REVIEW ARTICLE

Injectable Controlled Release Drug Delivery Systems

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Abstract

Nowadays conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Among, these the controlled release/sustained release dosage forms have become extremely popular in modern therapeutics. In the last few years, sustained release injections have developed. At targeted site, these injections showed the prolong effect of drug. Decrease in side effects, lesser frequency of dose, maximum dose-efficacy relationship, and improved patient compliance are the benefits received by controlled release of drugs. To the systemic circulation, parenteral drug delivery can achieve easy access with rapid drug absorption. It is always advantageous to achieve the systemic drug levels within the therapeutically effective concentration range of drug for obtaining the better treatment. With the arrival of novel carriers, the research in parenteral sustained release technologies has received huge boost up. So, many injectable sustained release products have received regulatory approval and launched in the pharmaceutical market. In the present review, efforts were put forth on the rationale and most recent progress done in the development and formulation of parenteral controlled release systems. The review focused on the current long-acting injectable preparations with special attention to marketed products.

Key words: *In situ* forming implants, liposomes, microspheres, resealed erythrocytes

INTRODUCTION

Parenteral preparations are sterile preparations which have one or more active ingredients administered by infusion, injection, or implantation into the body.[1] Excipients such as solvents, buffering agents, solubility enhancers, stabilizers or antimicrobial preservatives suspending agents, isotonic agents are added to the parenteral preparations.[2] Excipients are added to a minimum level. No incompatibility among the added substances of the dosage form. Water for injections is used as the vehicle for aqueous injections. Many advanced drug delivery systems are evolved over the years and parenteral drug delivery system being one of them.[3] In parenteral drug delivery system, injection is directly administered into the tissue fluid or blood instead of crossing intestinal mucosa.[4] The conventional intravenous injection may produce the high drug plasma concentration, near to the minimum toxic concentration. Due to the short duration of action, sometimes it becomes essential to administer the drug repetitively in traditional systems. To overcome the problems faced by conventional intravenous injections, the advanced parenteral controlled release drug delivery systems are developed, which give predictable, consistent, or desired drug release profiles.[5] Liposomes, niosomes, suspensions, microparticles, emulsions, and implants are identified as parenteral controlled release drug delivery systems.[6] This drug delivery system is beneficial only if drugs have short half-lives and poor absorption by other routes of administration. Two approaches can be used to obtain constant drug level in the blood. First is controlling the rate of drug absorption and the second approach is controlling the rate of drug excretion. Implants and parenteral injections are the most commonly used drug delivery systems, which can release drugs longer than 1 week. Drugs delivery for more than 1 year can be obtained with various implant systems, and the longest delivery of drug can be obtained by nonbiodegradable or biodegradable implant.

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Received: 19-09-2016
Revised: 01-10-2016
Accepted: 08-10-2016

Few advantages offered by parenteral controlled release systems are as follows:[7,8]

1. It maintains a high drug concentration in the blood or prolongs the duration of drug action
2. Improved drug pharmacokinetics
3. Improvement of physical stability
4. Decrease in side effects by achieving a constant drug level via parenteral depot systems
5. Reduction in systemic adverse effects and increase in specificity for targeted drug delivery
6. A chance to control a specific rate of drug release
7. Improved patient compliance
8. More uniform effect.

ROUTES OF ADMINISTRATION FOR CONTROLLED RELEASE INJECTABLES

Parenteral drug delivery systems have various routes of administration such as intravenous, subcutaneous, intraperitonial, intraethical, intradermal, intramuscular, intracutaneous, intra-arterial, intraspinal, and intracardiac. To achieve the longer release pattern of injectable formulations, subcutaneous and intramuscular routes are highly used.[3,9] Many factors need to be considered in determining the injectable route of administration for long-term delivery of drugs, such as ease of administration, area for target injection sites, safety profile, cost of therapy, patient's limited mobility, and quality of life.

