REVIEW ARTICLE

A REVIEW: PARENTRAL DEPOT DRUG DELIVERY SYSTEM

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ABSTRACT
In recent years, considerable attention has been focused on the development of drug delivery system. There are number of reasons for the intense interest in new system. Recognition of the possibility of repeating successful drugs by applying the concepts and techniques of controlled release parenteral depot formulation drug delivery systems coupled with the increasing expense bringing new drug entities to market has encouraged the development of new drug delivery system. New systems are needed to deliver the novel, genetically engineered pharmaceuticals, i.e. peptides and proteins to their site of action without incurring significant immunogenic or biological inactivation. Treating enzyme deficient disease and cancer therapies can be improved by better targeting. Therapeutics efficacy and safety of drugs, administered by conventional methods, can be improved by more precise spatial and temporal placement within the body. Thereby reducing both size and number of doses.

KEYWORD: Depot, Parenteral injection

INTRODUCTION
Primarily due to the steadily increasing number of biotechnology-derived drugs, parenteral depot formulations and their drug delivery technologies have received much attention in recent years. For many compounds which cannot be administered via the oral route, injectable or implantable depot formulations are presently the only viable option for reducing the frequency of administration, thereby increasing patient convenience and potentially improving compliance. Depot formulations have been developed for a broad range of applications, providing therapeutic effectiveness over periods ranging from one day to several years. A significant patient benefit, which should be the driving force for initiating the development of any depot formulation, not only requires that the dosing frequency can be substantially reduced in comparison with the corresponding standard formulation, but also that dosage form-related risks, such as dose dumping or poor carrier tolerability, are largely avoided.

The Parenteral administration route is the most effective and common form of delivery for active drug substances with metabolic bio-availabilities drug for which the bio-availability in limited by high first pass metabolism effect of other physicochemical limitation and for drugs with a narrow therapeutic index. For this reason, whatever drug delivery technology that can reduce the total number of injection throughout the drug therapy period will be truly advantageous not only in terms of compliance, but also for potential to improve the quality of the therapy. Such reduction in frequency of drug dosing is achieved, in practice, by the use of specific formulation technologies that guarantee that the release of the active drug substance happens in a slow and predictable manner[1].
For several drugs, depending on the dose, it may be possible to reduce the injection frequency from daily to once or twice monthly or even less frequently. In addition to improving patient comfort, less frequent injection of drugs in the form of depot formulation smooths out the plasma concentration time profiles by eliminating the peaks and valleys. Such smoothing out of the plasma profiles has the potential to not only boost the therapeutic benefit but also to reduce unwanted events and side effects.

1.1 Introduction of Depot
Long acting parenteral drug formulation are designed, ideally to provide slow constant, sustained, prolonged action. A depot injection is an injection, usually subcutaneous or intramuscular, of a pharmacological agent which releases its active compound in a consistent way over a long period of time. Depot injections are usually either solid or oil-based[2].

1.2 Injection site for depot
Various challenges are classified under the general heading of “injection site”. It is recognized that the dose to be administered will have implications on the formulation injected. A drug with high potency can be given in smaller amounts than a drug with low potency. The size limit for solid implants appears to be a thickness of micrometers to millimeters and length of millimeters to several centimeters. Alternatively, systems can be administered as micro particulate systems or solutions that undergo a physical change at the injection site to form an implant in situ. The limits for the amount of material that can be administered by injection are less well defined but will still be subject to injectability issues relating to the ease of flow of the formulation through appropriate sized needles and acceptance of the injected material by the host tissues. Consideration of the normal structure and physiology of subcutaneous and intramuscular sites will give information that may be useful in defining the limits of formulation morphology.

1.3 Intramuscular injection is the injection of a substance directly into a muscle. In medicine, it is one of several alternative methods for the administration of medications. It is used for particular forms of medication that are administered in small amounts. Depending on the chemical properties of the drug, the medication may either be absorbed fairly quickly or more gradually. Intramuscular injections are often given in the deltoid, vastus lateralis, ventrogluteal and dorsogluteal muscles. Intramuscular injections are made deeper into the skeletal muscle underlying the subcutaneous layer. In all species the basic unit of this tissue is the muscle fibre. These are long cylindrical structures that contain numerous nuclei encased in a plasma membrane or the sarcolemma. The muscle fibres are organized into bundles or fasciculi of varying sizes. Complete muscles contain many fasciculi and are attached to the skeleton via tendons. Connective tissue surrounds the muscle fibres and is classified by location within the muscle. Connective tissue that surrounds individual muscle fibres is called the endomysium, which surrounding the fasciculi is the perimysium and the epimysium surrounds the whole muscle. Two separate blood circulations flow through the muscle tissues. These are the nutritive supply that flows through an extensive capillary network in the endomysium while the non-nutritive pathway flows in mainly in larger vessels through the perio- and epimysium with only a few capillaries. The lymphatic system starts in capillaries within the perio- and epimysium that drain into regional lymph nodes. The lymphatic vessels do not appear to enter the endomysium.
**1.4 Subcutaneous injection** is administered as a bolus into the subcutis, the layer of skin directly below the dermis and epidermis, collectively referred to as the cutis. Subcutaneous injections are highly effective in administering vaccines and such medications as insulin, morphine, diacetylmorphine or goserelin.

