SUSTAINED RELEASE INJECTABLE FORMULATIONS: ITS RATIONALE, RECENT PROGRESS AND ADVANCEMENT.


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ABSTRACT
Oral drug delivery plays a prominent role among all the other routes of drug delivery. But nowadays in our fast going world, injectable drug delivery helps out to get instant results. Parenteral route is mostly avoided by the patients due to its pain while administering the drug. To get rid of patient incompliance in the case of frequent dosing, the concept of sustained release parenteral formulation was discovered. The concept benefits not only rapid onset of action but also helps in reducing frequent dosing and maintains a proper systemic level of drug. This article will briefly cover current options for extended release injectable drug delivery system consisting microsphere, implants, suspension, emulsion, liposome, noisome, protein and peptides.

KEYWORDS: injectable, microsphere, liposome, implants.

1. INTRODUCTION
According to patient’s perspective, drug delivered orally is more desirable than any other routes. Parenteral route plays vital role in pharmacotherapy by its rapid onset of action and maintaining drugs systemic level. Various pharmaceutical agents, particularly protein, peptides and other therapeutics agents, can only be administered by injectable routes. As many therapeutic agents get inactivated in gastrointestinal tract if administered orally. Parenteral formulations should carry some basic characteristics, that is sterility, safety, pyrogen free, stability, free from particulate contamination, compatibility and isotonicity. [1, 2]
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. This system also leads to alleviation of pain during administration and reducing costing of parenteral drug treatment.

Safety issues relating to an injectable sustained-release system cannot be overlooked. Premature termination of treatment in case of drug toxicity can be extremely difficult for most of the parenteral sustained-release systems once administered. The adverse response of local tissues to the drug and/or the system on prolonged exposure can be clinically alarming.[5, 6]

In recent years, the research in parenteral sustained-release technologies has been fuelled mainly by the advent of novel carriers. The growth of injectable sustained-release products in the pharmaceutical marketplace is also evidenced by the increasing number of products that have been granted regulatory approval during the last 5 years. This review focuses on the rationale, advancement and recent progress in the development of parenteral sustained-release systems using novel carriers.

2. ROUTES OF ADMINISTRATION FOR SUSTAINED RELEASE INJECTABLE
The various routes of administration in parenteral drug delivery are Intravenous, Intramuscular, Subcutaneous, Intrarterial, Intraethical, Intracardiac, intradermal, Intrapertional etc. But among this Intramuscular (IM) and subcutaneous (SC) routes are widely used for extending the release pattern of injectable formulations. For determining the routes for depot drug delivery, several circumstances need to be examined such as safety profiles, ease of administration, patient's mobility, targeted injection sites, quality of life and cost of therapy. In many cases, SC is the most desirable route for administering a drug by injection because of wide area for target injection sites, utilizing of shorter needles, ease of self-administration, relief and inconvenience for patients, and better safety profile. However, the volumes of SC injection are usually bounded to no more than 1–2 mL, and only nonirritant substances are permitted to be injected by a SC route because irritants can cause pain, necrosis, and sloughing at the injection site. On the contrast, larger volumes of injection are administered through IM route. Mild irritants, oils, and suspensions can be dispensed by IM route in the large skeletal muscles (i.e., deltoid, triceps, gluteus maximus, and rectus.
femoris) because these muscles are less richly supplied with sensory nerves and are more vascular.[1]

3. SUSTAINED RELEASE INJECTABLE FORMULATIONS

3.1. Injectable Suspensions

3.1.1. Introduction

Injectable suspensions are dispersed, heterogeneous system consisting insoluble drug molecules and excipients which need to be resuspended or redispersed in either aqueous or vegetable oil vehicles before administering to patient. To achieve a pharmaceutically acceptable suspension, it should take into consideration the below mentioned checkpoints.

- They should maintain their sterility, pyrogenicity, resuspendibility, syringe ability, stability and isotonicity.
- They should be either being formulated as ready to use injection or as reconstitution prior to use.
- Suspensions should usually contain solids between 0.5-5.0 percent, having particle size less than 5 micrometer for I.M or S.C. administration.

3.1.2. Merits and Demerits of Injectable Suspensions

Every pharmaceutical formulation has some merits and some demerits. Some merits and demerits of injectable suspension are brief out in figure 1.

