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Sustained and controlled drug delivery: role of depot formulations in modern therapeutics

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Abstract

Depot formulations are innovative drug delivery systems designed to deliver the active pharmaceutical ingredient in a "sustained" or "controlled" manner, consequently aiding in the maintenance of a stable drug concentration level in the bloodstream. The depot formulations help in addressing a major obstacle in the clinical management and improvement of chronic illness, which is poor patient adherence and compliance to the lengthy treatment regimen. This article throws light on the background of depot formulations from how they evolved from simple oil-based solutions to modern polymer-based systems. It comprehensively discusses the development, classification and clinical significance of depot formulations. Further, the article covers their mechanism of action with a key focus on polymer-based depots, oil-based depots and microparticles. Additionally, the review addresses the key challenges in the formulations and production of the depot systems such as drug candidate selection, encapsulation efficiency and biocompatibility. It also highlights future directions, with an emphasis on the rapidly developing fields such as nanotechnology, polymer technology and digital health tools which could potentially produce numerous beneficial innovations in the field of depot formulations.

Keywords: Depot formulations, drug delivery system, injectable depot, implants, oral depots, microparticles.

1. Introduction

In the clinical management of chronic diseases, poor patient compliance and adherence to the long treatment regime are major obstacles to clinical improvements. According to the World Health Organisation, patient adherence in developed countries averages only 50 %, raising concern in the context of poor and developing countries (Sabaté, 2003). The poor adherence and compliance could be associated with various factors such as the need for frequent check-ups and drug administrations and the costs related to the lengthy treatment. While these are concerns associated with patient burden, another issue in conventional treatments when it comes to chronic diseases is the unstable drug concentration profile. Most traditional drug delivery systems fail to achieve a stable plasma concentration consequently causing undesirable side-effects. The fluctuating levels of the administered drug in the bloodstream produce random peaks and troughs. The peaks could produce adverse side-effects while the troughs could produce undesirable sub-therapeutic effects.

To mitigate these issues, researchers delved into the concept of "sustained-release" or "controlled-release" drug delivery systems. Such drug delivery systems formulated to release the active pharmaceutical ingredient over a definite period are referred to as depot formulations. The primary aim of designing such a drug delivery system is to ensure a stable level of the therapeutic in the bloodstream, minimising the need for frequent dosing and improving patient adherence.

The notion of depot formulations dates back to the 1950s when oil-based solutions containing an active drug were introduced (Rahnfeld & Luciani, 2020). The first-ever depot formulation to hit the market was fluphenazine decanoate, an antipsychotic drug developed for the treatment of schizophrenia (Kane et al., 1998). Fluphenazine decanoate was also developed based on the oil-based solutions mentioned above. Following this, more depot formulations of antipsychotics, such as haloperidol decanoate and risperidone, were developed.

The advancements in polymer technology and drug delivery systems in the late 20th century stirred the evolution of depot formulations. With the discovery of biodegradable polymers such as polylactic acid (PLA) and polylactic-co-glycolic acid (PLGA), the first-ever polymer-based depot formulation was introduced, namely, Decapeptyl (triptorelin pamoate). This drug was developed using a PLGA matrix for the treatment of prostate cancer. Owing to the polymer's biodegradability and versatility, it could be degraded by the body into non-toxic products and also modified to ensure sustained release.

Depot formulations come in various physical forms and also work based on varying mechanisms of action. These depend on factors such as drug profile, bioavailability, route of administration and so on. The clinical significance of depot formulations in the following decades extends over a wide range of clinical departments including psychiatry, endocrinology and oncology.

With the advent of drug delivery technologies, polymer technology, biotechnology and also fields such as nanotechnology, depot formulations continue to evolve. This review article aims to provide a general overview of depot formulations, their mechanisms of action and clinical applications. We will also discuss the current trends and future perspectives in the field and highlight ongoing research and advancements.

