Research Article

Drug Delivery Research: Current Status and Future Prospects

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ABSTRACT

Nowadays the development of new drug delivery systems plays a major role in pharmaceutical industries. The drug delivery practice has been altered in last years and even many advanced innovations happened in recent times. Newer drug delivery technologies are largely influencing the current medical practice. Alterations of a current drug into a new drug delivery technology can positively changing the bioavailability, safety and efficacy of the drug and also it can produce improved patient compliance. At this time, a number of pharmaceutical companies are forwarded to initializing multiple drug delivery technologies for creating excellent advantages, prolonging patent and better outcome for their marketed products. One of the main challenges in newer drug delivery is, huge molecules are rapidly dissolved in the blood volume and they have a lined capacity to cross barriers. Drug delivery technologies can be performed on many available dosage forms like tablets, capsules, pills, injections, suppositories etc. Conventional drug delivery may produce problems regarding oral bioavailability. This can be improved by introducing newer drug delivery techniques like oral controlled drug delivery, site targeted delivery, rate programmed drug delivery, feedback regulated delivery, fastly disintegrating dosage form by oral route, topical and nasopulmonary drug delivery.

Keywords: Drug delivery, Macrocap, Regel, Fast disintegrating.

INTRODUCTION

Conventional drug delivery system is the administration of a therapeutic agent or any other pharmaceutical compound to humans or animals for achieving therapeutically effective range of medication, the medication need to be administered several times a day means the dosing frequency is increased. This will lead to the fluctuation in drug levels significantly.[1] To overcome this scenario, developments of some pharmaceutical technologies are introduced into the drug delivery; controlled drug delivery is one among them.

Nowadays, the scope of controlled drug delivery system is tremendously influencing the pharmaceutical dosage forms, including tablets, capsules, ointments, creams, pills, suppositories, injections etc and it gives effective therapeutic benefits to the patients by controlling the rate of drug delivery, prolonging or sustaining the release of therapeutic agents and thus, delaying the pharmacological action.[2] Release of a therapeutic agent is carried out in a predetermined rate over a certain target organ is necessary in developing a drug delivery system and pharmacokinetics. Moreover, carriers that may covalently or non-covalently bound to the drug and helps in the release of a bioactive agent. In some cases, theses carriers may possess their oscillatory behavior that has emerged as a significant problem in design of a new drug and its formulation.

Current Drug Delivery Technologies

Assimilating a current medicine into a controlled drug delivery system which may significantly improve the therapeutic effectiveness of the drug, safety and improved patient compliance with reduced toxicity. Recently, many of the pharmaceutical companies are able to develop new delivery systems for the drug release in an excellent way. This may leads to the bring up of multipotential drug delivery with high therapeutic efficiency. Nowadays, a number of controlled drug delivery system has been designed like feedback regulated delivery system, rate programmed drug delivery system, oral controlled delivery system, site-targeted delivery system, fastly disintegrating dosage form by oral route, topical delivery, nasopulmonary delivery.[3]

Oral Controlled Drug Delivery System

Oral route is the most convenient and extensively used route for drug administration. Over the years, the oral dosage forms have become sophisticated with development of controlled release drug delivery system. The main challenge in the development of oral controlled drug delivery system is to modify the GI transit time (transportation of drug to the desirable site) to increases the duration of drug release and thereby beneficially improve the bioavailability, development of drug delivery system (release of a drug at therapeutically effective rate to targeted site) and minimization of first pass metabolism, dose dumping, reduced potential for accurate dosage adjustment, stability problems. Controlled drug delivery system posses a number of obstructions for their therapeutical acceptance involving, cytotoxicity, biological compatibilities of the device, in-vivo studies, approval from Food and Drug Administration (FDA), efficiency, patient incompliance etc.[4] Few

techniques are used to achieve controlled release of the drug shown in Table 1.

Site-Targeted Delivery System

Targeted drug delivery is the delivery of a therapeutic agent to a particular part of the body in an increased concentration.[10] So, the desired amount of the therapeutic agent released to diseased area for a prolonged period of time. It is categorized on the basis of system where the delivery system is administered; in first order targeting, drug is delivered to the capillary bed or active site. In second order targeting, drug delivers to the special cell type and in third order targeting, delivers intra-cellular. A good approach for the targeted drug delivery is to design a newly developed material with efficient controlled properties.[11,12]