![Figure 1: Representing merits and demerits of Injectable suspension.](image)


Two basic methods used for preparation of parenteral suspension are

a) Aseptically combining sterile powder and vehicle.
b) Insitu crystal formation by combining sterile solution.
Lyophilization of the product or direct fill of the dry powder in the final package can be used for parenteral suspension.

3.1.4. Stability and Evaluation of Parenteral Suspension:
As suspensions are thermodynamically unstable system, physical stability of suspensions becomes as important as the chemical and biological stability. In addition, a parenteral suspension needs evaluation of characteristics such as syringeability, injectability, isotonicity, sterility and preservative effectiveness. Rheological properties of an parenteral suspension can provide some formidable challenge in their administration and delivery.\[10\]

3.2. INJECTABLE EMULSIONS\[13\]

3.2.1. Introduction
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.

**Common types of emulsions are found in parenteral drug delivery systems**
- **Water in oil emulsions** (W/O) used in sustained release of steroids and vaccines by intramuscular injection.
- **Oil in water** (O/W) or lipid emulsions can be administered by a variety of parenteral routes (for example subcutaneous, intramuscular and intra-arterial) but are mainly injected intravenously in parenteral nutrition applications.

Mostly, injectable emulsions are oil-in-water emulsion. They are milky white in appearance and have an average globule size of 1.0 micrometer to 5 micrometer. Emulsions are primarily used for parenteral nutrition and infused intravenously. These are terminally sterilized with the sterilization cycle designed to maintain globule size distribution.

3.2.2. Formulation, development and Manufacture of Injectable emulsion
Formulation variables affecting the quality of the emulsion are the type and concentration of oil and emulsifier used, pH and drug concentration dispersed in the matrix. Processing conditions that affecting the quality of an emulsion during manufacture are the pressure, temperature and the number of passes used. Emulsions are formulated in specialized equipment such as a homogenizer or microfluidiser that pumps liquid under high pressure...
through a valve or interaction chamber, generating shear and cavitations forces that reduce the size of large oil drops into submicron droplets of a narrow size distribution.

Emulsions for drug delivery can be manufactured by an extemporaneous or de novo method. The extemporaneous method is commonly used in preliminary emulsion feasibility evaluations, which involves the salvation of drug in the solvent (e.g. ethanol, dimethylsulphoxide, dimethylacetamide) and then after addition and mixing into a commercially available fat emulsion. The de-novo method involves addition of the drug to the oil phase prior to the homogenization process. This is the preferred route in the manufacture of drug emulsions due to the optimization of the formulation parameters with respect to the active pharmaceutical ingredient, and sterility assurance can be performed during the process by aseptic or terminal heat sterilization.

### Table 1: List of marketed preparation of Parenteral Emulsion

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Drug</th>
<th>Indication</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazemuls</td>
<td>Diazepam</td>
<td>Sedative</td>
<td>Pharmacia</td>
</tr>
<tr>
<td>Diprivan Liple</td>
<td>Propofol</td>
<td>Anaesthetic</td>
<td>Astra Zeneca</td>
</tr>
<tr>
<td></td>
<td>Alprostadil</td>
<td>Vasodilator, platelet inhibitor</td>
<td>Mitsubishi Pharmaceutical</td>
</tr>
<tr>
<td>Ropion</td>
<td>Flurbiprofen axetil</td>
<td>Non-steroidal analgesic</td>
<td>Kaken Pharmaceuticals</td>
</tr>
<tr>
<td>Vitalipid</td>
<td>Vitamins A, D, E, K</td>
<td>Parenteral nutrition</td>
<td>Fresenius Kabi</td>
</tr>
<tr>
<td>Angiomax®</td>
<td>Bivalirudin</td>
<td>Anticoagulant</td>
<td>Sunovion Pharmaceuticals</td>
</tr>
<tr>
<td>Cleviprex®</td>
<td>Clevidipine</td>
<td>Antihypertensive</td>
<td>The Medicines Company</td>
</tr>
<tr>
<td>Limethason®</td>
<td>Dexamethasone palmitate</td>
<td>Anti-inflammatory</td>
<td>Crystal Pharma</td>
</tr>
<tr>
<td>Etomidat- Lipuro®</td>
<td>Etomidate</td>
<td>Anesthesia</td>
<td>Troikaa Pharmaceuticals Ltd.</td>
</tr>
<tr>
<td>Lipofundin® N20%</td>
<td>Soyabean Oil</td>
<td>TPN</td>
<td>Braun</td>
</tr>
</tbody>
</table>

