection method. There are many marketed nasal products for topical delivery (Table 2). In recent years, the nasal route is an attractive alternative way to invasive administration, which provides a direct access to the systemic circulation.

Nowadays, the nasal administration of systemic effects has been widely concerned (Table 3). Nasal spray has become the main route of biological drugs. The peptide oxytocin was the first peptide hormones administered nasally. Whereas, there are many factors that limit the absorption of peptide and protein drugs from nasal mucosa for systemic delivery, so that only a few peptide and protein preparations are commercially available.

A number of physiological barriers are presented in human's nose for peptide and protein drug absorption, which mainly include the physical exclusion from the site of deposition in the nasal cavity by the mucociliary clearance, enzymatic degradation and the low permeability of the nasal epithelium. So the understanding of the structure, composition and function of the nasal cavity can help us to find a better solution. Meantime, the use of the absorption enhancer contributes to the significant absorption of the peptide and protein drugs . In addition, the development of nasal drug delivery devices is also crucial, which can meet the various requirements of the customer. Nasal drug delivery devices can be divided into multidose and unit-dose/bi-dose systems currently. And employing these single/dual-use disposable systems makes therapies precise. It has a large number of more mature patented products, for example, researchers at the University of Oslo in Norway have developed a single-dose capsule-type nasal spray device (Opti Nose) that improves the drawbacks of traditional liquid multi-dose sprays. Kurve also designed a nasal drug delivery device called Via Nase, which was assembled by a nasal nebulizer and a spray bottle through a compact electronic spray. Compared with conventional spray bottles and inhalers, it is more comfortable and more effective . The application by nanosized carriers has attracted a lot of people's attention in recent years, because it have many advantages, such as good stability, protection from degradation, as well as the release of the ability to control the therapeutic agent.

Table 2: Marketed nasal products for topical delivery

Product name	Drug	Indication
Allergocrom, Vividrin	Cromolyn sodium	Allergic rhinitis
Astelin , Allergodil	Statins	Allergic rhinitis
Bactroban	Mupirocin	Eradication of nasal staphylococci
Beconase,Vancenase	Beclomethasone dipropionate	Management of seasonal and perennial (allergic) rhinitis
Decadron	Dexamethasone	Treatment of inflammatory nasal conditions or nasal polyposis
Flixonase	Fluticasone propionate	Management of seasonal and perennial (allergic) rhinitis
Nasacort	Triamcinolone acetonide	Management of seasonal and perennial (allergic) rhinitis
Nasalcrom	Sodium cromoglicate	Treatment of symptoms of seasonal and perennial rhinitis
Nasivin	Oxazolines	Temporary relief of nasal congestion
Bisolnasal	Tramazoline	Decongestion
Nasonex	Mometasone furoate	Management of seasonal and perennial (allergic) rhinitis
Patanase	Olapatadine	Treatment of symptoms of seasonal and perennial rhinitis
Beconase	Topical steroids	Allergic rhinitis
Rhinocort	Budesonide	Management of seasonal and perennial (allergic) rhinitis
Sinex	Phenylephrine	Temporary relief of nasal congestion
Syntaris	Flunisolide	Management of seasonal and perennial (allergic) rhinitis
Flixonase	Fluticasone pripionate	CRS with Nasal polyps

Table 3: Marketed nasal products for systemic delivery

Product name	Drug	Indication
Aerodiol	Estradiol	Management of menopause symptoms
Atronase	Ipratropium bromide	Treatment of bronchospasm
Instany	Fentanyl	Pain management
Miacalcic	Calcitonin	Osteoporosis
Migranal	Dihydroergotamine mesylate	Management of migraine
Vapodrops	Menthol	Rhinitis ,common cold
Stadol NS	Butorphanol tartrate	Migraine
Minrin,Octostim	Desmopressin acetate	Nocturnal enuresis, Management of diabetes insipidus, hemophilia
Suprecur, Profact , Suprefact	Buserelin (acetate)	Prostate carcinoma, endometriosis
Synarel	Nafarelin acetate	Treatment of central precocious puberty
Syntocinon	Oxytocin	Promote lactation
Imitrex Nasal Spray	Triptans	Polypmigraine&cluster headache
Nascobal	Cyanocobalamine	Vit-B12 deficiency

Long-acting drug delivery system

Pulsatile drug delivery system（PDDS)

