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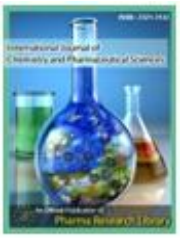

Advance drug Delivery system for Formulating Bio Active

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ABSTRACT

Nano delivery systems are a relatively new but rapidly developing science technology where materials in the nanoscale range are used as diagnostic tools or to deliver therapeutic agents to specific targeted sites in a controlled manner. Nanotechnology offers multiple benefits in treating chronic human diseases by site-specific and target-oriented delivery of precise medicines. Currently there are more applications of the nanomedicine includes chemotherapeutic agents, biological agents, immunotherapeutic agents etc. in the treatment of various complex diseases. As nanoparticles comprise materials designed at the molecular level, they are usually small sized nanospheres. It can move more freely in the human body as compared to bigger materials. The use of large sized materials in drug delivery poses major challenges, including in vivo instability, poor bioavailability, and poor solubility, poor absorption in the body, issues with target-specific delivery, and tonic effectiveness, and probable adverse effects of drugs. Therefore, the design of novel advanced drug delivery systems for targeting drugs to specific body parts could be an option that might solve these critical issues.

Keywords: Nano delivery systems, controlled release delivery system, absorption, nanomedicine, bioavailability, and solubility.

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1. Introduction

The conventional drug delivery systems represent the classical method for delivery of drugs orally. These common dosage forms are often accompanied by systemic adverse effects that are primarily attributable to their unspecified bio-distribution and missing controllability of the drug release characteristics. Furthermore, conventional drug delivery systems have been found to have severe constraints including non-controlled release, higher doses and a frequent application. Another major challenge in the formulation of drugs is the improvement of bioavailability. To overcome the limitations of conventional drug delivery systems, pharmaceutical companies focused on the development and design of novel drug delivery systems. The need for high performance, flexibility and controlled release systems are provoked by the compelling advancements in patient compliance, clinical efficacy, prolonged product life through a controlled drug release and economic aspects like reduced frequency and expenses of administration. For

this reason, novel drug delivery systems might be among the fastest expanding segments in the drug industry. Novel drug delivery systems are engineered according to a rational design to enhance the delivery and the performance of existing drugs with respect to traditional systems. Novel drug delivery systems in comparison to traditional ones combine advanced techniques and new dosage forms in order to target, control and modulate the delivery of drugs. By the evolution of a drug from a conventional to a novel drug delivery system the performance regarding efficacy, safety and patient compliance can be remarkably improved[1-6].

There are two prerequisites that novel drug carriers aim to fulfill: the delivery of the drug to the specific target site at a pace and extent geared by the demands of the body and the monitoring of the active unit directly during the treatment. In contrast, the term "drug delivery system" is limited to only those systems that involves the delivery of drug to a target site for a specific period. The main rationale for the advancement of novel drug delivery systems is to enable a sustained and controlled drug delivery, to maintain efficient drug level and simultaneously reduce adverse effects. Amid the different novel drug delivery systems, fast dissolving drug delivery systems have acquired remarkable importance regarding oral route of administration. Initially developed as alternative to tablets, capsules and syrups for pediatric and geriatric patients with the fear of suffocation, fast dissolving drug delivery systems have the major benefit of a quick disintegration or dissolution in the salvia without the need of additional liquid. Amid the various approaches to improve oral bioavailability of hydrophobic drugs, self-emulsifying drug delivery systems (SEDDSs) also possess significant potential. After oral administration, dispersion in gastrointestinal fluid is formed and produces micro-emulsified or nano-emulsified drug that easily gets absorbed *via* lymphatic pathways and hence bypasses the first past metabolism in the liver. Traditional oral formulations have almost no control over drug release and the effective concentration at target site, which may lead to fluctuations in plasma concentration[8-15]. By using osmotic pressure as driving force, osmotic devices allow a controlled drug delivery independent upon gastrointestinal conditions. Part of this emerging interest in novel drug delivery systems has also been stimulated by the advances in nanotechnology and the variety of nanoscale platforms. Due to their size in the nanoscale, nanoplatforms can selectively accumulate and specifically bind to the target site with a controlled release behavior.