The main challenge involving in targeted drug delivery is to identify the desired target. It is may be a tissue, cell or intracellular material like DNA. In ligand-targeted drug delivery, a carrier system is needed (coupling). This will recognize the area affected by the disease where the delivery of the drug is occurs.[13] A number of factors that depends the selection of target. i.e., expression of target is very important and obviously influencing the specificity of the delivery. It is spatial expression (site specificity and expression showing uniformity in given tissue or cell type) and temporal expression (constitutive and down regulated during pathology). Target trafficking is the other important factor. It is non-internalizable (may be cell surface delivery or extracellular), endocytosis (uptake into the vesicular compartment of the cell). Potential side effects may determined by the function of target. It is may be beneficial (by blocking the role in disease), harmful (by blocking the physiological function) or unknown (unidentified target). Target accessibility, sub-cellular transport of the target (membrane target, cell penetration, lysosome, Golgi & ER, nucleus, mitochondria), the target moiety (showing affinity towards the target) are other important challenge that facing by the targeted drug delivery.[14] Various site targeted delivery techniques is shown in Table 2.

Feedback Regulated Drug Delivery System

Feedback regulated drug delivery system shows a controlled drug delivery by the release of the drug is activated by a triggering agent. It is mainly three types; bioerosion-regulated bio-responsive and self regulated drug delivery system. In present scenario, Diabetes mellitus is a chronic disease that caused to most of the peoples in this world.[20] There is a number of ways to delivering insulin and it solving the problems with insulin administration. We can regulate the insulin delivery rates by using the glucose modulation and this shows the self regulated drug delivery significantly. The main challenge is to design a delivery system which posses the natural pattern of insulin release found *in-vivo*. There are two types of insulin release i.e., basal and augmented insulin release. The rate of this release in response to post meal glucose is important for maintaining the normal blood glucose level. The most commonly used method for the insulin delivery is an insulin infusion pump and it is stimulated by external sources like heat, sound or magnetic sources. Glucose sensitive polymers and encapsulated islet cells are the latest approaches for the insulin delivery. Any changes in the specific conditions to this approach, it unable to produce the desired insulin delivery.

Fastly Disintegrating Dosage Form by Oral Route[21]

An oral fast disintegrating dosage form may defined as, any solid drug (tablet, capsule, granules) that easily dissolved in the oral cavity without the any administration of water. This delivery is also known as fast-dispersing, fast dissolving, rapid disintegrate and quick dissolving tablets. These fastly disintegrating dosage forms are very useful in certain cases like pediatrics and geriatrics because they may have some swallowing difficulties. It allows the rapid absorption of the drug, therapeutic activity and improved patient compliance. Other techniques are used is shown in Table 3.

Rate Programmed Drug Delivery System

Rate programmed drug delivery is delivering the therapeutic agent from the system preprogrammed at specific rate. Molecular diffusion of drug across the barrier or surrounding the delivery system is an important aspect for this type of delivery and the system design controls the molecular diffusion. It is further categorized into polymer-membrane permeation controlled, polymer-matrix diffusion controlled and micro-reservoir partition controlled. In polymer- membrane permeation controlled, the drug may encapsulate wholly or partially with the drug and the surface of the drug is layered with a rate-limiting membrane and it shows some specific permeability. So, the main challenges in this system is that, the release of the drug may actively occurs when we considering certain factors like controlling the partition coefficient, molecular diffusivity of the drug and also the thickness of membrane. Polymer-matrix diffusion controlled delivery possessing preprogrammed delivery of the drug and this drug is dispersed in a rate controlling polymer matrix which may be hydrophilic or hydrophobic. Lack of controlling the loading dose, optimum solubility of the polymer and diffusivity in the matrix of the polymer are the main challenges facing by this system. In Micro-reservoir partition controlled delivery system; fabrication is done by the micro dispersion of drug suspension using a high energy dispersion technique. Physiochemical properties of the drug and the nature of polymer is very important in this system. One of the other problems faced by the CDDS includes development of bio-responsive system, in which the drug delivery responds to the changes in physiochemical environment.[27]

Topical Delivery[28]

Topical delivery is also known as Transdermal drug delivery system (TDDS) in which the drug delivers through

the skin and reaches the systemic circulation for the desired effect. So, it avoiding the first pass metabolism by the liver and enzymatic degradation of the drug in GIT. The permeability of the transdermal drug can be improved by the addition of penetration enhancers, sonophoresis, iontophoresis, prodrugs etc. advanced technologies include in Table 4.

Nasopulmonary Delivery

Nasal and pulmonary areas are rich in blood supply so rapid absorption of the drug may happen. Mucosal lining is responsible for the rapid absorption of the therapeutic agent. Nasal preparations are usually in dispersed form and it is kept in a tight container. Squeezing of the container may discharge the preparation.

Pulmonary preparations are used for treating respiratory disease. They are invasive in nature so it is painless.

It gives fast onset of action and improved bioavailability. Inhalation devices are usually used and it is broadly classified into; metered dose inhaler (MDI), drug powder inhaler (PDI) and nebulizers.[31] Pulmonary delivery techniques are described in Table 5.