2. Types of Depot Formulations

Depot formulations include a wide range of drug delivery systems and they can be broadly categorized into several types based on their composition, mechanism of drug release and application routes. However, the primary types of categorization involve the following: injectables, implantable devices and oral depots as shown in (Figure 1)

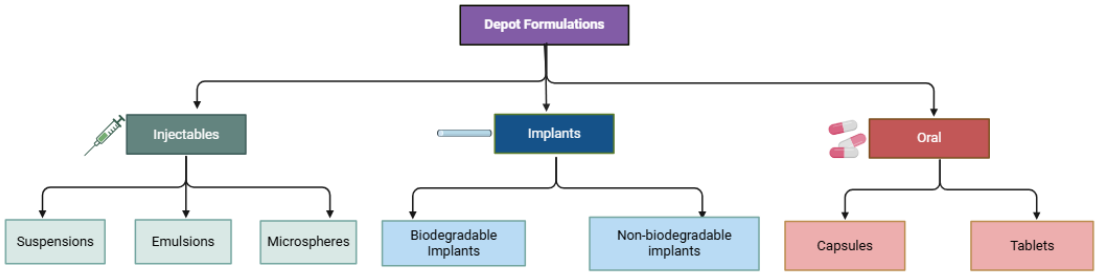

Figure 1. Illustration classifying different types of depot formulations.

Table 1. Types of Depot formulations.

Depot Type	Formulation	Example	Active Ingredient	Therapeutic Application
Injectables	Injectable Suspension	Depo-Provera	Medroxyprogesterone acetate	Contraception
	Injectable Microspheres	Lupron Depot	Leuprolide acetate	Prostate cancer, endometriosis
	Lipid-Based Injectable	Exparel	Bupivacaine	Post-surgical pain management
	In situ Forming Gel	Eligard	Leuprolide acetate	Prostate cancer
Implants	Subdermal Implant	Nexplanon	Etonogestrel	Contraception
	Subdermal Implant	Norplant (discontinued)	Levonorgestrel	Contraception
	Intravitreal Implant	Ozurdex	Dexamethasone	Macular edema, uveitis
	Intracranial Implant	Gliadel Wafer	Carmustine	Brain cancer
Oral	Oral Tablet (ER)	OxyContin	Oxycodone	Chronic pain
	Oral Capsule (ER)	Concerta	Methylphenidate	ADHD
	Oral Tablet (SR)	Wellbutrin SR	Bupropion	Depression
	Oral Capsule (DR)	Prilosec	Omeprazole	GERD, peptic ulcers

2.1 Injectables

Injectable suspensions are the earliest approach to depot formulations. For instance, fluphenazine decanoate, the first-ever antipsychotic-based depot formulation was based on injection for administration. Injectables come in various forms such as suspensions, emulsions and microparticles.

Injectable suspensions consist of solid active pharmaceutical ingredients dispersed in a liquid such as oil or aqueous medium. Once injected, the system gradually dissolves to release the API slowly over time, ranging from days to months. This results in slow and sustained release of the drug, maintaining a steady concentration of the drug in the bloodstream. For instance,

the antipsychotic suspension, haloperidol decanoate was formulated as a suspension to provide sustained medication levels and aid in reducing relapse rates in schizophrenia patients (Beresford 1987, n.d.). The main concerns associated with injectable suspensions are the possibility of sedimentation and aggregation of the API which could reduce clinical efficacy.

Microparticles are developed based on the concept of encapsulation, where the API is trapped inside a biodegradable polymer matrix such as polylactic-co-glycolic acid (PLGA) or polylactic acid (PLA). Once inside the body, the polymer matrix undergoes gradual degradation to release the drug. An example of a microparticle-depot formulation is the Lupron depot (leuprolide acetate) (Tunn et al., 2013). This drug is primarily used to treat hormone-sensitive conditions such as prostate cancer, endometriosis and uterine fibroids. While microparticles offer versatility in their designs, the process of their production involving drug encapsulation and polymer synthesis is costly, which serves as the major hindrance to their advancements.

Emulsions are systems consisting of two immiscible liquids such as oil-in-water (O/W) or water-in-oil (W/O) with one liquid containing the drug. The choice of liquid which acts as the drug carrier is decided based on the drug's solubility and desired release profiles. The drug diffuses from the dispersion phase into the continuous phase over time, leading to the sustained release of the drug. However, the phase separation could lead to stability issues if precise control of formulation and surfactant selection is not maintained. Some examples of emulsion systems include DepoCyt (cytarabine) for the treatment of meningitis and Doxil (doxorubicin) for breast cancer (Salehi et al., 2020).