Many of the physiological functions of the body present biological rhythm changes, such as blood pressure, gastric acid secretion, secretion of certain hormones, etc. Many diseases also present significant rhythmical and cyclical, for instance, asthma is easy to attack in the middle of the night and angina is easy to attack in the morning. The resolution of these problems needs a time-programmed treatment regimen where the drug is at the desired site at the desired time. And it can be achieved with the pulsed drug delivery system. The design of pulsatile drug delivery system is based on the principle of pharmacology and the pharmacokinetic principle of time, the entire dose is to achieve a rapid release after the lag time. The system is required to release the drug at a single or multiple times at a predetermined time to provide an effective plasma concentration and achieve the best therapeutic effect, not to maintain a stable plasma concentration. Such systems offer numerous advantages over traditional methods of drug delivery, it can not only provide regular quantitative release to meet the needs of the patient's treatment, which can reduce the administration times and increase patient compliance. It can also prevent the onset of the disease, reduce the adverse reactions of drugs and the risk of drug resistance. In addition, the occurrence of first pass effect can be avoided when drug pulse release in the colon or small intestine. Therefore, pulsatile drug delivery system has a positive effect in clinical. Pulsed drug delivery systems mainly rely on two mechanisms, one of which is stimulated by external factors, including biochemical signal stimulation (blood glucose levels, enzymes, etc.) and physical signal stimulation (magnetic field, electric field, ultrasound, light excitation, temperature, etc.) Drug release is triggered by an external signal applied after the capsule reaches the desired position within the alimentary tract. For example, a high frequency capsule is a drug system that releases the drug in a pulsed fashion after a high-frequency signal is applied externally to the human body . The other is triggered by the preparation itself, which releases the drug automatically and sequentially with a predetermined step. According to the mechanism of drug release, the pulsed drug delivery system can also be divided as follows: pulse release system formed by system dissolution, pulse release system formed by expansion pressure, and pulse release system formed by the above two .

The factors that affect the success of pulse-release preparations include a lag time, release degree and in vitro and in vivo correlation, the influence factors are different in various drug delivery systems, but the improvement and research of new pulse administration are based on the above three aspects, in which the lag time is the most important control index, such as pulse plug control system for the release, the lag time prior to the drug release can be controlled. If you want to extend the lag time, you can push the hydrogel into the capsule, or increase the volume of hydrogel plug. In recent years, the heterotypic pulsed plugging system has been able to achieve the effect of pulsed controlled release of the two-phase release and the double-pulsed multi-phase release, respectively. At the same time, to assure a rapid release, it is possible to add effervescent, disintegrating in the pharmaceutical preparation, especially for water-insoluble drugs, it can increase the solubility and produce sufficient energy to promote the rupture of membrane . At present, the pulse release agent covers oral (such as coated tablets, capsules, pellets), injection (such as injection of microsphere formulations), topical (such as transdermal patch) and other fields. They are widely used to meet some of the circadian rhythm disease treatment in the asthma drugs, cardiovascular drugs, receptor antagonists and insulin and other drugs. For instance, in the antiarrhythmic and hypertension treatment, the FDA approved the first time-selective preparation of verapamil osmotic pump tablets which have a good pulse drug release, there are pulsed controlled tablets and pellets for anti-asthma drugs, the pulsed system of methylphenidate can also be used to treat with attention deficit hyperactivity disorder in school-age children .

Transdermal drug delivery system (TDDS)

TDDS refers to a formulation that the drug transports to local tissue or systemic circulation through skin route then leads to local or systemic treatment. Among the advantages of TDDSs are as follows:(1)They can avoid the difficulties of gastrointestinal drug absorption, which are caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs. (2)They can substitute for oral administration of medication when that route is unsuitable, such as vomiting and diarrhea. (3)They can avoid the first-pass effect, possibly avoiding the deactivation by digestive and liver enzymes. (4)They are noninvasive, avoiding the inconvenience of parenteral therapy. Also, compared with other mucosal routes, the skin is in low proteolytic activity, thereby reducing degradation at the site of administration. Once absorbed, the hepatic circulation has not been passed, thus avoiding another major site of potential degradation. (5)They provide extended therapy with a single application, which improves compliance over other dosage forms requiring more frequent administration. (6)Drug therapy may be terminated rapidly when the application is removed from the surface of the skin.(7)Because topical or transdermal delivery leads to drug accumulation in the skin, which is several times higher than that ever achieved in the skin through systemic administration of that drug, the tissue concentration is raised above the response threshold . In order to improve the percutaneous absorption, addition of penetration enhancers, ultrasonic method, iontophoresis method, electroporation method, laser penetration method, electroosmosis method and other physical penetration method as well as liquid jet technology, powder injection technology and microneedle technology are used, in which addition of penetration enhancers is the most commonly used method. Commonly used enhancers include solvents, such as ethanol, butanol, propylene glycol, polyethylene glycol, dimethylsulfoxide, dimethylformamide (DMF), dimethylacetamide (DMA) fatty acids and fatty alcohols (such as oils Acid), as well as nonionic surfactants (such as lauricillin ketones and pyrrolidone derivatives), fatty acid compounds, volatile oils (such as mint, menthol, peppermint, borneol), surfactants (such as Pluronic, sodium dodecyl sulfate and Tween-80) and so on. Recently some penetration enhancement techniques, such as iontophoresis, are becoming possible, which are likely to make transdermal delivery a promising approach for delivering peptide, protein and other biotechnology-derived drugs . Other promising enhancement of techniques include the use of ultrasound energy (phonophoresis) and generation of microscopic holes (micropores) through microneedles or other thermal methods . Conventional transdermal dosage forms include topical ointments, plaster, as well as pastes, etc. At present, novel transdermal preparations include gels, emulsions, microemulsions, liposomes. The first transdermal system, Transderm Scop, was approved by the Food and Drug Administration (FDA) in 1979 for prevention of nausea and vomiting associated with travel. Transdermal delivery has become very popular and several more products have been introduced to the market such as capsaicin, clonidine, buprenorphine, rivastigmine, estradiol, fentanyl, methylphenidate, granisetron, rotigotine, nicotine, selegiline, scopolamine, nitroglycerin, oxybutynin and so on [37-39] .