DESIRABLE CHARACTERISTIC OF IDEAL PARENTERAL DRUG CARRIERS[10]

1. Versatile
2. High capacity to carry a sufficient quantity of drug
3. Uniform distribution
4. Restricting drug activity at the target site over a prolonged period
5. Protecting drug from inactivation by plasma enzymes
6. Biocompatible and minimal antigenic
7. Undergoing biological degradation with minimal toxicity

TYPES OF PARENTERAL CONTROLLED RELEASE FORMULATIONS

Parenteral controlled release formulations are of following types.[11]

A. Injectables
    1. Solutions
    2. Dispersions
    3. Microspheres and microcapsules
    4. Nanoparticles and niosomes
    5. Liposomes and pharmacosomes
    6. Resealed erythrocytes
    7. *In situ* forming implants (ISFIs)
B. Implants
C. Infusion device
    1. Osmotic pumps (Alzet)
    2. Vapor pressure powered pumps (infusaid)
    3. Battery powered

Injectable solution

Both aqueous as well as oil solution may be used for parenteral controlled drug release. With the aqueous solutions, the drug release may be controlled by increasing the viscosity of vehicle by use of methylcellulose (MC), carboxy MC, and polyvinylpyrrolidone and thus decreasing the molecular diffusion and localizing the injected drug.[11,12]

Injectable suspension

Injectable suspensions are heterogeneous and dispersed system having excipients and insoluble drug molecules which need to be redispersed or resuspended before administering to patient.[3] Injectable suspensions are either being formulated as reconstitution before use or as ready to use injection. The formulation of stable suspension mainly involves use of high solid content and/or increased viscosity of the system. However, most parenteral suspensions are usually dilute and have particles limitation for viscosity because of syringeability and injectability constraints.[13] Lecithin, polysorbate 20, polysorbate 80, pluronic F-68, and sorbitan trioleate are used as surfactant in injectable suspension.[14]

Injectable emulsion

They could be administered by intravenous, intra-arterial, intrathecal, intraperitoneal, intraocular, intramuscular, or subcutaneous injection.[15] The development of parenteral emulsion continues to play an important role in formulation and delivery of many drugs.[16] An emulsion formulation can avoid the use of conventional cosolvent systems and associated undesirable effects caused by precipitation of the drug at the injection site, as seen in case of anticancer drug taxol.[17,18] Parenteral emulsions are the best known as a source of calories and essential fatty acids for the nonambulatory patients, but significantly their physical properties and low toxicity make them excellent vehicle for the formulation and delivery of drugs with a broad range of application.[19,20] Investigators continue to study the various types of spans and Tweens that are approved by the various pharmacopoeias for parenteral administration and have been included in the parenteral emulsion formulation.[21] In recent years, the concept of tailored emulsion for delivery of oil-soluble lipophilic compound has gained significant attention in the field of parenteral drug delivery.[22] Parenteral delivery of the hydrophobic drugs is a very

challenging task. Microemulsions have evolved as a novel vehicle for parenteral delivery of the hydrophobic drugs.[23] Parenteral emulsion is special o/w emulsion used to feed patients whose medical condition makes them unable to eat normally.[24]

Microspheres

The most crucial factor in the design of injectable microspheres is the choice of an appropriate biodegradable polymer. The release of the drug molecule from biodegradable microspheres is controlled by diffusion through the polymer matrix and polymer degradation. It is thought that the more hydrophilic polyethylene glycol (PEG) may improve the affinity of protein for the matrix polymer and lead to better entrapment efficiency.[25,26] Polymer molecular weight can affect polymer degradation and drug release rates. As one might expect, an increase in molecular weight decreases diffusivity, and therefore, drug release rate.[27-30]

Microcapsules

To avoid the inconvenient surgical insertion of large implants, injectable biodegradable and biocompatible polymeric particles (microspheres, microcapsules, nanocapsules, and nanospheres) could be employed for controlled release dosage forms.[31,32] The polymers selected for the parenteral administration must meet several requirements such as biocompatibility, drug compatibility, suitable biodegradation kinetics and mechanical properties, and ease of processing.[33] Controlled-release microcapsules offer several profound advantages over conventionally administered medicaments.[34] It is reported that microcapsules obtained by the solvent extraction-solvent evaporation procedure have a relatively poorer quality, as compared with those obtained by solvent evaporation-solvent extraction.[35]