Subcutaneous injections are made under the skin (Fig. 1.3). By lifting the skin as shown in, and inserting the needle through the folded skin, the aim is to deliver the injection into the space between the dermis and the underlying subcutaneous fat layer.

In many species, subcutaneous injections are made into the area around the skin is loose and the subcutaneous site is more easily targeted. Examination of the skin structure shows the characteristic layers of epidermis, dermis and adipose tissue. Of interest in subcutaneous injections are the compositions of the reticular layer of the dermis and adipose layers as injection may result in deposition in these sites. The dermis is divided into two regions: the thin superficial
papillary layer (20% depth) and the deeper reticular layer (80% depth). Connective tissue of the dermis consists of cellular components (fibroblasts, macrophages, lymphocytes, mast cells, neutrophils and eosinophils) surrounded in a matrix of high molecular weight materials (collagen, elastin, glycoproteins, proteoglycans and polysaccharides) water, salts and other diffusible substances. In the papillary layer there is a loosely woven mat of fibres that is rich in blood capillary loops. The reticular layer is denser with bundles of collagen fibres that are thicker than those in the papillary layer and are interlace to form a strong yet deformable three-dimensional network. Underlying the dermis is the layer of subcutaneous adipose tissue, comprising predominantly fat cells with few blood and lymphatic vessels. In the dermis layer, an extensive capillary network (the reticular plexus) exists in the papillary layer and around the glands, hair follicles and nerve supply of the dermis. Other areas of the deeper layers of the dermis have relatively few capillaries as this area has low metabolic demands due to the low density of cells in the area. The lymphatic system of the skin comprises a numerous supply of lymph capillaries in the reticular layer which drain into plexuses in this layer then into deeper lymphatics.

The main site are -The outer area of the arm, Just above and below the waist, except the area right around the navel (a 2-inch circle),The upper area of the buttock, just behind the hip bone, The front of the thigh, midway to the outer side, 4 inches below the top of the thigh to 4 inches above the knee.

1.5 Drug absorption from intramuscular and subcutaneous injection sites

The absorptive processes that occur on injection or implantation of systems into muscle or subcutaneous sites are summarized in Fig. 1.5. Differences in drug absorption rates at different injection sites can be attributed to factors such as the tissue composition, relative dispersal forces due to muscular contractions at intramuscular sites and abundance and flow rate of blood and lymphatic supplies. On injection into either muscle or subcutaneous sites the material forms a depot. The size, shape and nature of the depot formed is determined by a balance between variables such as the formulation composition, the total volume injected, rheological properties of the system, relative dispersal rates of the formulation components and forces due to tissue movement and muscular contraction.
Fig -3 possible pathways for absorption of drugs from Controlled release parenteral depot formulation at intramuscular or subcutaneous sites

To illustrate this, the shapes of subcutaneous depots formed on injection of systems with different aqueous solubilities and vehicle viscosities. A useful classification of injected delivery systems has been given by Washington et al. They classified intramuscular injections according to whether the rate limiting step in drug absorption was release of the drug from the delivery system or perfusion of the muscle by the blood. Muscle perfusion has a greater effect on the drug absorption rate, when injected drug is immediately available in the intercellular fluid following injection. In advanced CR-PDFs, the aim is to move control of the absorption to the delivery system, thereby reducing the potential for inter-injection and inter-animal variability caused by differences in injection site perfusion. If drug release is the rate limiting step in drug absorption, the rate of drug absorption from the injection site tissue (ka) should exceed the rate of drug release from the delivery system or depot (kr) (Fig.1.5). When drug is present at the injection site as a solid, Ballard and Nelson reported its absorption rate is predominantly dissolution kinetic rate controlled.