Sustained parenteral drug delivery

Sustained parenteral drug delivery (including long acting injections and implants) offer a number of advantages. First, it can extend duration of action. Repeated administration can result in the classic “peak and valley” pattern wherein peak plasma concentration can exceed the toxic threshold producing undesirable side effects or valley plasma concentration can fall below the minimum threshold for efficacy. Long acting injection can result in steady plasma levels that resulting in prolonged therapeutic efficacy without unwanted side

effects.

Such drug delivery system has a significant advantage, embodied in reducing frequency of administration, total dose of drug and side-effects, thus providing a more efficient utilization of drug and improving patient compliance. Drugs are combined with the vehicle of the system in the form of solid, which can increase the stability of the drug storage and application. A great interest from domestic and foreign researchers and pharmaceutical companies was aroused by its technical advantages and clinical value. With the development of a variety of drug delivery technology, there are a variety of long-acting injection products already listed. The earliest long-acting injection administration system was a depot long-acting injection that controls the rate of drug diffusion through the substrate by using an oil solution or adjusting the aqueous matrix to achieve the purpose of slow release. It is water-based gel, oily solution or oily suspension solution. And the release rate will be affected by the injection site, injection volume and the degree of dispersion after injection and other factors. For example, Depo Medrol developed by Pfizer Pharmaceuticals, is a glucocorticoid used as an anti-inflammatory and immuno suppressive agents to treat a range of indications. Its half-life is increased to 12 ～ 17 h and the patient was administrated only once every 1 to 2 weeks, such feature greatly reduces the interference of the patient's life and the risk of frequent injections. In addition, the insoluble salt technology also controls the diffusion rate, which makes the water-soluble drug form insoluble salt to control the release of the drug and extend the drug action time effectively. Although this is a simple method, it has the following disadvantages: less saltable species, poor targeting, more adverse reactions, making it not widely be used. At present, pamoate is widely studied in the insoluble salt technology, Zyprexa Relprev is a dry powder of olanzapine pamoate monohydrate, marketed by Eli Lilly Pharmaceuticals . Olanzapine is an effective phenothiazide antipsychotic drugs with a half-life of 21 to 54 h, and the frequency of administration is reduced from qd to administration once every 2 weeks or 4 weeks . The pethionine salts being studied are: aripiprazole and haloperidol dihydroxynaphthalate, risperidone dihydroxaproate, peptidic acid, etc. Long-acting injections, such as injectable implants and microsphere formulations, are released in the form of a preparation skeleton in vivo, the release of which is controlled not only by diffusion but also by the dissolution of the biodegradable material. The skeleton material of the injectable implants is made from biodegradable polymers, which can be injected directly and have no surgical implantation and removal to improve the shortcomings of low compliance with medication. For instance, Goserelin injectable long-acting implants (Zoladex ®) developed by Astra Zeneca, was prepared by peptide drug goserelin and PLGA (50: 50), whose PLGA matrix can be gradually degraded in the body to achieve the effect of slow release of drugs. In recent years, long-acting microspheres injection has become one of the hot spots in the research of novel drug delivery systems for peptide protein drugs, it is an injectable suspensions which adopts biodegradable polymer as a skeleton material as well, and the drug is embedded in a solid with a diameter of only a few tens of micrometers by using microcapsule technology. triptorelin microspheres Decapeptyl®, which can be released for one month for the treatment of prostate cancer. The first long-acting atypical antipsychotic drug Risperidal Consta was developed by Alkermes and Johnson using Medisorb technology . It encapsulates the drug in a suspension made of PLGA (75:25) microspheres, the administration frequency of risperidone was reduced to once every 2 weeks. Exenatide microspheres injection (Bydureon ®) was approved by the European Union in 2011, is the first depot injections for the treatment of type 2 diabetes.. Prolonging the half-life is an effective means to achieve long-acting efficacy of the drug. Prodrug technology and PEG technology are common chemical modification methods. To avoid peptide protein drug burst release due to large water solubility, weakly hydrophilic prodrugs were often prepared. In addition, PEG technology were often used in order to solve the problem that the short half-life of the polypeptide and the protein in the body. Depo Foam is a multi-capsule liposome drug delivery system, which is a new type of liposome technology. The outstanding advantage is that this enables act as a drug reservoir in the injection site to release the drug slowly and achieve long-acting effect for a few days or several weeks. Depo Foam liposomes are generally prepared by the method of complex emulsion. At present, the Depo Foam drug delivery system has three products listed: Depocyt, DepoDurTM and Exparel. Because injectable implants and microspheres injection are inconvenient, people began to develop in situ gel injection system. In situ gel is a solution in which the phase transition occurs immediately after the administration of the solution in the drug site, and the liquid is solidified to form a semi-solid gel. The research and application have been concentrated in the polymer precipitation and temperature-sensitive type .The polymer precipitation gel is prepared according to the phase separation principle that the polymer is precipitated at the injection site including AtrigelTM technology, Alzamer® Depot technology and SaberTM . The thermosensitive hydrogel will undergo a sol-to-gel reversible phase transformation when the ambient temperature reaches the critical temperature. In contrast to sustained-release injections such as microspheres, liposomes and micelles, thermosensitive in situ gel injection can delay drug release, improve bioavailability, improve patient compliance and suppress the degradation of proteins and peptides. Currently, the available thermo-sensitive gels are Regel® (PEG-PLGA-PEG), BST-Gel® (chitosan-GP) and InGell® Gamma (PCL-PEG-PCL). The following products have been used clinically: Regel®-based thermosensitive gel CytorynTM (main drug: interleukin-2) and Oncogel® (main drug: paclitaxel), and BST-Gel®-based thermosensitive gel Paclige® (Main drug: paclitaxel). In future, its application will be more extensive, especially in protein and peptide drugs.