### 3.2.3. Advantages of injectable emulsions

The physicochemical advantages of using emulsions as a drug delivery system is

- The solubilisation of drugs with low aqueous solubility.
- Stabilization of labile drugs against hydrolysis or oxidation.
- Therapeutic advantages can be exhibited by a decrease of toxicity of drug.
Other therapeutic benefits can be the elimination of irritation and toxicity associated with formulations containing high organic solvents or alkaline conditions (e.g. phenytoin).
Continuous infusion, sustained release and potential drug targeting applications.

3.2.4. **Commercial preparation of injectable emulsion**
Various marketed parenteral preparations are available. Some of them are list in the table 1.

3.3. **MICROSPHERES AND MICRO PARTICLES**

3.3.1. **Introduction**

3.3.1.1. **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 (shown in figure 2).

![Figure 2: It display, A. Microcapsule and B. Microsphere](image)

3.3.1.2. **Microparticle**
Micro particles are spherical encapsulated particles with size ranging between 1 to 1000 μm. For injection purpose, micro particles smaller than 125 μm are preferred as shown in figure 2. Micro particles depend on biodegradable polymers that have been extensively investigated for controlled release delivery system over last 3 decades. Micro particles can be injected through rarely used needle and alleviate the pain during injection.

3.3.2. **Techniques of preparation of microparticle and microsphere.**
Microparticle and microsphere can be fabricated by various methods, but the most widely used techniques are phase separation (coacervation), spray drying, and solvent evaporation.
The fabrication techniques have much great impact on the structure and release properties of the microparticles and microspheres.

In the following sections, the various production techniques to make this formulation are briefly introduced, but a detailed discussion is beyond the scope of this review.

3.3.2.1. Phase Separation (A Traditional Technique)

Coacervation technique depends upon a decrease of the polymer solubility by adding of non-solvent. At a point, two liquid phases are formed i.e. a polymer rich coacervate and a supernatant liquid phase depleted in polymer. The drug dispersed in polymer solution is thereby entrapped by coacervate.\[^{10, 11, 12}\]

Microencapsulation by coacervation proceeds along three main steps:
(i) Phase separation of the polymer solution;
(ii) Adsorption of the coacervate around the drug particles;
(iii) Solidification of the microparticles.

3.3.2.2. Spray drying

This method involves dissolving the polymer in volatile organic solvents, such as dichloromethane or acetone. The drug is either dissolved or dispersed in polymer solution.\[^{13}\]

This solution or dispersion is then atomized in a heated air. The solvent instantaneously evaporates resulting in the formation of solid microparticles. In comparison phase separation method, spray drying is easily to be scaled up. However, there is large amount of product loss during process, which results in a low yield. Moreover, spray drying is also prone to produce agglomeration of microparticles.\[^{14}\]

A novel spraying into liquid nitrogen technique has been developed to encapsulate recombinant human growth hormone. This so called cryogenic process includes the mixing of zinc stabilised recombinant growth hormone with PLGA/dichloromethane solution that results in suspension which is sprayed into container filled with frozen ethanol overlaid with liquid nitrogen. Solid ethanol liquefies on warming, and extracts the polymer solvent and hardens the microparticle.

3.3.2.3. Solvent evaporation\[^{15}\]

Solvent evaporation method is the most widely used technique of preparing microparticles. It involves emulsifying a drug-containing organic polymer solution into a dispersion medium,
It can be classified into oil in water (o/w), water in oil (w/o), and water in oil in water (w/o/w) double emulsion method.

### 3.3.2.3.1. o/w cosolvent method

This technique widely used to encapsulate hydrophilic drugs. Drug dispersion is formed in the polymer solution. This technique recently so called as cosolvent method. The preparation steps carried out in this process are shown in the figure 3.