![Diagram](image)

Fig-4 Systemic absorption of drugs from extravascular injections showing rates of release from the delivery system or depot (kr) and absorption tissue capillaries (ka).

The development of new injectable drug delivery system has received considerable attention over the past few years. This interest has been sparked by the advantages this delivery system possess, which include ease of application, localized delivery for a site specific action, prolonged delivery periods, decreased body drug dosage with concurrent reduction in possible undesirable side effect common to most forms of systemic delivery and improved patient compliance and comfort. The release can either be continuous or pulsatile depending on the structure of the device and the polymer characteristics, continuous release profiles are suitable to generate on ‘infusion like’ plasma level time profile in the systemic circulation without the necessity of hospitalization.

**Factors Influencing the Design and Performance of depot delivery**

To establish criteria for the design of controlled release parenteral depot formulation products, a number of variables must be considered.
Reason for development of PDS (Parenteral Depot System)

1. No surgical removal of depleted system is required as it is metabolized in non toxicological by product.
2. The drug release from this system can be controlled by following
   • Diffusion of drug through the polymer
   • Erosion of the polymer surface with concomitant release of physically entrapped drug.
   • Cleavage of covalent bond between the polymer bulks or at the surface followed by diffusional drug loss.
   • Diffusion controlled release at the physically entrapped drug with bio adsorption of the polymer until drug depletion.

Advantage and Disadvantages

This interest has been sparked by the advantages these delivery systems possess, which include ease of application, localized delivery for a site-specific action, prolonged delivery periods, decreased body drug dosage with concurrent reduction in possible undesirable side effects common to most forms of systemic delivery, and improved patient compliance and comfort. Generally, parenteral depot systems could minimize side effects by achieving constant, ‘infusion-like’ plasma level time profiles, especially important for proteins with narrow therapeutic indices. A dose reduction resulting from the avoidance of peaks and valleys, as well as the enhancement of patient compliance by reducing the frequency of application, are further potential benefits.

(a) Convenience
(b) Compliance Potential for controlled release
(c) Avoiding the peak (risk of toxicity) at troughs (risk of ineffectiveness of conventional therapy)
   • Reducing the dosing frequency.
   • Increasing patient compliance.
(d) Improved drug delivery
(e) Flexibility

Disadvantages:

(a) Invasive
(b) Danger of device failure
(c) Limited to potent drug
(d) Commercial disadvantage
1.6 Injectable gels
More recently, depot formulations in the form of injectable gels have been developed. These gels, which may be understood as semisolid implants, are either injected as such or in the form of a viscous liquid which solidifies after injection at the site of administration ("in-situ gelling systems"). The solidification may be caused by an incorporated polymer which is desolvated either by the migration of a biocompatible solvent or through the thermal, ionic, or pH-conditions in the tissue.

1.7 Mechanism of in situ depot system
A solid implant is formed in situ from the liquid formulation (see figure a & b), and releases the drug over a specified period of time (see figure c). The implant biodegrades during this process so that it does not have to be removed after the drug is depleted. The only injectable gels for systemic use that have become commercially available so far are a series of 1, 3, 4, and 6 month depot formulations of leuprolide (Eligard®). Platform technologies for the formulation of such gels have been developed by several drug delivery companies such as by QLT formerly Atrix laboratories.

Fig-5 Formation of in situ depot
1.8 Types of in situ Depot system
Semi-solid biodegradable injectable in situ depot systems are divided into four categories based on the mechanism of achieving solidification in vivo:
1.1.7.1 Thermoplastic pastes,
1.1.7.2 In situ crosslinked systems,
1.1.7.3 In situ precipitation, and
1.1.7.4 In situ solidifying organogels.

1.9 In situ crosslinked systems
Crosslinked polymer networks can be formed in situ in a variety of ways, forming solid polymer systems or gels. Means of accomplishing this end include free radical reactions initiated by heat (thermosets) or absorption of photons, or ionic interactions between small cations and polymer anions.

1.10 Thermosets
Thermoset polymers can flow and be molded when initially constituted, but after heating, they set into their final shape. This process is often called “curing” and involves the formation of covalent crosslinks between polymer chains to form a macro molecular network. Reheating a cured polymer only degrades the polymer. This curing is usually initiated chemically upon addition of heat. In two US patents, Dunn et al. introduced the application of thermoset systems unfortunately; In particular, the reaction conditions for in vivo applications are quite stringent, including a narrow range of physiologically acceptable temperatures, requirement for nontoxic monomers and/or solvents, moist and oxygen-rich environments, the need for rapid processing, and clinically suitable rates of polymerization.