Insoluble drug delivery system

In the novel drug development process, nearly 40% of the compounds were eliminated due to the poor adaptability of biopharmaceuticals and pharmacokinetics, and the main influencing factors were the solubility and permeability of the drug in water. Many water-insoluble drugs have low oral bioavailability due to its poorly water solubility, or have caused difficulties in the development of formulation into pharmaceutically acceptable vehicles, so there are different strategies involving surfactants, inclusion complex, prodrugs, salt formation and nanoscale drug delivery systems to solve this problem. Cyclodextrins (CDs) and meglumine (MEG) are pharmaceutical excipients that are widely used to improve solubility of poorly water-soluble drugs. The higher proportion of the oil phase, as well as the presence of beta-cyclodextrin (ßCD), methyl ßCD and MEG, favors drug incorporation. At present, Cyclodextrins are used in liposomes, which increases the rate of drug entry into liposomes, thereby expanding the range of liposomal inclusion of water-insoluble drugs; Spray freezing into liquid (SFL) is the drug embedded in the skeleton of the auxiliary materials in the form of molecules.A variety of novel nanoscale drug delivery system have been developed, including micelles, polymer nanoparticles , inorganic nanoparticles, microemulsion, liposomes and nanosuspension. The insoluble drug can be encapsulated in these nanocarriers, both polymeric micelles and nanoparticles are typically stabilized by surface-bound hydrophilic polymers. Polysaccharides, such as chitosan, dextran and heparin can be used as substrates for conjugates, Poly (ethylene glycol) (PEG) used in the form of amphiphilic copolymers is often considered to be the ideal coating for colloidal drug delivery systems.Geneviève Gaucher designed a polyethylene oxide (PEO) binary hydrophilic matrix controlled system using anhydrous drugs as a model drug, PEO was selected as the main polymer added in the hydrophilic matrix system, and the low viscosity hydrophilic material was used as a sustained agent to change the drug release rate.NK105, a new micelle carrier system for paclitaxel, was developed by T Hamaguchi, it is a PTX-incorporating 'core-shell-type'

polymeric micellar nanoparticle formulation and the polymeric micelle carrier of NK105 is composed of a block copolymer of PEG (molecular weight of about 12000) and modified polyaspartate. PEG is believed to form the outer shell of the micelle and hydrophobic modified polyaspartic acid chains are thought to form the hydrophobic inner core of the micelle in aqueous solutions. The study finds that it has the potential to enable the sustained release of the drug inside a tumour when the micelles accumulate in the tumor tissue. Liu et al. have developed a new type of hydrophobic photosensitizers for nano drugs, associated with the coordination-triggered ultrafast interfacial assembly around nanocores of hydrophobic PSs. Because of the coordination polymerization of tannic acid (TA) and ferric (Fe (III)), the hydrophobic Ce6 nanoparticles are stably present in the aqueous medium through the interface assembly film. It is a nanoscale drug delivery system with high loading content of over 65%, and has been demonstrated that it has selective accumulation and can prolong blood circulation time in tumor tissue, leading to an enhanced antitumor PDT. Another example is a selective drug-delivery system based on folate-functionalized silica nanoparticles which is believed to be a promising candidate for targeting water-insoluble drug delivery. Cellax™ is a polymer-based nanoparticle drug delivery system designed to solubilize hydrophobic drugs and target them to solid tumors, thereby enhancing the efficacy and reducing the side effects . Whereas, it is challenging to enlarge the manufacture of polymeric conjugates and nanoparticles. At present, The Cellax™ platform has been exemplified with DTX, PPT, and CBZ . The Cellax –DTX will be very effective for subsequent dose chemotherapy in targeting tumor epithelial cells, as it can deplete tumor stroma and reduce tumor collagen, leading to increased tumor perfusion. When the Cellax™ platform was then employed to deliver PPT, it has significant potential to enable this PPT-based innovative therapy for MDR tumors, intending to provide enhanced therapy for MDR tumors. The latest example generated with the Cellax™ platform is Cellax-cabazitaxel (CBZ), which may be effective against taxane-resistant solid tumors. Cellax™ is alsopossible that this technology can be employed to deliver multiple drugs for synergistic effect.

