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Review

A review of drug release mechanisms from nanocarrier systems

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ABSTRACT

The most common methods used for drug administrations are pills, injections, lotions and suppositories. The preferred means is oral dosage forms as it is simple, painless and self-administered. However, the drugs are usually degraded within gastrointestinal tract or not absorbed in sufficient quality to be effective. Over the years, a variety of other administration means have evolved to show specific advantages for particular agents and certain diseases. In this review, various nano-delivery systems consisting of different covalent linkages to conjugate the therapeutic molecules as well as those that carry the unmodified drug molecules by encapsulating or complexation are summarized, including ester, amide/peptide, disulfide, hydrazone, hypoxia-activated and self-immolative linkages. The mechanisms for controlled drug release are also discussed. In addition, the new mechanism of the recently developed photochemistry or thermolysis to trigger controlled drug release and the applications are also covered.

Contents

1. Introduction

More than four thousand years ago, Egyptian physicians started using drugs in the form of pills, ointments and salves as treatments for illnesses. The first intravenous injection was done in human in 1665 and subcutaneous injections were introduced in 1853 [1]. Subsequently, the modern hypodermic syringe was developed in 1884. The current means of drug administration still have close resemblance with these ancient methods and undergo little change throughout the years. Some of these administration means developed over the years have specific advantages for particular agents or certain diseases [2]. Table 1

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shows a brief summary of the common routes of drug administration [3].

Research and developments in creating new and innovative drug delivery systems are increasing at a fast pace globally due to the increasing demands in low cost and higher efficiency for better therapies [4]. To meet this demand, many well-known and effective applied drugs will be reformulated in new drug delivery system to provide enhanced efficiency or more beneficial therapy. One of the most promising drug delivery systems is nanotherapeutic delivery system [5]. It is a drug delivery concept in nanoscience and it is often refers to as an strategy that develops platforms and nanoscales devices for selective delivery of therapeutic genes as well as small drug molecules to the cells of interest [6]. In this paper, the release mechanisms of the drug in nanotherapeutic delivery systems will be covered based on the linker types for the various drugs that are conjugated to nanocarriers. A discussion on how the mechanisms are designed and used in the delivery platform to provide specific targeted release to specified cells will also be mentioned.

1.1. Nanocarriers based therapeutic delivery

There are infinite possibilities to the application of nanotechnology in current drug delivery systems. Most biological functions are highly dependent on nanoscale dimension units like viruses, ribosomes and molecular motors [7]. Thus by having nanoparticles that are small enough for direct interaction with subcellular compartments, it opens up the possibility of activating intracellular events [8].

In general, the nanocarriers based therapeutic drug delivery systems are preferred over normal drug delivery due to the numeral promising advantages [9]. Firstly, the larger surface-to-volume ratio of the nanocarriers could allow a larger contact area of the drug with the body in the same drug concentration condition, thus the same dose of drugs makes the delivery more effective [10]. The reduced dosage will in turn reduce the drug's side effects and toxicity issues. Secondly, nanocarriers have tuneable surface chemistry for different drugs and targeting molecules. For example, the highly efficient drug doxorubicin (DOX), which is used to treat various types of tumours also has a major side effect of causing serious cardiotoxicity due to the lack of tumour specific cytotoxicity. The tuneable surface chemistry allows the possibility of having prolonged and sustained drug release, this improves the bioavailability of the drug to where and when it is most needed and also allows longer period of drug circulation than the drug alone [7]. For instance, one can make drugs that are hydrophobic and has low aqueous solubility to be transported *in vivo* conditions. The surface chemistry modification allows efficient navigation in the complex *in vivo* environment by protecting the drug from undue degradation. The surface chemistry modification also enables not only the drug to be directed to specific cell types for targeted delivery but even to special regions of the cell making enhanced intracellular trafficking of the drug possible [11]. Lastly, the nanocarriers can provide the flexibility in the forms of having more diverse routes of drug administration and also in terms of drug formulation.

The nanocarriers that carry the drugs can be made in different forms like dendrimer, liposome, rods and many other forms. These nanocarriers can be organic based dendrimer nanoparticles (NPs) [12], polymer [13], polymer based micelles [14], hydrogels [15,16] or inorganic based like gold nanoparticles(AuNPs), magnetic nanoparticles [17], semiconductor nanoparticles [18], carbon nanotubes(CNTs) or even ceramics like iron oxide nanoparticles (IONPs) [19]. The different forms of nanocarriers are as shown in Fig. 1 [20]. They are versatile and often have many different functions. Normally the therapeutic agents are dissolved, adsorbed, entrapped, encapsulated or attached on the surface or inside the nanocarriers. These nanocarriers are currently used as targeted nanotherapeutics and also in diagnostic test for inflammatory, infectious and autoimmune diseases as well as cancer [21–23]. When the nanocarriers are in the blood streams, the plasma proteins, cells and other blood components will interact extensively with the material, some of the interactions aids the transportation of the nanocarriers with the drugs to the targeted sites [24].

The nanocarriers can be modified to have its own chemical and physical properties by altering the synthesis method, surface functionality and modification, size, shape and the bulk structure [25]. To develop an effective therapeutic delivery system, one needs to know the physicochemical properties of the material and how it interacts with the biological systems in our body [26]. For instance, optimal surface modifications are required to eliminate or reduce undesirable effects like intrinsic toxicity and immunogenicity, which some of the nanomaterials may have. Using cationic nanoparticles as an example,

Table 1
The common routes of drug administration.
(Reproduced from ref. [3] with permission.)

Administration routes	Examples	Pros	Cons
Intravenous injection	Antibiotics for sepsis	100% bioavailability	Discomfort to patient, Requires health care provider, Risk of overdose or toxicity, Risk of infection
Intravenous infusion	Heparin for anticoagulation	100% bioavailability, Continuous control over plasma levels	Requires hospitalization, Risk of infection
Subcutaneous injection		Usually high bioavailability	Discomfort to patient
Intramuscular injection	Insulin for diabetes	Usually high bioavailability	Discomfort to patient
Oral	Aspirin, acetaminophen, ibuprofen	Convenient, Self-administered	Drug degradation prior to absorption, Limited absorption of many drugs
Sublingual or buccal	Nitroglycerin for angina	Avoids first-pass metabolism in liver, Self-administered	Limited to lipophilic highly potent agents
Ophthalmic	Pilocarpine for glaucoma	Local delivery, Self-administered	Discomfort to some patients, Frequent administration
Topical	Antibiotic ointments	Local delivery, Self-administered	Limited to agents that are locally active
Intra-arterial injection	Chemotherapy, in some cases	Control of vascular delivery to specific regions	High risk
Intrathecal injection	Pain medication, in some cases	Direct delivery to brain	Limited drug penetration into brain tissue, High risk
Rectal		Avoids first-pass metabolism in liver, Self-administered	Discomfort leads to poor compliance in some patients
Transdermal	Nitroglycerin patches for angina	Continuous, constant delivery, Self-administered	Skin irritation, Limited to lipophilic, highly potent agents
Vaginal	Spermicides	Self-administered	Discomfort leads to poor compliance in some patients
Controlled release of implants	Norplant for contraception	Long-term release	Requires surgical procedure