![Diagram of o/w cosolvent method](image)

**Figure 3: Steps carried out during solvent evaporation**

### 3.3.2.3.2. w/o/w double emulsion method

In comparison to w/o method, w/o/w technique is more suitable for water soluble drugs. The microparticulates loaded with peptide, protein, DNA, and other small molecules are prepared successfully using this method. The advantage of this technique includes high yield and encapsulation efficiency. The steps involved in this method are

Aqueous drug solution or dispersion mixed with PLGA solution in organic solvent

Further mixed with large amount of water containing emulsifier

Forms water in oil in water (w/o/w), then subjected to solvent removal

Washing, drying and collecting the product

### 3.3.2.4. New trends in production methods

Several criteria’s such as reducing cost, reducing scale-up difficulties, improving drug stability, allowing for terminal sterilization, and eliminating the need for organic solvents motivate the development of new methods to manufacture micro particulates. Due
to many drawbacks of conventional methods, new and improved processes have been proposed and evaluated.

i. Modified Conventional Methods
The w/o/w solvent evaporation or extraction is one of the most widely used techniques for peptide and protein microencapsulation\cite{16}, despite its many drawbacks. Improvements and alternatives have therefore been proposed such as o/w, o/w (including cosolvent) and o/o. To improve solvent extraction, a novel method using a static micromixer was presented where a w1/o dispersion (aqueous BSA in organic PLGA solution) is fed into an array of microchannels and the extraction fluid (w2) into a second array of interdigitated channels. The two fluids, transported separately through the channels, are discharged through an outlet slit where alternating fluid lamellae are formed with the w1/o fluid lamella disintegrating into microdroplets, which harden quickly to form microspheres. This process offers easy scale-up, methodological robustness, continuous production, and a simple setup, making it ideally suited for aseptic production, a strongly needed feature for microspheres vaccine formulations.

ii. ProLease® Technology (Cryogenic Spray-drying)
A variation of the conventional spray-drying method is a cryogenic method, described subsequently below. A novel, low-temperature spraying technique (called ProLease® technology) for preparing microspheres has been reported by Khan et al.\cite{17} The method relies on the use of stabilising and release-controlling agents, low processing temperature, and non-aqueous microencapsulation. Typically, a protein powder is micronised, with a stabiliser, by spray-freeze-drying, and then suspended in an organic polymer solution.\cite{18,19} The suspension is atomised into a vessel containing liquid N\textsubscript{2} underlaid by frozen ethanol (extraction solvent). The atomised droplets freeze in the liquid N\textsubscript{2} and deposit on the surface of the frozen ethanol. As liquid N\textsubscript{2} evaporates, the frozen ethanol liquefies (Tm approximately –110 °C) so that the frozen polymeric droplets will transfer into the ethanol where the polymer solvent is extracted, yielding solid microspheres.

iii. Technique using Supercritical Fluids
Generally, the application of supercritical fluids for the encapsulation has been fueled by the recognition that the methods implicate some drawbacks. The application of supercritical fluids, especially of supercritical carbon dioxide (CO\textsubscript{2}) \cite{20}, can minimise or even eliminate the use of organic solvents and renders work at moderate temperatures possible. The second
is the aerosol solvent extraction system (ASES), also known as the gas antisolvent spray precipitation (GAS) process\textsuperscript{[21]}. Here, a solution of the active agent and the polymeric carrier is sprayed into a chamber loaded with supercritical CO\textsubscript{2}. The supercritical CO\textsubscript{2} extracts the solvent from the spray droplets and induces co-precipitating of the active agent and the polymeric carrier in form of small, solvent-free particles. However, the use of organic solvents cannot be avoided, which is to be deemed as a major disadvantage of both techniques.\textsuperscript{[22]}

iv. Ultrasonic Atomization

Ultrasonic atomization of w/o dispersions is presently under investigation for preparing especially protein antigen-containing microspheres.\textsuperscript{[23]} In one setup, the atomised antigen/polymer dispersion was sprayed into a nonsolvent where the polymer solvent was extracted, resulting in microspheres. The main advantages of these atomisation techniques encompass the possibility of easy particle size control and scale-up, processing at ambient or reduced temperature, and the suitability for aseptic manufacturing in a small containment chamber such as an isolator.\textsuperscript{[24, 25]}

3.4. LIPOSOMES

3.4.1. Introduction: Liposomes are small, spherical, bilayer phospholipid vesicles of size range 30 nanometer to micrometers. They are amphipathic in nature, so can transport both hydrophilic and hydrophobic drugs.\textsuperscript{[26]} They are extensively used as carrier for numerous cosmetic and pharmaceutical industries. 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. Many studies have been conducted on liposomes with the goal of decreasing drug toxicity and/or targeting specific cells.\textsuperscript{[27-30]} 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.\textsuperscript{[31]}