2.2 Implantable devices

While research for depot systems started in the early 20th century, the first implantable depot came to the market in the 1980s when Norplant was introduced as an implantable contraceptive (Segal, n.d.). Since then various innovations have led to the development of implantable depots for pain management and hormone therapies. Implantable depots could be broadly categorised as biodegradable and non-biodegradable implants.

Biodegradable implants are produced from materials that could be broken down by the body with no formation of toxic by-products. For instance, these could be the aforementioned biodegradable polymers such as PLA or PLGA. The general mechanism of action of these implants is the erosion or hydrolysis of the polymer matrix in order to release the drug slowly over extended periods of time. The major advantage with this type of depot system is the long

time period, ranging in years, over which the drug could be released without needing another implant. To give an example, Nexplanon (etonogestrel) is a contraceptive implant which could provide effective contraception upto three years (Palomba et al., 2012) and the first implant, Norplant, worked for upto five years (Segal, n.d.). Moreover, advancements in smart delivery systems that respond to physiological conditions such as pH or temperature changes have been incorporated into implant systems, making room for more precise drug delivery (Morsada et al., 2021).

Non-biodegradable implant systems are usually made from materials that do not undergo degradation inside the body such as silicone or metals. They are intended to remain at the surgical site for determined periods and their mechanism of action include the gradual diffusion of the drug into the target site. A well-known example of such an implant is Implanon which releases etonogestrel over three years (Mascarenhas, 1998). Previously discussed Nexplanon could be said to be an advanced version of Implanon. However, these implants are not the most favorable choice as they need to be removed surgically after the defined period which could result in patient burden.

2.3 Oral Depot Formulations

Oral depot formulations generally involve tablets and capsules which provide sustained release of the drug in the gastrointestinal tract. This is achieved through various formulation strategies such as reservoir systems, matrix systems or osmotic pumps which will be discussed in detail in further sections of the article. Notable examples of oral depot formulations include opioids such as OxyContin and anti-hypersensitive drugs such as nifedipine (Liu et al., 2018; Vadivelu et al., 2016). The use of depot formulations for opioids is such a beneficial strategy to address addiction and drug abuse associated with opioids. While oral depot formulations look favourable to address illnesses associated with the gastrointestinal tract, dose dumping is a major concern where a random release of the drug could take place leading to toxicity. Additionally, their design and production are costly.

3. Mechanism of Action in Depot Formulations

Depot formulation controls drug release through various mechanisms such as rate-limiting absorption, polymer sensitivity, erosion, solvent exchange, and liposome aggregation. The process is also influenced by numerous factors like viscosity, partition coefficient, and solvent characteristics, though, the most crucial factors considered while formulating the mechanism

of action of the depot system are the stability and release kinetics. The most commonly used systems for depot formulations are polymer matrices, microspheres or oil suspensions, all of which influence the duration of drug release by extending it. In this review, the mechanism of action of the three above-mentioned systems will be discussed briefly.

3.1 Polymer-based Depots

In these systems, the drugs are encoded in a matrix like PLGA and the drug diffuses through the polymer or the polymer itself degrades over time, releasing the drug gradually. The mechanism of action as observed in *in situ* forming gels, implants or polymer-based matrix, particularly those used for sustained release of peptides and proteins, involves complex processes such as polymer precipitation or phase inversion. In the process of polymer precipitation, the initial stage is gel formation, as the polymer swells and forms a gel-like barrier upon coming in contact with fluids (McHugh, 2005). Further, thermosensitive polymers can block certain copolymers which then undergo dehydration and transition from an aqueous liquid to a gel as the temperature increases past the sol-gel transition temperature. Phase inversion mechanism is where the polymer matrix, containing water-insoluble polymers like PLGA in a biocompatible solvent, forms gels upon injection due to solvent exchange (Brodbeck et al., 1999). As the organic solvent leaves the polymer solution, it starts to precipitate or form a gel. The main factors in the process are the polymer and solvent properties which influence the kinetics of solvent exchange and phase inversion that are critical for determining the duration of gel formation and thereby, the drug release profile. Another central factor is the rate at which the organic solvent leaves and water enters the polymer solution, as this decides whether the drug-release process exhibits burst release or zero-order kinetics.

