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Review article

Advanced injectable drug delivery system: A brief review

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Abstract

In modern therapeutics the controlled/sustained release dosage forms have become extremely popular. Development of sustained release injectable has occurred in the past few years. This was brought into existence to prolong the effect of drug at targeted site. This advancement also offers reducing dosing frequency, maximizing the efficacy dose relationship, decreasing adverse side effects and enhancing patient compliance. The Parenteral administration route is the most common and efficient for delivery of active drug substances with poor bio-availability and the drugs with a narrow therapeutic index. But parenteral route offers rapid onset of action with rapid declines of systemic drug level. For the sake of effective treatment it is often desirable to maintain systemic drug levels within the therapeutically effective concentration range for as long as treatment calls for. It requires frequent injection, which ultimately leads to patient discomfort. For this reason, drug delivery system which can reduce total number of injection throughout the effective treatment, improve patient compliance as well as pharmacoeconomic. Parenteral drug delivery with intravenous, subcutaneous or intramuscular injection can gain easy access to systemic circulation with rapid drug absorption. For the sake of effective treatment it is often desirable to maintain systemic drug levels within the therapeutically effective concentration range for as long as treatment calls for. This review focused on the brief discussion on the latest injectable controlled released dosage forms.

Key words: Parenteral drug delivery, Microspheres, Nanoparticles, Liposomes, Microcapsules

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1. Introduction

2.

Parenteral preparation is sterile preparation containing one or more active ingredients intended for administration by injection, infusion, or implantation into the body [1]. Parenteral preparations may require the use of excipients such as solvents, substances to enhance solubility, suspending agents, and buffering agents, substances to make the preparation isotonic with blood, stabilizers or antimicrobial preservatives [2]. Water for injections is used as the vehicle for aqueous injections [3]. Parenteral drug delivery refers to administration by injection which takes the drug directly into the tissue fluid or blood without having to cross the intestinal mucosa [4]. To avoid problems from conventional systems, parenteral controlled-release drug delivery systems are designed to achieve consistent, predictable or desired drug release profiles [5]. The main rationale behind the development of novel delivery systems is either to sustain the drug release or to maintain the effective drug concentration with reduced adverse effects. Suspensions, emulsions, liposomes, micro particles and implants are identified as parenteral controlled release drug delivery systems [6]. The most commonly used drug-delivery systems, which can release drugs longer than one week, are parenteral injections and implants. Advantages and disadvantages of parenteral controlled-release over conventional drug delivery systems are discussed below [7-8].

Advantages:

1. Improved patient convenience and compliance.
2. Reduction in fluctuation in steady-state levels.
3. Increased safety margin of high potency drugs.
4. Maximum utilization of drug.
5. Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing.

Disadvantages:

1. The dosage form must be administered by trained personnel and require more time than those administered by other routes.

2. Parenteral administration requires strict adherence to aseptic procedures, and some pain on injection is inevitable.
3. It is difficult to reverse its physiological effect.
4. The manufacturing and packaging requirements, parenteral dosage forms are more expensive than preparations of given by other routes.

Classification of Parenteral Controlled Drug Delivery System [9-11]**:**

A. Injectables
1. Solutions
2. Colloidal Dispersions
3. Microspheres
4. Microcapsules
5. Nanoparticles
6. Niosomes
7. Liposomes
8. Resealed erythrocytes
9. Polymeric Micelle
10. In situ forming implants

B. *Solid Implants*

C. *Infusion Device*
1. Osmotic Pumps (Alzet)
2. Vapor Pressure Powered Pumps (Infusaid)
3. Battery Powered

Injectable suspension:

To achieve a pharmaceutically acceptable suspension, injectable suspension should maintain their sterility, pyrogenicity, resuspendibility, syringe ability, stability and isotonicity [12]. They should be either being formulated as ready to use injection or as reconstitution prior to use. Suspensions should usually contain solids between 0.5- 5% having particle size less than 5 micrometer for I.M or S.C. administration. Probably the most important requirement for the parenteral suspension is a small and uniform particle size. Subcutaneous administration of a drug as an aqueous or oil suspension results in the formation of a depot at the injection site. The depot act as a drug reservoir, slowly releasing the drug continuously at a rate dependent upon both the intrinsic aqueous solubility of the drug and the dissolution of the drug particles into tissue fluid surrounding the drug particle in the subcutaneous tissue [13].