Nanocrystalline drugs mainly are divided into small to large (bottom-up) and from top to bottom (top-down) by controlling the crystallization . Bottom-up technology is a mean of adding the poor solvent of drugs in the drug solution, rendering the rapid formation of a large number of drugs nuclei and smaller nano-crystalline, and Top-down technology can smash larger drug particles into smaller particles, including wet milling, high pressure homogenization and micro jet. Solid lipid nanoparticles(SLN) have recently been suggested as an alternative drug delivery system, which is a new colloidal drug delivery system that can replace emulsions, liposomes and polymer nanoparticles. SLN combines the advantages of polymer nanoparticles and fat emulsions. The advantages are: It contains available and biodegradable solid fat components; it is less toxic compared with the polymer nanoparticles; there is no drug leakage in the storage process as the drug is encapsulated in the skeleton of solid lipid particles; it can achieve the purpose of slow release, controlled release and targeting, while avoiding the shortcomings that organic solvent can not be removed completely. Because of this advantage, SLN have come to social notice, whose emergences have led to development of carriers for water-insoluble drugs. Nano-suspension is a new formulation technology developed at the end of the 20th century without carrier material. It can disperse nano-scale drug particles in water to form a stable system through the stabilization of surfactants. It has considerable significance in enhancing the bioavailability and effectiveness of insoluble drugs. Self-emulsifying drug delivery system (SEDDS) has become a promising approach in improving solubility, absorption and bioavailability for poorly soluble drugs. It has been shown that SEDDS is suitable for lipophilic drugs, where resulting emulsions produce faster dissolution rates and absorption, and SEDDS can be an efficient vehicle for class II to Class IV molecules of biopharmaceutical classification system drugs. There are many clinical available nanocrystals listed. (Table 4).

Table 4: Clinically available nanocrystals

Trade name	Active drug	Indication	Company
Emend	Aprepitant	Antiemetics	Merck
Zanaflex	Tizanidine	Spasticity	Acorda
Rapamune	Sirolimus	Immunosuppression	Pfizer
Skelaxin	Metaxalone	Skeletal muscle conditions	King Pharm
Zyprexa	Olanzapine	Schizophrenia or manic depression	Lilly
TriCor	Fenofibrate	Hypercholesterolemia	Abbott Laboratories
Theodur	Theophylline	Respiratory disease	Mitsubishi Tanabe Pharma
Megace ES	Megestrol	Antianorexia, cachexia	Par Phamaceutical Inc
Triglide	Fenofibrate	Hypercholesterolemia	First Horizon Pharmaceutical
Gris-PEG	Griseofulvin	Mycotic infection	Novartis
Naprelan	Naproxen	Pain or inflammation	Wyeth
Cesamet	Nabilone	Chemotherapy caused nausea and vomitting	Lilly

Biopharmaceutical delivery system

A biological drug is defined as an agent intended for use in the diagnosis and treatment of disease, which involves the entire organism or an organisma primary and secondary metabolite, including amino acids and their derivatives, polypeptides and protein drugs, enzymes and coenzyme drugs, nucleic acids and their degradation products and derivatives drugs, carbohydrates drugs, lipids, cell growth factors, biological products and so on.. Mostly they are used for the treatment of cancer, AIDS, cardiovascular and cerebrovascular diseases, neurodegenerative diseases and other serious diseases, which has some pharmacological characteristics of the targeted treatment, high pharmacological activity, low side effects, high nutritional value and so on. Biological drugs play an extremely important role in the treatment of major diseases, in 1992, the United States approved 4446 biotech patents, 2094 of which were pharmaceutical patents. In order to allow the drug to be delivered to the target site effectively, Drug Delivery System (DDS) uses a multidisciplinary approach to regulate the pharmacokinetics, efficacy, toxicity, immunogenicity and biometrics of drugs, so that the biological drug can maintain activity and deliver itself to the target cells, target organelles efficiently to play the drug role.