3.2 Nanoparticles or microspheres:

These tiny particles can encapsulate and release the drug slowly as the particles degrade or as the drug diffuses out. Drug release from biodegradable microspheres usually occurs in phases. The initial phase is the burst release of the drug where, upon administration, there is a rapid release of the drug molecules that are near or at the surface of the microspheres (Berchane et al., 2007). After the initial burst phase, the drug release slows down and becomes sustained as the drug diffuses through the polymer matrix or as the matrix erodes slowly, primarily through hydrolytic degradation. The final phase occurs when the polymer matrix starts breaking down rapidly, creating an acidic environment due to which the microspheres undergo bulk erosion and the process accelerates, leading to a faster release of the remaining drug particles. The

factors that influence this process are the polymer composition and geometry. For instance, polyanhydrides, poly (ortha esters), and poly-e caprolactone have different degradation rates, biocompatibility and particle size distribution where smaller particles degrade more slowly by bulk erosion, thereby influencing the release profile. Moreover, the release conditions like temperature, agitation and medium can significantly affect the observed release profile.

3.3 Oil-based suspensions

In this system, the drug in suspended in an oil-based solution and the drug slowly diffuses out of the oil phase into the bloodstream. Drugs delivered via lipophilic solutions involve the formation of a drug depot at the injection site, where the drug is localized in an oil-based vehicle, which acts as a reservoir system. There is a partitioning between the oil phase and the surrounding aqueous phase of the tissues. Due to the concentration gradient of the drug in the oil vehicle (high) and aqueous phase (low), the drug diffuses out of the oil vehicle and enters the tissue fluids where it is absorbed into the bloodstream (Kalicharan et al., 2016). Factors like drug lipophilicity, the oil-vehicle composition, the interfacial tension at the oil-aqueous phases and the injection volume influence the release rate, transport and absorption of the drug into the blood stream. This can be measured by dialysis model studies which use rotating dialysis cell and float-A-lyzer systems to observe the drug release rate. The release kinetics can vary depending on the model used. To give an example, in cases with high agitation, the drug release follows first-order kinetics, where the release rate is directly proportional to the drug concentration.

4. Challenges in Formulations

Formulation of depot systems comes with countless challenges which span from the selection of drug candidates to the complex process of designing and manufacturing systems, all while also mitigating regulatory concerns. Here we will be discussing the key challenges in depot formulations.

4.1 Selection of Drug Candidate

The first challenge in depot formulations is the selection of drug candidates, given the fact that not all drugs are amenable to the formulation process due to their physiochemical properties. Some of the favourable characteristics of drugs for depot formulations include a long half-life, stability and broad therapeutic windows. For the drug to be released in a sustained manner, a sufficiently long half-life is critical. If not, the drug would degrade before even serving its

purpose. Moreover, any deviation from the designed release profile could lead to undesirable sub-therapeutic effects if the drug is unstable and possesses a narrow therapeutic window. For instance, the translation of peptide drugs such as insulin into a depot formulation proves difficult due to its susceptibility to enzymatic degradation and instability.

Table 2. Different Manufacturing Methods for Depot Formulation and their advantages and disadvantages.

Method	Description	Advantages	Disadvantages	Examples
Solvent Evaporation	Drug and polymers dissolved in a solvent, then the solvent is evaporated to form microspheres.	Simple, versatile	Residual solvent, limited to certain drugs	Lupron Depot (leuprolide acetate)
Spray Drying	Liquid formulation is sprayed into a chamber to form dry particles.	Fast, scalable, suitable for heat-sensitive drugs	High initial burst release, equipment costs	Pulmicort Respules (budesonide)
Coacervation	Phase separation technique to encapsulate the drug within a polymer.	High drug loading, suitable for proteins	Complex process, may require surfactants	Nutropin Depot (human growth hormone)
Hot Melt Extrusion	Drug and polymer are melted and extruded to form depot formulations.	Solvent-free, continuous process	High temperature may degrade some drugs	Exjade (deferasirox)
Emulsion-Based Methods	Drug is dispersed in an emulsion, then solidified to form depots.	Suitable for hydrophilic and hydrophobic drugs	Emulsifier residue, complex process	Eligard (leuprolide acetate)
In Situ Forming Systems	Injectable formulations that solidify upon administration.	Minimally invasive, adjustable release profiles	Requires careful formulation, potential for irritation	Atridox (doxycycline)

4.2 Drug Loading and Encapsulation Efficiency

Low drug loading with low encapsulation efficiency defeats the whole purpose of depot formulations as it could lead to the need for frequent dosing. So, achieving high loading and encapsulation efficiency is central in depot formulations. A multitude of techniques are available for encapsulating drugs these days such as solvent evaporation, spray drying and coacervation. However, optimizing these techniques to achieve high loading while also not compromising drug stability is a complex process. For example, the depot formulation of paclitaxel, a chemotherapy drug, and taxol require high loading efficiency to avoid frequent dosing and to ensure controlled release without burst incidences which could lead to toxicity (Ruan & Feng, 2003).