Injectable solutions:

Injectable solutions are available in two form i.e. aqueous and oil. In aqueous solutions viscosity of vehicle is increased, hence the diffusion coefficient of drug is reduced and localization of injected volume is achieved causing reduction in absorptive area. Gelling agents like aluminium monostearate is added in oil solutions. In oil solutions the drug release is controlled by partitioning of drug out of the oil in to the surrounding aqueous medium.

Injectable emulsion:

An emulsion is a thermodynamically unstable dispersion of two or more immiscible liquids stabilized by a surfactant or emulsifier coating the droplets and prevents coalescence by reducing interfacial tension or creating a physical repulsion between the droplets [14]. Mostly, injectable emulsions are oil-in-water emulsion. They are milky white in appearance and have an average globule size of 1 micrometer to 5 micrometer. The principal problem in the formulation of a parenteral emulsion is the attainment and maintenance of uniform oil droplets of 1to 5 microns in size as the internal phase [15]. The emulsion must be stable to autoclaving. Elevated temperature, however tend to produce coalescence of the dispersed phase, and excessive shaking has caused acceleration of rate of creaming. Emulsions are primarily used for parenteral nutrition and infused intravenously [16]. These are terminally sterilized with the sterilization cycle designed to maintain globule size distribution [17].

Microspheres:

It can be defined as the reservoir type system in which micron size (tiny particles) core material/internal phase (may be solid, liquid or gas as drug, cell, microorganism, proteins or peptides, enzymes, hormones etc.) is enclosed in a thin layer of wall/ shell material/external material (usually polymer) using a suitable microencapsulation method [18]. 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 [19]. The nature of the polymer, such as composition of copolymer ratios, polymer crystallinity, glass-transition temperature, and hydrophilicity plays a critical role in the release process. Although the microspheres structure, intrinsic polymer properties, core solubility, polymer hydrophilicity, and polymer molecular weight influence the drug-release kinetics [20]. The possible mechanisms of drug release from microsphere are as follows: initial release from the surface, release through the pores, and diffusion through the intact polymer barrier, diffusion through a water swollen barrier, polymer erosion, and bulk degradation [21]. All these mechanisms together play a part in the release process [22].

Microcapsules:

Micro capsules are spherical particles containing drug concentrated in the center core. The coating material can be selected from a wide variety of natural and synthetic polymers. These are depending on the material to be coated. Nylon, dipolylactic acid, albumin, and cross linked starch are the examples of polymers used in preparation of micro capsules [23]. Microcapsules differ from microspheres in having a barrier membrane surrounding a solid or liquid core, which is an advantage in case of peptides and proteins. Microspheres can be used for chemoembolization of tumors in which the

vasculature is blocked while anticancer agent is released from the trapped microparticles [24].

Nanoparticles:
These are solid, colloidal particles and consist of macromolecular materials [25-26]. Presently the polymeric nanoparticles are attracting much attention [27]. Their sizes can be easily optimized for penetrating through fine capillaries, crossing the fenestration into interstitial space, and efficient cellular uptake via endocytosis/ phagocytosis [28-29]. Furthermore, they can be equipped with a hydrophilic surface, for example, with a layer of poly(ethylene glycol) (PEG), to evade the recognition and subsequent uptake by the reticuloendothelial system (RES), and thus to have a circulation time that is long enough for passive accumulation in cancer tissues via the EPR effect [30-31]. Injectable nanoparticulate dosage forms can be classified into three main categories: (i) crystalline drug nanosuspensions, wherein the drug is available in a stable crystalline form; (ii) polymeric nanoparticles, wherein the drug is encapsulated within a polymer matrix in an amorphous state; and (iii) solid lipid nanoparticles, wherein the drug is encapsulated within a lipid matrix in an amorphous state.

Niosomes:
Niosomes are the highly ordered vesicular structure with bilayer membrane made up of Non-ionic surfactant with or without incorporation of cholesterol [32-33].The closed bilayer vesicular structure of niosome, formed by the self assembling of non ionic surfactants in presence of aqueous media. Although they structurally similar to liposomes [34]. Niosomes consist of hydrophilic tails of monomers of surfactant shielded away from the central aqueous core and hydrophilic head zone. Addition of cholesterol in the formation of niosomes provided the rigidity to the bilayer and thus results in limited drug leakage from them [35]. These vesicles are generally referred to as second generation vesicles possessing improved chemical stability, better entrapment efficacy, enhanced penetration as well as lower production cost as compare to the liposomes. Targeted drug delivery can also be achieved by using niosomes as drug is directly delivered to the specific site where therapeutic effect is desired [36].