Notable characteristics

The oral route is the most favored route for drug delivery for medical practitioners and manufacturers due to cost effectiveness, ease of administration and hence the highest level of patient compliance. Tablets and capsules are the most popular oral solid dosage forms. Although these have numerous benefits like precise dosing, painlessness and self-medication compared to other administration routes, they remain problematic. While tablets and capsules are hard to swallow especially for geriatric, pediatric and dysphagic patients with fear of suffocation, the major challenge for syrups and other liquid orals is accurate dosing. FDTs are also called porous tablets, fast melting/disintegrating tablets or orodispersible tablets in subject-related literature. Without the requirement of additional liquid and mastication in the administration process, the dissolution or disintegration takes place within one minute after being moistened by the salvia. By immediate absorption of the released drug and hence a direct entry to the systemic circulation the first pass metabolism is avoided. This way a better alternative to conventional oral dosage forms, particularly for patients suffering nausea and vomiting as well as bedridden patients, is provided. Efficacy at low doses, a pleasant taste and a sufficient stability in both water and salvia and an adequate permeability are ideal properties of the active pharmaceutical ingredient (API). Hydrophilic polymers are used to form films[16-20]. The molecular weight is directly related to the dissolution rate *i.e.* an increase in weight leads to a reduction of the quantity to be disintegrated. The mechanical features, a quick dissolution upon contact with a wet surface along with a good mouth feel are affected by the choice of the hydrophilic polymer. Along with the ease of administration FDOFs have many advantages compared to traditional oral dosage forms such as a higher dissolution rate due to a larger surface area and a quick disintegration leading to an enhanced bioavailability especially for lipophilic, insoluble drugs. By avoiding the first pass effect due to a direct entry to the blood stream the bioavailability is improved. Additionally, there is no need of water for oral administration, an unpleasant taste of the drug can be overcome and the risk of suffocation is eliminated. This drug carrier enables an enhanced stability as well as dosing accuracy and is easy to manufacture, transport and package. FDOFs still suffers from a few limitations. In comparison to fast FDTs it is only possible to integrate low doses.

Recent advances in formulations

Today FDOFs are the state-of-the-art in rapid dissolving drug delivery systems and are becoming increasingly important lately. Amitriptyline hydrochloride, which is administered to treat severe depression has a poor bioavailability of 30–60% due to a significant first pass metabolism. Salman et al. presented a study to enhance the bioavailability and patient compliance and accordingly optimize the therapeutic effect of amitriptyline hydrochloride by developing oral films. Ten formulations were produced, made of various kinds of polymers, plasticizers and surfactants using the solvent casting method. After visual inspection, the thickness, drug content uniformity, folding endurance and tensile strength were evaluated as well as the surface pH was calculated to

prevent oromucosal irritation. Additionally, *in vitro*/*in vivo* disintegration tests and an *in vitro* dissolution study were conducted. The formulation containing 22.67% *w*/w maltodextrin and HPMC 15cp each showed the best results concerning an *in vitro/in vivo* disintegration time of 16.8/13.2 s, 80% drug release within 1.1 min and 89.77% of the drug dissolved after two minutes along with satisfying mechanical properties. As proof of concept a cross-over study using rabbits was designed to compare the pharmacokinetic data of the optimized formulation with a commercially available solution (Amitriptyline Hydrochloride). The bioavailability study showed a rise of the peak blood concentration (0.927 µg/mL) in a short time (2 h) which suggests a fast absorption. In conclusion fast dissolving films of amitriptyline HCl are appropriate to treat depression if rapid onset of action and increased patient compliance is desired[21-29].