<table>
<thead>
<tr>
<th>Merits</th>
<th>Demerits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased therapeutic index efficiency of drug</td>
<td>Low solubility</td>
</tr>
<tr>
<td>Increased stability</td>
<td>Short half life</td>
</tr>
<tr>
<td>Reduce toxicity of encapsulated drug</td>
<td>Leakage and fusion</td>
</tr>
<tr>
<td>Site avoidance effect</td>
<td>Production cast is high</td>
</tr>
</tbody>
</table>

Table 2: Advantages and Disadvantages of Liposomes
Liposomes are non-toxic, flexible, biocompatible, completely biodegradable, and non-immunogenic for systemic and non-systemic administrations. Phospholipid undergoes oxidation and hydrolysis-like reaction Fewer stables

3.4.2. Method of Preparation

All the methods of preparing the liposomes involve four basic stages:\[32\]:

1. Drying down lipids from organic solvent.
2. Dispersing the lipid in aqueous media.
3. Purifying the resultant liposome.
4. Analyzing the final product.

The different techniques used in preparation of liposomes are shown in figure 4.

![Figure 4. Different technique used in preparation of liposomes](image)

3.4.3. Commercial preparation of parenteral liposomes

Various commercial preparation of parenteral liposomes are listed down in table 3.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Drug</th>
<th>Indication</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abelcet®</td>
<td>Amphotericin B</td>
<td>Fungal infection</td>
<td>Enzon</td>
</tr>
<tr>
<td>Ambisome</td>
<td>Amphotericin B</td>
<td>Fungal infection</td>
<td>Astellas</td>
</tr>
<tr>
<td>Amphotec®</td>
<td>Amphotericin B</td>
<td>Fungal infection</td>
<td></td>
</tr>
<tr>
<td>Depocyte®</td>
<td>Cytarabine</td>
<td></td>
<td>Pacira/Enzon</td>
</tr>
<tr>
<td>Depodur</td>
<td>Morphine</td>
<td>Anti-depressant</td>
<td>Pacira/EKR</td>
</tr>
<tr>
<td>Doxil®</td>
<td>Doxorubicin</td>
<td>Ovarian cancer</td>
<td>Sequus pharma/ortho Biotech</td>
</tr>
<tr>
<td>Daunoxome™</td>
<td>Daunorubicin</td>
<td>Kaposi’s sarcoma(skin cancer)</td>
<td>Nexstar pharmaceuticals</td>
</tr>
<tr>
<td>Visudyne®</td>
<td>Verteporfin</td>
<td>Myopia, ocular histoplasmosis</td>
<td>Novartis pharmaceuticals</td>
</tr>
</tbody>
</table>
3.5. NIOSOMES

3.5.1. Introduction\textsuperscript{[45, 46]}: Niosomes are the highly ordered vesicular structure with bilayer membrane made up of Non-ionic surfactant with or without incorporation of cholesterol. The closed bilayer vesicular structure of niosome formed by the self assembling of non-ionic surfactants in the presence of aqueous media.

Niosomes are very small, and microscopic in size. Their size lies in the nanometric scale. Although they structurally similar to liposomes. Niosomes have both advantages and disadvantages, some are listed in table 4.

Table 4: Advantages and Didadvantages of Niosomes

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve oral bioavailability of poorly absorbed drugs.</td>
<td>Physically instable</td>
</tr>
<tr>
<td>Osmotically active and chemically stable.</td>
<td>Aggregation</td>
</tr>
<tr>
<td>Act as depot for short acting peptide drugs.</td>
<td>Fusion</td>
</tr>
<tr>
<td>Enhance skin penetration of drug.</td>
<td>Leaking of entrapped drug</td>
</tr>
<tr>
<td>Improve therapeutic performance.</td>
<td>Hydrolysis of encapsulated drug</td>
</tr>
</tbody>
</table>

3.5.2. Method Of Preparation Of Niosomes\textsuperscript{[45]}

a. Ether Injection Method.
b. Hand Shaking Method (Thin Film Hydration Technique).
c. Reverse Phase Evaporation Technique (REV).
d. Bubble Method.
e. Micro Fluidization Method.
f. Multiple Membrane Extrusion Method.
g. Sonication Method.