Liposomes:
Liposomes are small, spherical, bilayer phospholipid vesicles. They are amphipathic in nature, so can transport both hydrophilic and hydrophobic drugs. They are extensively used as carrier for numerous cosmetic and pharmaceutical industries [37]. Because of their biocompatibility, biodegradability, low toxicity, and aptitude to trap both hydrophilic and lipophilic drugs and simplify site-specific drug delivery to tumor tissues, liposomes have increased rate both as an investigational system and commercially as a drug- delivery system. These microscopic vesicles comprising phospholipid bilayer, which when comes in contact of water, gets hydrated and results in the formation of liposomes [38]. These lipid vesicles are composed of mainly phospholipid with or without using additives [39]. Liposomal encapsulation technology (LET) is the newest delivery technique used by medical investigators to transmit drugs that act as curative promoters to the assured body organs [40]. Liposomes have an ability to protect the encapsulated drug from external environment, exhibits sustained release of drug [41]. Liposome technology has been hindered by problems including purity of lipid components, possible toxicity, vesicle heterogeneity and stability, excessive uptake and manufacturing or shelf-life difficulties [42].

Resealed Erythrocytes:
Red blood cells (RBCs) have been studied the most of all the cellular drug carriers [43]. When RBCs are placed in a hypotonic medium, they swell, leading to rupture of the membrane and formation of pores [44]. Resealed erythrocytes are biodegradable and nonimmunogenic [45]. They can be modified to change their resident circulation time, depending on their surface; cells with little surface damage can circulate for a longer time. The entrapped drug is shielded from immunological detection and external enzymatic degradation. In resealed erythrocytes entrapment of wide variety of chemicals are possible, released with zero order kinetic [46]. Resealed erythrocytes offers prolong systemic activity of drug by residing for longer time in the body. Antineoplastic drugs such as methotrexate, bleomycin, asparginase and adiramycin have been successfully delivered by erythrocytes [47].

In Situ Forming Implants:
In situ forming implants based on a drug containing polymer semi solid or solution, which after entering into the body undergo chemical or physical change to form a unit implant for the controlled drug delivery [48]. Injectable in situ forming implants are classified into five categories, according to their mechanism of depot formation as follows [49]:

1) Thermoplastic pastes
Polymers with low melting point can be instilled into body as a melt and form depot upon cooling to the body temperature. The melting point or glass transition temperature of the polymers should fall in range from 25-65 °C and the intrinsic viscosity of the polymers should be in range from 0.05 to 0.8 dl/g (25 °C). Before injecting into body, the polymers are gently heated above their melting point. The drug is admixed with molten polymers without application of solvents. Original theroplastic pastes are formulated from monomers such as D, L-lactide, glycolide, dioxanone, ε-caprolactone, trimethyl carbonate [50]. The admixing of drug in this system can be achieved by simple mixing at room temperature without using any organic solvent.

2) In situ cross linked systems
The formation of solid polymers or gels is achieved by in situ cross-link of the introduced macromers. It is initiated by the reaction involving photon absorption or ionic

interaction between multivalent anions and cation macromers. The advantage of this system involves rapid polymerization rates at physiological temperature due to photo initiated reaction.

3) In situ solvent removal system

The method of in situ solvent removal systems depends on the phenomena of solute precipitate from the solution by solvent removal. It could be further classified into three techniques.

i. Atrigel

ii. Alzamer (base on biodegradable PLA/PLGA polymer)

iii. Saber (uses non-polymer sucrose acetate isobutyrate as drug carrier)

4) Thermally induced gelling system

This system is based on polymers that undergo abrupt changes in solubility in response to the variation in environment temperature. Triblock copolymer PEG-PLA-PEG has been also applied in thermally gelling system and are claimed to have good biodegradability and biocompatibility. The aqueous solution of polymer have low viscosity at room temperature but once enters the body, it turns into a gel with very high viscosity. However, similar to other gel forming system, when a polymer undergoes gelation, it contracts and reduces its volume. This lead to diffusion of encapsulated drug out of the gel and hence a high initial release [51].

5) pH induced gelling system

Acidic solutions of chitosan when subjected to alkaline pH form viscous gels. The in situ gel formation has been employed for controlled delivery of several drugs via oral or parenteral routes. A polymer complex of polyethylene (PEG) and polymethacrylic acid (PMA) or polyacrylic acid (PAA) has also been known as a pH sensitive gelling system [52].

Conclusion

Targeted and controlled drug release is an effective approach in avoidance of hepatic first pass metabolism, rapid onset of action, better patient compliance, enhancement of bioavailability etc. Hence there is a need to develop novel drug delivery systems in order to achieve better drug performance.

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