Biopharmaceutical delivery can be divided into two aspects: peptide

and protein drugs gene drugs. Polypeptides and protein drugs have a certain three-dimensional structure, such structure will lead to changes in protein stability and decreased activity; at the same time, the high dose will lead to adverse reactions, such as immune response. Therefore, to maintain the stability and activity of peptide protein drugs is the main research direction of this type of drug delivery system. At present, the delivery systems of polypeptides and protein drugs are: liposomes, nanoparticles, microspheres, microgels, microcapsules and the like, which can achieve a variety of routes of administration. Liposomes are microscopic vesicles composed of lipidmembranes surrounding discrete aqueous compartments , which has some characteristics such as non-toxic, non-immunogenic, targeting and better containing ability of water-soluble drugs and insoluble drugs, and it mainly used in anti-tumor, anti-infection and other fields. Functional therapeutic proteins are deliveried into targeted living cells by lipid vesicles, which is one of the most promising strategies for treatment of different diseases and cancer . Microsphere particle size is generally 1-250 μm, it can be used for oral, intramuscular injection, subcutaneous injection, mucosal administration and so on. For example, Patel and his partner use diffusion and adsorption method with gelatin microspheres wrapped bone morphology to generate protein BMP-2,the study turned out that the gelatin microspheres with particle size of 10 and 14μm were the least, and the drug was released for 28 days. Microgel is a kind of polymer microspheres with molecular size between 50 ～ 5000nm, the cross-linked structure consists of an interaction between physical and chemical interactions or covalent bonds, therefore, changing the conditions in vivo or in vitro can control the drug release, so sensitive microgels is the current research focus. For example, Wong et al prepared a temperature and magnetic dual sensitive material Fe-PNIPAM, N-isopropylacrylamide (PNIPAM) is a temperature-sensitive material that is locally heated by oscillating the magnetic field. When the temperature rises, the gel shrinks and breaks the drug. Liposomes and particles are not easy to pass through the endothelium or blood-cerebrospinal fluid barrier, while the nano-delivery system has a smaller particle size that can pass through the barrier to reach the target site. Nanoparticle technology is an emerging way to resolve difficult-to-manage internal diseases. Particularly, because of the congenital ability of certain nanoparticles to accumulate in the porous environment of the tumor and to be toxic to cancer cells, it is highly regarded for medical use in treatment of cancer. However, the therapeutic success of nanoparticles is limited by the technical difficulty of completely penetrating and thus attacking the tumor. In addition, while nanoparticles possess seeming-specificity due to the unique physiological characteristics of tumors themselves, it is difficult to tailor the delivery of nanoparticles or drugs in other models, such as usage in cardiac disease, to the specific target . Neurotoxin (NT-I) is limited in brain targeting applications due to low permeability. Cheng et al used polylactic acid PLA as carrier, and prepared the NT-I PLA nanoparticles by two-emulsion solvent evaporation method, the drug loading was 35% and the diameter was 65 nm. NT-I PLA nanoparticles can significantly increase the concentration of NT-I in the brain, and provide a new direction for the application of central nervous system drugs. Gene therapy refers to the method that it transfers some genetic material to the patient's body, express it in the body, and ultimately achieve the purpose of treating a disease. It is needed to deliver the nucleic acid to a specific portion of the cell. Currently, a viral vector or a non-viral vector is used to deliver a gene drug to a target site. Viral vectors are commonly used including retrovirus (RV), lentivirus, adenovirus (AV), adeno-associated virus (AAVs) and herpes simplex virus (HSV-1), these five viral vectors account for more than 50% of human gene therapy. Compared with the viral vector, non-viral vector is safe, non-toxic and easy to prepare, it will have more application prospects. The non-viral vectors are commonly used including cationic polymer carriers, inorganic carriers and their complex carriers, biological carriers, and ultrasound-sensitive carriers. Representative nucleic acid drug delivery systems include Arrowhead Research's dynamic polyconjugates (DPC) , transferrin-targeted cyclodextrin nanoparticle delivery systems (RONDELTM) , Silan's si RNA delivery system based on Lipids (Atu PLEXTM) , Tekinira's lipid nanoparticle (LNP) technique , Alnylam Pharmaceuticals' GalNAc-si RNA (a combination of N-acetylgalactosamine and si RNA) liver targeting delivery system and the like. Ultrasound microbubbles (UTMD) is a novel gene drug delivery system, in which ultrasound will increase the permeability of the cell membrane, microbubbles are taken into the cell through this effect and release the target gene. Ultrasound targeted microbubble destruction (UTMD) has evolved as a new system for non-invasive, organ- and tissue-specific drug and gene delivery. A great deal of principle studies have been demonstrated to demonstrate the wide potential of UTMD as a site-specific, non-invasive therapeutic tool, delivering microbubble payload to a variety of target tissues and organ systems or facilitating uptake of bioactive substances into tissues or cells. This review focuses on current in vivo research and therapeutic ways of UTMD.