Mechanism: - This system is liquid outside the body and is capable of being injected via a syringe and needle and once inside the body, it cures. The multifunctional polymers in their thermosetting system were first synthesized via copolymerization of either D,L-lactide or L-lactide with e-caprolactone using a multifunctional polyol initiator and a catalyst (e.g., peroxides) to form polyol terminated liquid prepolymers. This prepolymer was then converted to an acrylic ester-terminated prepolymer. Curing the liquid acrylated terminated pre-polymer is initiated by the addition of either benzoyl peroxide or N,N-dimethyl-p-toluidine, prior to injection into the body. After introduction of initiator, the polymer system is injected and polymer solidification occurs. The estimated time of reaction is between 5 to 30 min. The advantages of using this system is its facile syringeability.

1.11 Photocrosslinked gels
Photopolymerizable, degradable biomaterials would provide many advantages over chemically initiated thermoset systems. In this approach, prepolymers are introduced to the desired site via injection and photocured in situ with fiber optic cables. This approach has many advantages. Photo initiated reactions provide rapid polymerization rates at physiological temperatures. Further, because the initial materials are liquid solutions or moldable putties, the systems are easily placed in complex shaped volumes and subsequently reacted to form a polymer of exactly the required dimensions. These characteristics have encouraged the investigation of using this system for tissue engineering orthopedic applications cell transplantation local drug delivery dentistry and tissue adhesion prevention.

Mechanism: - By exposing the mixture of macromers and photoinitiator to the light source, the macromer undergoes rapid crosslinking and forms a network. These networks can be used to entrap water-soluble drugs and enzymes and deliver them at a controlled rate. Use of an argon laser as a light source offers a greater depth and degree of polymerization, less time is required and an enhancement of the physical properties of the polymer is realized. These advantages are offset by reports that the increased polymerization caused by the laser results in increased shrinkage and brittle-ness of the polymer[4-5].
1.12 Ion-mediated gelation

Alginates are natural polymers, which have been widely investigated for drug delivery. Alginates conform a gel upon contact with divalent cations such as calcium ions. They can be used directly as a drug carrier or as a carrier of another delivery system such as liposomes. Liposomes are capable of increasing the local retention of liposome-entrapped drugs over that of free drugs. In order to overcome this problem, Cui et al. used thermally sensitive Ca-loaded hydrogel. Reproduced from Ref. 1,2-bis(palmitoyl)-glycerol-3-phosphocholine (DPPC) and 1,2-bis(myristoyl)-glycerol-3-phosphocholine (DMPC) were used to prepare both Ca-loaded and drug-loaded phospholipid vesicles. The molar ratio of DPPC: DMPC was adjusted to 9:1 to bring the melting point of the liposomes below body temperature. It is well known that the permeability of the phospholipid bilayers is strongly temperature dependent. At temperatures below the lipid chain melting transition, phospholipid bilayers are relatively impermeable to multivalent ions. However, phospholipid permeability has been shown to be several orders of magnitude higher at the melting temperature.

1.13 In situ polymer precipitation

Another strategy that has been utilized to produce an injectable drug delivery depot is the phenomenon of polymer precipitation from solution. This precipitation can be induced by solvent-removal, a change in temperature, or a change in pH.[6]

2. DISCUSSION

The aim of the study was to develop and physico-chemically characterized in situ injectable gel of haloperidol based on a block copolymer. Haloperidol, an older antipsychotic medication used to treat schizophrenia, is given as 1 to 2 mg doses 3 to 4 times per day. A long-term delivery system, which would maintain a steady state level of drug in the plasma, eliminates the potential for missed doses. The marketed formulation is available for haloperidol depot in oily bases with one month but doctors are not recommending much more because if any patient is not suitable for the drug then it is difficult to remove the dosage form and patient convenience may also affected. So, one week depot preparation of haloperidol was developed. Development of controlled release formulation of haloperidol can be advantageous, that can provide prolong release and increase efficacy of the dosage form advantageous for patient.

3. CONCLUSION

The results of in vitro studies demonstrate that the prepared systems characterized by sol-gel transition under the effect of temperature increase may be used as vehicles for active substance administered as direct intramuscular injection. Transition of the prepared formulations at physiological temperature ranges of the body makes possible their injection in the liquid state and subsequent jellification in situ providing a prolonged release of the active substance at the application site.

4. REFERENCES