Table 1: Oral Controlled Drug Delivery Techniques

S No.	Techniques	Description
1.	MODAS[5]	It is multiporous oral drug administration system. Itconsists of an active drug with an excipients, layered with a polymer which is insoluble in nature. After the food intake, it reaches GI fluid, excipients gets dissolved and leaving the insoluble polymer. It results in the formation of a small channel which linking the fluid portion from the GIT to inner core of the drug. This fluid moves through the tiny channel and reaches the drug core thus, dissolves and this solution diffuse out in a controlled way to the outside.
2.	Macro cap	A pellet system. Pellet is layered with a plasticizer and a polymer, controlling the rate of drug release in GIT.
3.	SCOT[6]	It is a single composition osmotic tablet system. Osmosis is the basic principle is behind this and follows zero order release of the drug by using different osmotic modulating agent.
4.	Rhotard	It posses double-matrix technology and two types of granulation stages are present during the manufacture.
5.	Symatrix	Formulation regarding microparticle. Encapsulation of symatrix with therapeutic agent results in an improved absorption of the drug.
6.	Gastric retention system[7]	E.g. Floating tablets because it contains a potent drug with a polymer and they retained in the stomach for a longer period of time after the intake of food. Thereby, we can reduce the dosing frequency and shows therapeutic efficiency.
7.	Meter release	It is used for drugs that may showing the release of over 8-12 hours and also it possess a different pattern of releasing properties
8.	DPHS	It is delayed pulsatile hydrogel system. These may contain a hydrogel matrix. It follows a zero order release of the drug and shows rapid delivery of the therapeutic agent.
9.	Ceform microsphere technology[8]	Microspheres are small, spherical shaped structures that may shows size in the range of 150-180mm. these microspheres helps to improve the absorption and they are available in a number of dosage forms like effervescent tablets, capsules, sachets etc.
10.	PPDS[9]	Pellets are used to control the release of a drug, thus it is known as pelletized pulsatile delivery system. Certain polymers are used to coat the pellets and it helps for the controlled drug delivery. The drug delivery pattern can be varying with the changes in the composition of the polymer mixtures.

Table 2: Site Targeted Drug Delivery Techniques

S. No.	Techniques	Description
1.	Durasite[15]	It is an eye drop preparation in which a cross- linked carboxyl containing polymer is present. This may leads to the effective delivery of the drug to the eye.
2.	Matrix delivery system[16]	The drug is combined with an aqueous-based protein matrix and a vasoconstrictor which create an injectable gel. Localizing the delivery of drug in an increased concentration to the tumor site.
3.	Retinal delivery system[17]	It provides the controlled release of the drug to the retinal part of eye and it is a nonsurgical delivery.
4.	Atrigel[18]	It is designed to provide the targeted delivery of the drug by a single application without any surgical requirement.
5.	Microsphere delivery system	It is achieved by the application of biodegradable polymers and allows the microencapsulation of water soluble and water insoluble compounds. It gives the prolonged release of the medicament.
6.	ReGel injectable controlled–release system[19]	These are available as liquid formulations. Once it injected into the body, through 25 gauge needle, It forms a gel under favorable conditions within the body. It forms a depot and gives prolonged release over four weeks.

Table 3

S. No.	Techniques	Description
1.	Fast melt[22]	It is a highly porous, matrix tablet. Rapid absorption of the drug may occur when the drug is placed on the tongue.
2.	EFVDAS[23]	Effervescent drug absorption system. The drug absorption occurs by adding the sachet content to the boiling water. E.g. Effervescent Paracetamol, Cimetidine, Ibuprofen.
3.	LYOC and Quicksolv	Technology is based on the lyophilization process and producing oral fast disintegrating tablets.
4.	Multiflash[24]	Tablets containing micro granules and fast dissolving excipients. Allows avoidance of mucosal adhesion.
5.	Wow tab	It contains a unique mixture of fast dissolving but poorly compressible saccharides like mannitol, glucose etc and slowly disintegrating saccharides. Tablet compressed well and gives required hardness thus fast disintegration.
6.	Flash dose[25]	This forms floss as a matrix. Floss is similar to fibrous structures and it is usually made up of sucrose and dextrose. This fibrous floss is further milled and mixed with active pharmaceutical ingredients (API) and compressed into rapidly disintegrating tablets.
7.	Zydis[26]	Zydis is a combination of water soluble matrix with a drug. Also, it contains excipients which show some specific functions that may produce blister pockets. Further it undergoes lyophilization to eliminate water content by the process of sublimation. The product are fastly dissolve upon interacting with water.