Targeting drug delivery system

The targeting drug delivery system (TDDS) allows the drug to concentrate in the lesion tissue, reduce the drug concentration of the non-lesion tissue, improve the ability of the drug to pass through the tissue barrier and trans-cell membrane transport, and even increase the drug distribution in the specific organs, thus enhance the effect of drug treatment, reduce the toxicity and adverse reactions . As a drug carrier, nanoparticle has the characteristics of small particle size, large specific surface area and good adhesion performance. It is easy to enter the target tissue through the vessel wall, increase the contact time and area between the drug and the tumor. In general, targeting drug delivery systems involves passive targeting, and active targeting. Passive targeting refers to the preferential accumulation of nanoparticles at tumor site in the absence of targeting receptors, depending on the physiological and pathological characteristics of the target site and the nature of the drug delivery system itself. Active targeting is a method that enhances the preferential accumulation of nanoparticles at the tumor site by surface modification. Due to the low requirement of the passive targeting strategy for drug delivery systems, it has been studied and developed extensively. The accumulation efficiency of the target nanoparticles in the tumor site depends solely on the physicochemical properties of the nanoparticles, such as size, shape, surface charge, etc. This type of preparation is a natural tendency for drug-loaded particles to be phagocytosed by macrophages when introduced into the body, resulting in the distribution characteristics in vivo, where the main forms are liposomes, microspheres, nanocapsules and nanospheres. Although it does not have the function of actively identifying specific sites, it can be achieved by designing functionalized nanomaterials to respond to tumor microenvironment or directly regulate tumor microenvironment, so as to achieve better targeting delivery effect.

Basing on the different targeting cells, the active targeting strategies can be divided into the following categories: Tumor cells targeting. Selective killing of tumor cells becomes the primary choice of cancer treatment. Due to rapid growth, a variety of receptor expression such as transferrin receptor, folate receptor, low density lipoprotein receptor and glucose transporter on tumor cells' surface was significantly higher than those of normal cells, thus the corresponding ligands are often used as targeted molecules for tumor cell delivery.

Active targeting involves functionalizing the surface of nanoparticles by ligands which have specific affinity to the receptors that are over-expressed on the cancer cells, it is considered to be a supplemental strategy to EPR effect to increase the efficiency of cancer therapy . For example, ATNH remarkable inhibited cancer cell growth through delivering more HK into HNE-1 cells via folate-mediated endocytosis . Interleukin-13 receptor subtype 2 (IL-13Rα2) is highly expressed in

brain tumor cells, and the specific ligand IL-13p of IL-13Rα2 is modified on the surface of nanoparticles for targeted delivery of docetaxel, indicating that IL-13p modified nanoparticles were significantly superior to unmodified nanoparticles in the selectivity of brain tumor cells . Tumor stem cells targeting. It is generally believed that there are only 0.01% to 1% of tumor stem cells in tumor cells, but the tumor stem cells have greater tolerance for chemotherapy, radiotherapy and other anti-tumor therapy may lead to tumor stem cell enrichment, rapid proliferation or metastasis. Therefore, targeted delivering anti-tumor drugs to tumor stem cells will assist in improving the anti-tumor effect and the prognosis as well as reduce tumor recurrence and metastasis. Wang et al. used anti-CD133 antibody as a target molecule to modify on the surface of carbon nanotubes (anti-CD133-SWNT), to target brain tumor stem cells. The results showed that the drug delivery system could be selectively ingested by CD133 + brain tumor stem cells, and the concentration was significantly higher than that of CD133- tumor cells. After the heat treatment, brain tumors almost disappeared, the treatment effect is far superior to ordinary unmodified carbon nanotubes. Tumor neovascularization targeting. Tumor tissue contains a large number of new blood vessels, which is an important basis and characteristic for maintaining tumor growth. It indirectly destructs tumor tissues by cutting off their supplies of oxygen and nutrients through targeting and killing the endothelial cells of the tumor vessels, so as to achieve the "starved to death" tumor purposes.④ Tumor-associated macrophage targeting. Tumor-associated macrophages (TAM) have low cytotoxicity to tumor cells, and with anti-inflammatory and tissue repair function, it will promote tumor growth, angiogenesis and even metastasis.⑤ Other stromal cell targeting. In addition to the above-mentioned several cells, there are tumor-associated fibroblasts, tumor-associated pericytes, tumor-associated extracellular matrix, tumor-associated lymphocytes and so on. These cells or matrices play an important role in maintaining tumor microenvironment, promoting tumor growth and metastasis, so targeting of these stromal cells can also play an anti-tumor effect. ⑥ A variety of cell targeting. Although targeting a single cell can selectively kill the tumor cells, due to the complexity of the tumor microenvironment, it often produce unexpected adverse reactions. Therefore, targeting multiple tumors simultaneously can treat tumors more efficiently.

For active targeting strategies, although the targeted receptor is highly expressed at the tumor site, it is still expressed to some extent in the normal tissue, so that the targeted delivery system may also be distributed in other tissues, therefore, finding specific receptors and related ligands have become the research goals in this field .