3.5.3. Commercial Niosomal preparations: Various Niosomal preparation are available in the market. Some of this are listed below in table 5.

Table 5: Marketed formulation of sustained release niosomal preparation

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug</th>
<th>Indications</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>M Cam</td>
<td>Meloxicam</td>
<td>Acute exacerbations of osteoarthritis, Rheumatoid arthritis</td>
<td>Unichem Laboratory</td>
</tr>
<tr>
<td>Loxicom</td>
<td>Meloxicam</td>
<td>Alleviation of inflammation and pain in both acute and chronic musculo-skeletal disorders and reduction of post operative pain and inflammation</td>
<td>Nor brook</td>
</tr>
<tr>
<td>Fngizone</td>
<td>Amphotericin B</td>
<td>Fungal infection</td>
<td>Abbott</td>
</tr>
</tbody>
</table>
3.6. 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. The development of in situ forming implants was originated by Dunn in the early 1980s. They used injectable depot system loaded with antibiotics for local treatment of periodontal diseases. Thereafter, approval of Eligard® containing drug leuprolide acetate by FDA spurred interest in In-situ forming implant system development. According to different formation mechanism, this system can be classified into different categories.

3.6.1. 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 thermoplastic pastes are formulated from monomers such as D, L-lactide, glycolide, dioxanone, ε-caprolactone, trimethyl carbonate. The admixing of drug in this system can be achieved by simple mixing at room temperature without using any organic solvent.

3.6.2. In situ cross-linked polymer system

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 photoinitiated reaction. Along with advantages of this system it also have some disadvantages that is, the use of free radical initiator causes the risk of tumor.

3.6.3. Thermally induced gelling systems

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. The advantage of this
system includes the low viscosity of the preparation and the free of organic solvent. 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.

3.6.4. pH induced gelling system
The change of polymer solubility in aqueous medium can also be achieved in response to the change in environmental pH. 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.[55]

3.6.5. Insitu solvent removal systems
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.[56-58]
   i. Atrigel®
   ii. Alzamer® (base on biodegradable PLA/PLGA polymer)
   iii. Saber® (uses non-polymer sucrose acetate isobutyrate as drug carrier)

3.7. PROTIEN AND PEPTIDES[59, 60]

3.7.1. Introduction
Therapeutic Peptides and proteins have risen in prominence as potential drug future. Protien drugs which will be utilized should be highly concentrated and purified and have extremely short half life and shelf life atleast two years. Recombinant technology has permitted production of protein drugs at an reasonable cost, allowing treatment of severe, chronic and life-threatening diseases such as diabetes, rheumatoid arthritis, hepatitis, etc. Currently, over 160 protien drugs are made available in the world market and several hundred are in clinical trials. The total market protein is already 30 billion, and 10% a year increase is expected. Many therapeutic proteins currently in use are injected by invasive routes such as via subcutaneous injections. Alternative routes for delivering proteins are under investigation to overcome the drawback of invasive route of administration.
3.7.2. Instability of protein and peptides
Protein instability can conclude in loss of native molecules and thus efficacy of the drug. In literature, proteins instability is subdivided into physical and chemical instabilities (see table 6).

Table 6: Different types Protein Instability.

<table>
<thead>
<tr>
<th>Physical Instability</th>
<th>Chemical Instability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denaturation</td>
<td>Deamidation</td>
</tr>
<tr>
<td>Adsorption</td>
<td>Disulphide Exchange</td>
</tr>
<tr>
<td>Aggregation</td>
<td>Oxidation</td>
</tr>
</tbody>
</table>

3.7.3. Analytical methods for stability assessment of therapeutical protein formulations
Till date, several analytical techniques have been brought up to assess the stability of proteins. These analytical techniques are dedicated to give information on protein denaturation and aggregation or conformational and structural changes of protein and peptides. Number of different methods for aggregation detection is already well-established (see table 7).

Table 7: Different analytical methods for stability assessment in proteins.