Table 4

S. No.	Technologies	Description
1.	D-trans[29]	It possess a rate controlling drug delivery to the skin and required weekly dosing. Improved patient compliance.
2.	E-trans	A low power electric current is used to control the drug delivery to the skin and it is achieved by an electron transport system.
3.	Therapatch	It is a self adhering patch to deliver the desired drug into the skin for the relief from pain.
4.	Dermasite	It is used for the topical application to the skin and semisolid in nature.
5.	Dermaflex	It is a type of passive transdermal patch using a hydrogel matrix and the drug is incorporated in the matrix for the drug delivery.
6.	Polytrap system[30]	It is developed for reducing the oil content in the skin and they possess an unruffled feel to desired preparations, releasing different ingredients into an individual care product and liquid transferring to powders.

Table 5

S. No.	Techniques	Description
1.	Spiros[32]	Electro chemical energy is used to disperse drug to make an aerosol for inhalation process. the major parts of an aerosol involved the impeller, the motor, the breath-actuated switch, and the dosing chamber
2.	AERx system[33]	It is an aerosol generation technology and it may aerolizes the formulations (liquid) are kept in a unit–dose packets for inhalation.

Commercially Available Drugs

Two figures are given below and it shows the marketed available products and its indications.

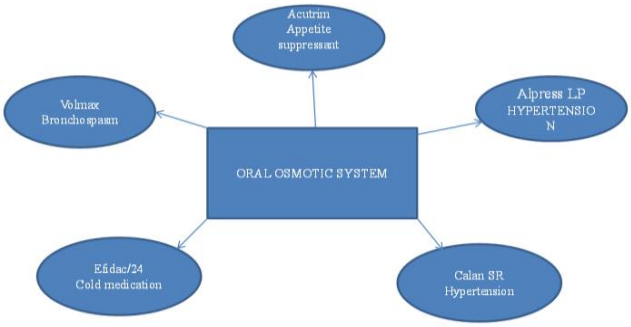

Figure 1: Oral Osmotic System

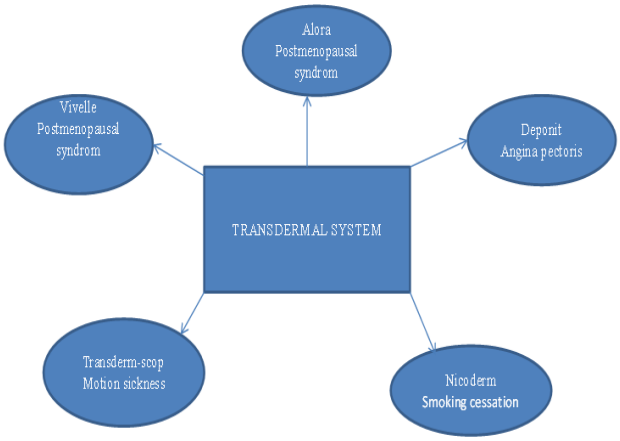

Figure 2: Transdermal System

Future Possibilities

Even though, controlled drug delivery faces these many challenges but, still it posses a tremendous way of future prospects. Therefore, a huge dedication deserves for its growth and exposure.

Also, we can modify the design and development of controlled drug delivery by the application of different types of polymers which showing the characteristic features.

Challenges in controlled drug delivery such as compounds having large molecular weight that fastly degrade in the blood therefore, some proteins, carbohydrates, nucleic acids and peptides are found in the form of DNA.

These biopharmaceuticals having a limited capacity to pass the biological barriers and less oral bioavailability. To overcome this problem, we have to develop a number of drug delivery technologies. It can be achieved by contributing some more ways;

1. Designing a new drug- delivery system with drug which showing multipotential activity.
2. Designing a drug delivery which acts locally.
3. More accurate route for making the drug responsive and greater sensitivity.
4. Delivering the insulin orally with body- friendly polymers with improved systemic absorption.
5. We can increase the commercial availability by reducing the cost.

Nowadays, controlled drug delivery technologies are able to incorporating a drug with newer delivery systems to provide maximum therapeutic efficacy and safety. A number of pharmaceutical companies are forwarded to develop new delivery technologies and marketing a number of products.

CONCLUSION

From this review, we could conclude that various types of drug delivery technologies can be used for delivering the medications in a proper manner. It may include oral, targeted, topical, naso-pulmonary etc. By developing newer delivery technologies, it can give much more therapeutic and commercial benefits by improving the safety and reducing the toxicity. Today, many pharmaceutical companies are introducing their own newer products to the market which may give good therapeutic response when compared with conventional drug delivery. The development of upcoming drug delivery technologies can be applied for solving problems regarding pharmaceutical, biopharmaceutical and pharmacokinetic aspects thus, the delivery systems are growing worldwide.

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