Due to the presence of the blood-brain barrier (BBB), only a small number of drugs may pass through the BBB, and more than 98% of other drugs, especially when genetic drugs and peptide protein drugs are into the brain, it will be subject to varying degrees of obstruction, which affects the treatment of brain disease seriously. At present, it is one of the most effective methods to increase the BBB permeability of drugs (especially polypeptide proteins) through the adsorption-mediated mechanism, which is mainly through the electrostatic effect of BBB membrane on the anion and delivery system on the surface of the positive charge, to induce adsorption-mediated migration of drugs into the brain, such as cationized albumin. Further, the cationic protein-bound nanoparticles or liposomes have the advantages of high drug loading, less positive charge and so on. If it is modified by PEG, it can also extend the plasma half-life. In addition to brain targeting, the focus of targeting drug delivery systems also includes bone marrow targeting administration.

The current targeting strategy is mainly giving the drug-containing system the ability to adjust the environmental response through the design of nanomaterials, or giving it the initiative to target by modification of the surface-targeted molecule. Although these studies have achieved some achievements and have improved drug delivery and anti-tumor effects to some certain extents, but these strategies still have some problems. For the nano-carrier with environmental responsiveness, the specificity and sensitivity of response is an important issue that needs attention. Endogenous environments, such as differences of pH and enzyme, can make the nanosystem in a timely and sustained response, which is advantageous for systemic administration. Exogenous environmental stimuli, such as ultraviolet, ultrasound and other local stimuli, has large intensity, so that the nano-carrier response specificity is better and faster, but this stimulus can only choose a specific time to stimulate intermittently and the duration is short, so that the nano-carrier can not be responsive in the non-stimulating period. ② For active targeting strategies, the specificity and effectiveness of targeted molecules are the focus of attention: On the one hand, although the targeting receptor is highly expressed at the tumor site, it is still expressed in the normal tissue to some extent, so that the targeted delivery system may also be distributed in other tissues, so to search for more specific receptors and related ligands have become the research goals in this field. Some clinically available new targeted drugs are listed as follows (Table 5).

Table 5: Clinically available new targeted drugs

Drug/trade name	Indication	Company	Time-to-market
Axitinib/Inlyta	Advanced renal cell carcinoma	Pfizer	2012
Regorafenib	Anti-VEGF and anti-EGFR treated CRC patients	TargetMol	2012
Crizotinib/xalkori	ALK-positive locally advanced and metastatic NSCLC	Pfizer	2011
Nilotinib/Tasigna	Newly diagnosed CML patients with chronic phase	Novartis	2010
Dasatinib/Sprycel	CML of Philadelphia chromosome PH + with resistant to imatinib mesylate or intolerance	Bristol-Myers Squibb	2010
Everolimus/Afinitor	Patients with advanced renal cell carcinoma	Novartis	2012
Pertuzumab/Perjeta	Targeted therapy for HER2 in tumors	Roche	2012
Brentuximab vedotin/Adcetris	HL and ALCL	Takeda	2012
Lpilimumab/Yervoy	Malignant melanoma	Bristol-Myers Squibb	2011
Lbritumomab tiuxetan/Zevalin	Follicular lymphoma	IDEC	2002
Ziv-aflibercept/Zaltrap	mCRC	Regeneron	2012
Tositumomab/Bexxar	NHL patients	GSK	2005
Sipuleucel T/Provenge	Prostate cancer	Dendreon	2010
Denosumab/Xgeva	Prevent serious bone problems	Amgen	2010
Nintedanib(BIBF1120)/Apexbio	Various solid tumor patients	Apexbio	2013
Carfizomib/Kyprolis	Multiple myeloma patients	Onyx	2012
Neratinib	HER-2 positive breast cancer and EGFR mutations in NSCLCs	Puma	2016
Ramucirumab/ Cyramza	Stomach cancer	Lilly	2014

Conclusion

At present, novel DDS improve the administration and efficacy of drugs. Research in drug delivery now has focused on exploring additional routes of administration including pulmonary, transdermal and nasal routes. Many novel DDS that make use of these routes are beginning to enter clinical trials and some have already commercially available. This review highlights some of the successful technologies that have made this transition. Seven categories of DDS including, immediate release drug delivery system, pulsatile drug delivery system, transdermal delivery system, sustained parenteral drug delivery system, insoluble drug delivery system, biopharmaceutical delivery system and targeting drug delivery system are highlighted. The article discusses their advantages and limitations in the clinic, and current clinical and commercial status of new products in the field.

Today, the research and application of novel drug delivery systems play an increasingly important role in the field of innovative drugs. Studying the intelligent delivery technology and new functional materials can improve the efficacy of drugs, reduce adverse effects and further improve the application value of novel drug delivery system.

Conflicts of Interest

The authors confirm that this article content has no conflict of interest.

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