<table>
<thead>
<tr>
<th>Techniques</th>
<th>Examples</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column Chromatography</td>
<td>HPLC, FPLC, low pressure LC, size exclusion, reversed phase</td>
<td>Physical and chemical degradation, excipient impurities, leacheates</td>
</tr>
<tr>
<td>Electrophoresis</td>
<td>SDS-PAGE, native PAGE, isoelectric focusing, capillary electrophoresis</td>
<td>Degradation with changes in size or charge</td>
</tr>
<tr>
<td>Spectroscopy</td>
<td>FTIR, UV, NMR, RAMAN, etc</td>
<td>Structural changes, chemical modification of side group</td>
</tr>
<tr>
<td>Thermal Analysis</td>
<td>DSC, TGA, etc</td>
<td>Protein structure and powder characterization</td>
</tr>
<tr>
<td>Light scattering</td>
<td>Turbidity, particle size determination etc</td>
<td>Aggregation, precipitation, molecular weight determination</td>
</tr>
<tr>
<td>Micro characterization</td>
<td>Peptide sequencing, amino acid analysis</td>
<td>Identification of impurities</td>
</tr>
</tbody>
</table>

There are various sustained release injectable formulation and those formulations having wide range of applications. These applications are briefly listed in table 8.
Table 8: List of various applications of sustained release parenteral formulations.

<table>
<thead>
<tr>
<th>VARIOUS APPLICATIONS OF SUSTAINED RELEASE PARENTERAL FORMULATIONS</th>
<th>APPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral suspension</td>
<td>≈ Sustained drug delivery</td>
</tr>
<tr>
<td>Parenteral Emulsion</td>
<td>▼ Prolong drug delivery</td>
</tr>
<tr>
<td>Microparticles and microspheres</td>
<td>▼ Sustained drug delivery</td>
</tr>
<tr>
<td></td>
<td>▼ Controlled drug delivery</td>
</tr>
<tr>
<td></td>
<td>▼ Local drug delivery</td>
</tr>
<tr>
<td></td>
<td>▼ Pulsatile drug delivery</td>
</tr>
<tr>
<td></td>
<td>▼ Targeted drug delivery</td>
</tr>
<tr>
<td></td>
<td>▼ Prolong drug delivery</td>
</tr>
<tr>
<td></td>
<td>▼ Enteric coated dosage form</td>
</tr>
<tr>
<td>Liposomes</td>
<td>➢ Drug Targetting</td>
</tr>
<tr>
<td></td>
<td>➢ Topical drug delivery</td>
</tr>
<tr>
<td></td>
<td>➢ Protection against enzymetic degradation.</td>
</tr>
<tr>
<td></td>
<td>➢ Gene therapy</td>
</tr>
<tr>
<td></td>
<td>➢ Prophylaxis</td>
</tr>
<tr>
<td>Niosomes</td>
<td>• Drug targeting</td>
</tr>
<tr>
<td></td>
<td>• Delivery of peptides</td>
</tr>
<tr>
<td></td>
<td>• Carriers for Hemoglobin</td>
</tr>
<tr>
<td></td>
<td>• Studying Immuno response</td>
</tr>
<tr>
<td></td>
<td>• Ophthalmic drug delivery</td>
</tr>
<tr>
<td>Implants</td>
<td>✓ Targeted drug delivery</td>
</tr>
<tr>
<td></td>
<td>✓ Controlled drug delivery</td>
</tr>
<tr>
<td></td>
<td>✓ Topical drug delivery</td>
</tr>
<tr>
<td>Protein and peptides</td>
<td>❖ Prolonged drug delivery</td>
</tr>
<tr>
<td></td>
<td>❖ Carrier for microparticles</td>
</tr>
</tbody>
</table>

4. CONCLUSION

Extended release parenteral products are complex dosage forms, requiring careful development of test methods and acceptance criteria for the specifications. In particular, the in vitro release test method and acceptance criteria require rigorous scientific consideration and should be developed with an eye toward understanding the mechanisms of drug release. The final specifications need to ensure the safety, identity, strength, performance, and quality.
of the drug product at release and during storage through the end of its shelf-life. Major
progresses in the development of parenteral sustained-release systems have been made in
recent years as evidenced by the regulatory approval and market launch of several new
products. Both the availability of novel carrier materials and the advances in method of
fabrication have contributed to these commercial successes. With the formulation challenges
associated with biologics, new delivery systems have also been evolved specifically to
address the unmet needs in the parenteral sustained release formulations.

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