4.3 Release Kinetics and Reproducibility

A major goal in depot formulation is to ensure predictable and reproducible release kinetic profiles. However, achieving this is no simple feat given the complex factors associated with *in vivo* conditions such as local pH, temperature, enzymatic activity and site of administration. Improving accuracy in *in vitro-in vivo* correlation models is critical to ensure predictable and reproducible release profiles. However, the complexity of the biological system and its variance in each individual proves the process to be quite difficult.

4.4 Biocompatibility

Ensuring the biocompatibility of the materials used in depot formulation is central to ensuring that there are no adverse side effects or sub-therapeutic outcomes. The chosen material, whether polymers or metals, must be non-toxic, biocompatible, and capable of providing the desired release profiles. If the chosen material is not biocompatible, it could lead to the production of toxic by-products or other reactions. For instance, at times, PLGA could cause local acidity at the site of injection which could potentially cause inflammation, irritation or pain (Paolini et al., 2019).

Table 3. Clinical signifance of depot formulations across various medical fields

Therapeutic Area	Depot Formulation	Drug Example	Description
Contraception	Injectable suspension, implant	Depo-Provera (medroxyprogesterone acetate), Nexplanon (etonogestrel implant)	Provides long-term contraception by continuously releasing hormones to prevent ovulation.
Oncology	Injectable microspheres, implants	Lupron Depot (leuprolide acetate), Gliadel Wafer (carmustine)	Used to deliver chemotherapy or hormone therapy directly to the tumour site, reducing systemic side effects.
Endocrinology	Injectable suspensions, implants	Sandostatin LAR (octreotide acetate), Estring (estradiol)	Provides hormone replacement or suppression therapy for conditions like acromegaly, carcinoid tumours, or menopause.
Psychiatry	Injectable suspensions	Risperdal Consta (risperidone), Abilify Maintena (aripiprazole)	Used for long-term management of psychiatric disorders such as schizophrenia and bipolar disorder.
Pain Management	Lipid-based formulations, implants	Buprenorphine implants, Exparel (bupivacaine liposome injectable suspension)	Provides sustained analgesia for chronic pain or post-surgical pain management, reducing the need for frequent dosing.
Rheumatology	Injectable suspensions	Depo-Medrol (methylprednisolone acetate)	Used for the management of inflammatory conditions such as rheumatoid arthritis by delivering corticosteroids over an extended period.
Infectious Diseases	Injectable microspheres, in situ forming systems	Bicillin L-A (penicillin G benzathine), Atrigel (various antibiotics)	Provides long-term antibiotic therapy for chronic infections, reducing the need for frequent injections.
Ophthalmology	Injectable implants, suspensions	Ozurdex (dexamethasone intravitreal implant), Iluvien (fluocinolone acetonide)	Delivers sustained release of corticosteroids to treat chronic eye conditions like macular edema.

5. Conclusion

Depot formulations serve as a significant mark in the advancement of drug delivery. They offer sustained and controlled drug release profiles, thereby ensuring patient compliance and adherence which are critical to improving clinical outcomes in long treatment regimes. In spite of their advantages, the process of designing and producing a stable and efficient depot formulation is complex. Ensuring high drug loading and encapsulation efficiency along with drug stability and biocompatibility serve as critical factors in the formulation of depot systems.

To mitigate the aforementioned issues, more technological and innovative advancements are required. Nanotechnology could lead to the production of nano-sized depot formulations which might enhance precision in targeted delivery. Smart polymers respond to various physiological factors which upon employment in polymer-based depot systems could pave the way for responsive drug release. The incorporation of digital health technologies such as accessorized sensors and mobile health apps to depot formulations could facilitate real-time monitoring of patient conditions. In conclusion, depot formulations offer immense potential, however, further intensive research is required to mark significant therapeutic outcomes in the field.

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