Nanoparticles

Nanoparticles are colloidal solid particles, having size in range of 10-1000 nm. Nanoparticles have been actively examined as carriers for drug delivery system, which make it possible to improve therapeutic efficacy and to suppress side effects of the parent drug.[36-40] Recently, polymeric nanoparticles are also applied as carriers for contrast agents in the field of *in vivo* imaging.[41-43] Parenteral application is a very wide field for solid lipid nanoparticles. Subcutaneous injection of drug loaded solid lipid nanoparticles can be employed for commercial aspect, e.g., erythropoietin and interferon-β.[44] Currently, the polymeric nanoparticles are receiving much consideration. Optimization of size of nanoparticles can be done easily, which is helpful in penetration through fine capillaries, crossing the fenestration into interstitial space, and cellular uptake via phagocytosis/endocytosis.

Niosomes

Niosomes are very small and microscopic in size. Their size lies in the nanometric scale. Niosomes are formed mostly by cholesterol incorporation as excipients.[45] Niosomes are the vesicles devised by using nonionic surfactants.[6,46] Niosomes can deliver targeted drug delivery of drug directly to the specific site where therapeutic effect is needed.[47] It consists of cholesterol to provide rigidity to the vesicles and proper shape.[48] They are prepared using nonionic surfactants such as polyglycerol alkyl ethers, gluosyl dialkyl ethers, polyoxyethylene alkyl ether, brij, span series, and Tween series.[49] Niosomes can entrap both hydrophilic and lipophilic drugs in aqueous layer and vesicular membrane, respectively.[50] Niosomes containing anticancer drugs, if suitably designed, will be expected to accumulate within tumors in a similar manner to liposomes. The niosomal encapsulation of methotrexate and doxorubicin increases drug delivery to the tumor and tumoricidal activity of the drug.[51]

Liposomes

Liposome is a spherical vesicle with a membrane composed of a phospholipid bilayer used to deliver drug or genetic material into a cell.[52] These microscopic vesicles get hydrated when comes in contact with water and formation of liposomes takes place.[53,54] It comprises one or more concentric lipid bilayer, consisting an aqueous portion within its inner region.[55] Liposomes as pharmaceutical drug carriers were developed to increase antitumor efficacy and decrease drug toxicity. Doxorubicin HCl liposomal injection was the first liposomal encapsulated anticancer drug to receive clinical approval.[56] Liposomes may act as a solubilization matrix, as local depot for controlled release of active compound, as permeability enhancer, or as rate limiting membrane barrier for the modulation of systemic absorption of drug through the skin.[57-60] Present applications of the liposomes are in the immunology, dermatology, vaccine adjuvant, eye disorders, brain targeting, infective disease, and in tumor therapy.[61-63]

The use of liposomes as anticancer drug delivery system was originally hampered by the realization that liposomes are rapidly cleared form the circulation and largely taken up by the liver macrophages.[64]

Resealed erythrocytes

These are fully biodegradable, biocompatible, and nonimmunogenic. There is protection of the drug from enzymatic inactivation.[65] There isolation is easy and large amount of drug can be loaded with prolong systemic activity of drug by residing for a longer time in the body.[66]

Application of erythrocytes as promising slow drug release or site-targeted delivery systems for a variety of bioactive

agents from different fields of therapy has gained a remarkable degree of interest in recent years.[67] Remarkably, longer life-span of the carrier erythrocytes in circulation in comparison to the synthetic carriers.[68-70] Erythrocytes have been used as circulating intravenous slow-release carriers for the delivery of antineoplasms antiparasitics, antiretroviral agents vitamins, steroids, antibiotics, and cardiovascular drugs.[71-77] In a hypotonic medium, if red blood cells (RBCs) are added, swelling of RBC occur which results in rupturing of membrane and development of pores. Encapsulation of 25% of the enzyme or drug in solution takes place. By restoring the tonicity of the solution, the membrane is resealed.