Osmotic drug delivery systems

Conventional drug carriers often lack in control regarding the drug release and the effective concentration at site of action. This may engender unanticipated, variable plasma concentrations Although research has shown that frequent dosing leads to a low patient compliance, standard drug therapy in terms of dosage level and frequency is designed to provide plasma concentration within the therapeutic range. Apart from that, some drug substances suffer from a poor oral bioavailability due to solubility and permeability difficulties. The design of controlled drug delivery systems facilitates an ongoing release of the bioactive component at a predestined rate over a defined, extended time with forestalled and replicable kinetics. Among the several pharmaceutical attempts to develop a long-acting pharmaceutical form for a single administration per day, osmotic devices are the most dependable ones. Osmotic pressure acts as driving force to release the API in a monitored manner. Both oral and parenteral administration are possible, whereby a distinction is made between gastrointestinal therapeutic systems, respectively oral osmotic pumps and implantable pumps.

Osmosis can be conventionally described as the net motion of water across a semi-permeable membrane created by the disparity in osmotic pressure across this membrane. The selectivity of the membrane allows only the passing of water, but declines the entrance to most solute molecules and ions. The release of bioactive agents from osmotic devices is regulated by the osmotic pressure impelled through the penetration of liquid from external surroundings. Moreover, the extent of drug release is directly proportional to the osmotic pressure in the core. Solubility, osmotic pressure, dimension of the delivery orifice and membrane properties mainly affect the drug release from ODDSs. A current trend in the design of novel drug delivery systems is the usage of strategies based on two steps. The first phase is aimed to improve the solubility of the API by *e.g.* micronization, while the second step enables the control of drug liberation by using osmotic systems[30-32].

Nanoparticulate drug delivery systems

Properties of nanodevices

Nanoparticulate drug vehicles are solid, colloidal systems with a high surface-to-volume ratio due to their small size (1–1000 nm) and properties and morphology determined by the design. Since nanomaterials are either composed of lipids and polymers (synthetic or natural) or inorganic metals. Nanoparticulate drug delivery systems are usually composed of two fundamental constituents: the nanoparticle itself and the carried therapeutic agent. The drug is either covalently attached to the surface or alternatively, entrapped and encapsulated by the nanoparticle in order to be protected from demotion and denaturing. The optimum particle size is about 100 nm small, so that instantaneous clearance by the lymphatic system is averted, the blood brain barrier is penetrated and an adequate amount of drug is delivered due to a large surface area. More recently, polymer coating with water-soluble polymers such as polyethylene glycol (PEG) or polysorbate 80 was invented to prolong circulation in the blood stream. Common approaches for the synthesis of nanoparticles are the top-down method and the bottom-up method.

Targeted delivery and triggered release

Nanocarriers can be designed to enhance the efficacy and at the same time to minimize adverse effects by delivering the API to a certain target-site. In anticancer therapy, for example, nanoparticles can take advantage of the enhanced permeability and retention effect of tumor cells due to their small size and leave the systemic circulation in order to get into the extravascular space to amass in tumor tissues. But multiple limitations are associated with passive targeting like a poor drug diffusion and controllability, which led to the development of active targeting[33-34]. Active targeting is based on the molecular recognition *via* antigen-antibody or ligand-receptor interactions and is achieved with the help of surface modification through attaching different ligands such as peptides, antibodies or oligosaccharides.

Types of nanoscale drug delivery systems

Polymeric nanoparticles

Basically, nanospheres are spherical, solid particles with a size ranging from 10 to 200 nm, based on a matrix system and a homogeneous structure throughout. In comparison nanocapsules are vesicular systems consisting of a rather oily than aqueous liquid core surrounded by a polymer membrane or coating. jIn the inner core the drug is encapsulated either in dispersed or dissolved form, in the polymeric membrane entrapped and amid the pseudo-phase distributed. The wall forming polymer is mostly made of a biodegradable material of natural or synthetic origin. Since nanocapsules as drug vehicles have been investigated in various studies for different routes of administration indicating their diversity, several other

benefits can be achieved by the entrapment of the API. On the on hand the chemical stability along with photoprotection are provided due to the polymer in the nanocapsules interface. Further, there is an enhanced interaction with tissues and cells since the therapeutic agent is usually taken up while being entrapped within the nanocapsules. By using nanocapsules as drug delivery system, the bioavailability and efficacy is improved and at the same side effects are reduced. While a large number of research has been published, only a few products are currently available in the market.