ISFIs

In the area of parenteral controlled release formulations, ISFIs are attractive alternatives to preformed implants and microparticles. ISFI avoid the use of large needles or microsurgery, and they can be manufactured in simple steps with a low requirement of equipment and processes. They are injected as low viscous solutions and transform in the body to a gel or solid depot.[78] Injectable ISFIs are classified into five categories, according to their mechanism of depot formation: (1) Thermoplastic pastes, (2) *in situ* cross-linked systems, (3) *in situ* polymer precipitation, (4) thermally induced gelling systems, and (5) *in situ* solidifying organ gels.[79] The ability to inject a drug incorporated into a polymer to a localized site and have the polymer form a semi-solid drug depot has a number of advantages. Among these, advantages are ease of application and localized, prolonged drug delivery. For these reasons, a large number of *in situ* setting polymeric delivery systems have been developed and investigated for use in delivering a wide variety of drugs.[80]

Injectable *in situ* forming depots (ISFD) that contain a peptide or a protein within a polymeric solution comprise an attractive but challenging application system. Beyond chemical compatibility, local tolerability, and acute toxicity, an important factor for an ISFD is its storage stability as a liquid.[81] Intratumoral injection of taxol or application of the paste within tumor resection sites are examples for the thermoplastic paste approach.[82]

DRUGS DELIVERED AS SUSTAINED/ CONTROLLED RELEASE INJECTABLES

Few examples of drugs for controlled release injectable delivery systems are showed in Table 1.[9]

Different polymers used in injectable controlled release formulations

Different types of polymers which are used for the formulation of controlled release injectable preparations are depicted in Table 2.[83-85]

Table 1: Examples of drugs for controlled release injectable delivery systems

Class	Drugs
Post-operative pain therapeutic agents	Ketorolac tromethamine
Recombinant human bone morphogenetic protein-2	Superoxide dismutase, salmon calcitonin, insulin
Gene delivery	Plasmid DNA
Protein therapeutics	Analog of glucagon-like peptide-1
Drugs to treat alcohol dependence	Naltrexone
Schizophrenia drugs	Aripiprazole, olanzapine
Immunosuppressive drugs	Rapamycin
Hormone therapy	Human somatropin
Cancer therapeutic agents	Bleomycin, paclitaxel, cisplatin

Examples of few marketed products of parenteral controlled release drug products are given in Table 3

In-vitro testing of parenteral depot formulation

A variety of methods have been used for *in vitro* release testing of controlled release parenterals. Currently used methods for *in vitro* release testing from these dosage forms can be broadly divided into three categories: (1) Membrane dialysis methods (such as dialysis sac), reverse dialysis sac, microdialysis, and Franz-diffusion cells, (2) sample and separate methods (vial/tube/bottle method) with centrifugation or filtration after sampling, and (3) flow-through cell methods (USP apparatus 4).[86] The rotating dialysis cell was assessed as an *in vitro* release method to be used in formulation development work and quality control of parenteral oily depot solutions.[87]

FUTURE SCOPE

The unique advantages possess by injectable controlled drug delivery system offers potential commercial success of these pharmaceutical products that have novel active pharmaceutical ingredients.[1] Recently, in the market, the launch of number of controlled release injectables products is increased, and long-term drug delivery injectable depot systems are become the most efficient systems. In the near future, more sophisticated injectable depot systems will be expected to be developed and commercialized with the advancement in polymer science and drug formulation. Formulation scientists are focusing on development and optimization of nanotechnology devices for the delivery of high potency drugs. In pharmaceutical dosage forms, injectable controlled drug delivery is attaining dominance in

Table 2: List of polymers used in injectable controlled release formulations

Name of polymers
PLA
PGA
PLGA
PCL
Polyglyconate
Polyanhydrides
Polyorthoesters
Poly (dioxanone)
Polyalkylcyanoacrylates
PHB
Poly (ethylene glycol) (PEG)
Poly (propylene glycol) (PPG)
PEG-grafted chitosan polymer (Chitosan–PEG)
N-(2-(dimethylamino) ethyl)-methacrylamide) and Concanavalin A
PCL-PEG-PCL triblock copolymer
Poly (DL-lactide)
Polyurethan
Poly (hexamethylene adipamide)
Polycarbonate
Poly (phosphoesters)
Poly (phosphazenes)
Poly (peptide)
PLGA-PEG-PLGA triblock copolymer
Poly ethyl polyalkyl cynoacrylates
Poly (2-hydroxy ethyl methacrylate)
Poly(N-vinyl pyrrolidone
Poly (vinyl alcohol)
Poly (acrylic acid)
Poly (methyl methacrylate)
Ploy acryl amides
PHA
Poly (L-lactide)
Poly (lactide-co-glycolide)
Poly (cyanoacrylate)
Starch
Gelatin
Hemoglobin
Dextran
Albumin
Collagen

PLA: Polylactides, PGA: Polyglycolides, PLGA: Poly (lactide-co-glycolide), PCL: Poly(ε-caprolactone), PHB: Poly-[(*R*)-3-hydroxybutyrate], PEG: Polyethylene glycol, PHA: Poly (hydroxyalkanoates)

Table 3: Examples of parenteral controlled release drug products

Drug	Formulation
Olanzapine	Suspension
Fluphenazine	Sesame oil solution
Paliperidone	Nanosuspension
Flupentixol	Vegetable oil solution
Haloperidol	Sesame oil solution
Risperidone	Suspension
Naltrexone	Suspension
Leuprolide	Suspension/*in situ* microparticles
Methylprednisolone acetate	Suspension
Medroxyprogesterone acetate	Suspension
Testosterone	Cotton seed oil solution
Goserelin	Polymer implant
Exenatide	Suspension
Amphotericin	Liposome
Doxorubicin	Liposome
Etonogestrel	Implant
Abarelix	CMC complex
Doxorubicin	Lipid complex
Triptorelin	Microparticles
Somatropin	Microparticles
Buserelin	Solid implant
Carmustine	Targeting solid implant
Doxycycline	*In situ* implant
Octreotide	Microparticles

CMC: Carboxy methyl cellulose

market and becoming the fastest growing field demands its availability in lower prices.

CONCLUSION

Approximately, 15% of the current drug delivery market is injectable products. Long-acting parenteral drug formulation is designed ideally to provide slow, constant, and sustained release of drug over a prolong period, essentially to stimulate and replace the more hazardous, continuous intravenous infusion of a drug. Rarely, if ever, is the ideal achieved, but extensive research has resulted in depot dosage form that approaches the desired goal. So, many injectable sustained and controlled release products have received regulatory approval and launched in the pharmaceutical market.

Several chemosynthetic biodegradable and natural polymers are used in injectable microspheres techniques, for example, poly amino acid, gelatin, and hemoglobin. Poly lactic acid and co glycolic acid received approval from FDA to be used

as biomedical material due to its *in vivo* biodegradability. Propylene fumarate found to be an ideal biomaterial with no toxicity, cellular affinity, and sustained release behavior, used in repairing bone defects. Formulation scientists are trying to improve the sustained release effect of liposomes using some auxiliary material like PEG grafting on the chitosan. Efforts are also put forth to push the *in situ* forming gel to a broader field, i.e., formulation of a temperature and pH sensitive hydrogel as a sustained injectable insulin delivery system. Hydrogel as drug delivery system can be very promising material if combined with the technique of molecular imprinting.

Advances in the method of formulation and availability of novel polymers are resulting in commercial successes of controlled release products. To address the unmet needs in new drug delivery systems, the parenteral controlled release products have been evolved specifically.

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Source of Support: Nil. **Conflict of Interest:** None declared.