Solid lipid-based nanoparticles

Solid lipid-based nanoparticles were designed with the intention to accomplish a substitute drug delivery system to polymeric nanoparticles, liposomes and emulsions. Initially developed to combine the advantages and to conquer the difficulties of several drug carriers, SLNs offer many reasons to be considered as promising drug delivery system. By replacing the liquid with a solid lipid not only a controlled release of the bioactive agent is enabled, but also, the chemical degradation is reduced due to the decrease of mobility in the solid matrix. Additionally, the biocompatibility and biodegradability of the employed lipids lead to a reduced acute and chronic toxicity and an improved bioavailability of the incorporated drug. To overcome said complications the next generation of lipid nanocarriers was developed: nanostructured lipid carriers. The matrix of NLCs comprises a mixture of solid and fluid lipids but remain in a solid condition at room and human body temperature. Firstly, variations in the structure of the solid and liquid lipid lead to an imperfect crystal structure allowing an increased drug loading capacity. Secondly, the presence of liquid drug release is inhibited. But at the same time no significant reduction of the cytotoxicity is reported.

Gels

Hydrogels consist of a three-dimensional network with porous characteristics made of cross-linked, hydrophilic polymers from natural or synthetic sources, imbibing large amounts of water and therefore have high levels of flexibility. The resemblance to living tissue in the swollen state permits high biocompatibility and makes them suitable for numerous applications. Nanogels, also called the next era of hydrogels, have similar structure and characteristics to hydrogels, apart from their size in the nanoscale. The classification is either based on the type of cross-linking of the three-dimensional network or on the behavior towards an explicit stimulus. Most noteworthy are pH or temperature sensitive nanogels exhibiting ideal drug loading and drug release properties due to their swelling and shrinking property[35].

Vesicular drug delivery systems

Highly ordered units of one or more concentrical lipid bilayers formed when amphiphilic building blocks are in contact with water are called vesicular systems. Frequently used materials for the preparation are cholesterol, phospholipids and non-ionic surfactants. Additionally, there is a varied assortment of amphiphilic components. The efficacy is heavily affected by the form, size, construction, lamellarity and encapsulation capacity. Vesicular drug delivery systems (VDDSs) are favorable over conventional dosage forms due to the fact that both lipophilic and hydrophilic drugs can be entrapped in the bilayer, respectively in the aqueous core. Furthermore, the positives include an improved bioavailability, especially of hardly dissolvable drugs, a retarded metabolization, a prolonged systemic circulation and a reduced toxicity.

Liposomes

Liposomes are self-assembling, globular blisters composed of an aqueous core surrounded by one or several concentric lipid bilayers ranging from 20 nm up to a few micrometers.

Niosomes

Niosomes are considered as alternative to liposomes regarding the similarity in terms of structure and physical features but slightly differ in composition. Due to a high susceptibility and cost intensity of lipids included in the first vesicular drug carriers, niosomes are formulated by using non-ionic surfactants. The decisive difference is a better chemical and physical stability as well as lower expenses[36-42].

Transfersomes

The concept of transfersomes was first invented in 1990s and describes an utmost malleable vesicle with an elastic nature that enables penetration through pores minor than its own size. Conveyance of therapeutic agents through skin is considered as an advanced and fortunate route for drug delivery since the skin is the largest human organ in terms of surface with 2.5–3 m^2 . Apart from phospholipids, edge activators such as tween 80 or span 60 are the main constituents in the formulation of transfersomes[43-44]. This single chain surfactants effect the destabilization of the lipid bilayers leading to an increase in its malleability making them particularly suitable for skin penetration.

2. Conclusion

The drug delivery systems has come a long way and will proceed to grow at an extraordinary rate. The available of more therapeutic as well as commercial merits are provided by the incorporation of drug molecules in advanced drug delivery systems. However, there is a required for improvement and all newly developed drug delivery systems will need to be thoroughly studied, characterized and investigated before being approved to do clinical research in humans.

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