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A REVIEW ON ADVANCED PARENTERAL DRUG DELIVERY AND MANUFACTURING TECHNOLOGY

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ABSTRACT

Parenteral drug delivery refers to the administration of pharmaceuticals directly into the body through non-oral routes, bypassing the gastrointestinal tract. It offers several advantages such as rapid drug absorption, precise dosing, and enhanced bioavailability, making it a critical method for delivering a wide range of therapeutic agents. To ensure safe and effective parenteral drug delivery, the development and utilization of advanced manufacturing technologies are essential. It highlights the importance of manufacturing technology in ensuring the characters, assurance and efficiency of parenteral drug products. Various manufacturing techniques have been employed in the production of parenteral drugs, including formulation development, sterile drug manufacturing, and packaging. Manufacturing technology plays a crucial role in the production of parenteral drug products, as it directly impacts product quality, stability, and patient safety. Key manufacturing considerations include selection and characterization of suitable excipients, optimization of formulation parameters, aseptic processing, and ensuring product sterility throughout the manufacturing process. Moreover, advancements in manufacturing technology leads to upliftment of innovative drug delivery systems, such as prefilled syringes, autoinjectors and implantable devices, which offer improved convenience, patient

compliance, and controlled drug release. In order to emphasize the significance of integrating advanced manufacturing technology in the upliftment and production of parenteral dosage form, the need for robust quality control measures, adherence to regulatory guidelines, and continuous process improvement is to meet the ever-increasing demands of the pharmaceutical industry and deliver safe and effective therapies to patients.

KEYWORDS: Drug delivery, Parenteral, Extended release, Packing, Syringes, Carriers.

INTRODUCTION

Parenteral drug delivery, which involves the administration of pharmaceuticals through routes other than the gastrointestinal tract, has become an indispensable method in modern medicine. This approach offers numerous advantages, including rapid onset of action, precise dosing, and high bioavailability. Parenteral drug delivery routes include intravenous (IV), intramuscular (IM), subcutaneous (SC), intradermal (ID), and intrathecal (IT) administration.[1] These routes bypass the digestive system and allow drugs to directly enter the bloodstream or target specific tissues, resulting in faster therapeutic effects and increased patient compliance. Various routes of administration are figured out as shown in figure1.

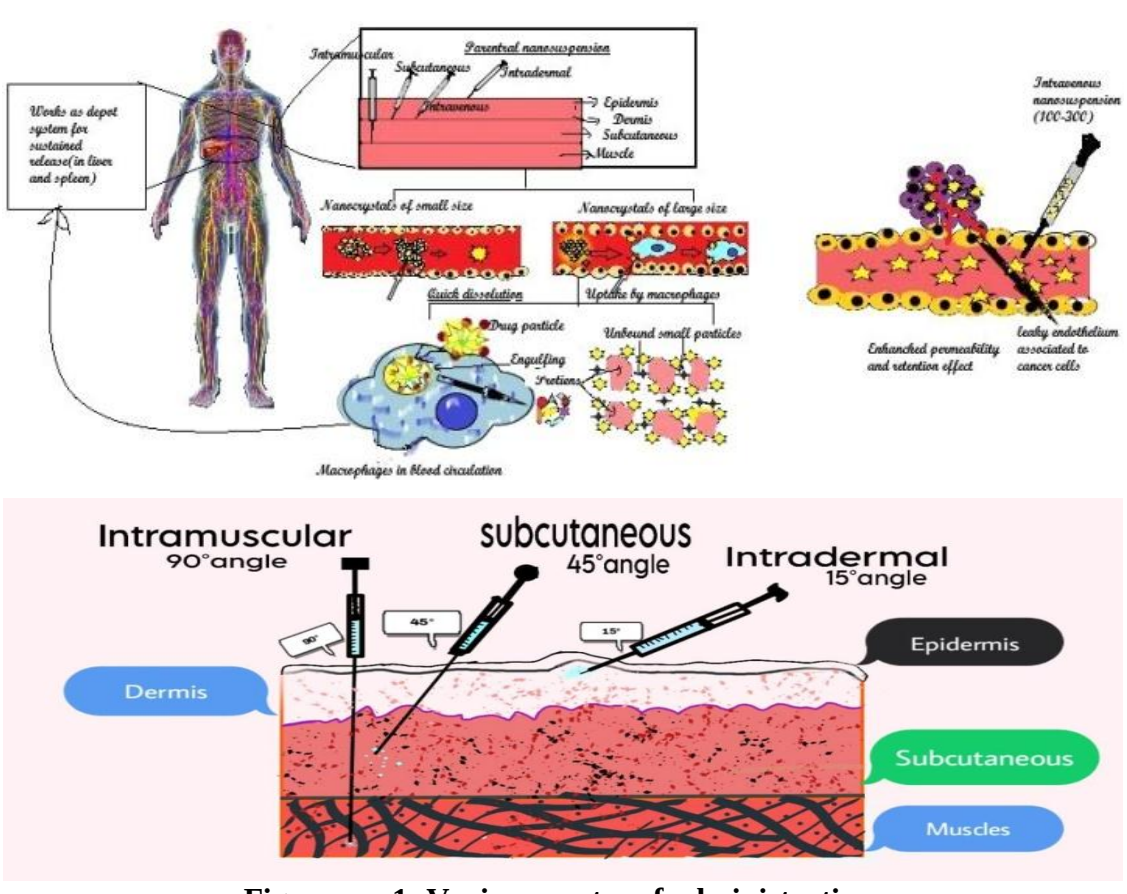

Figure no. 1: Various routes of administration.

Manufacturing technology in the context of parenteral drug delivery encompasses various aspects, including formulation development, sterile drug manufacturing, and packaging. The formulation development stage involves selecting suitable excipients, optimizing drug solubility and stability, and designing delivery systems tailored to specific therapeutic goals. Advanced manufacturing technologies facilitates the development of complex drug formulations, such as nanoparticles, liposomes, and microspheres, which enable controlled release, improved targeting, and enhanced drug efficacy. Various technologies with descriptive features of parenteral formulations are enlisted in table 1.

Table 1: Salient features of parenteral technology.

Parenteral technology	Descriptive features
Intravenous (IV)	Administration of drugs directly into a vein for rapid systemic delivery. Commonly used for fluids, antibiotics,chemotherapy, and emergency medications.
Intramuscular(IM)	Injection of drugs into the muscle tissue, allowing for slower absorption and longer duration of action. Commonly used for vaccines, certain antibiotics, and hormonal preparations.
Subcutaneous(SC)	Injection of drugs into the fatty tissue layer beneath the skin. Provides sustained release and is often used for insulin, certain biologics, and hormones.
Intradermal (ID)	Administration of small amounts of drugs into the dermal layer of the skin. Commonly used for tuberculin skin tests,allergen immunotherapy, and local anesthetics.
Intrathecal (IT)	Delivery of drugs directly into the spinal canal or cerebrospinal fluid. Used for pain management, chemotherapy, and administration of anesthetics in specific cases.
Intraosseous (IO)	Administration of drugs directly into the bone marrow cavity. Used in emergency situations when intravenous access is not feasible, typically in pediatric patients.
Implantable Drug DeliverySystems	Devices implanted under the skin or within specific body tissues that slowly release drugs over an extended period. Examples include subcutaneous implants and drug-eluting stents.
Liposomes	Spherical vesicles composed of lipid bilayers used to encapsulate drugs. Liposomes can improve drug stability,increase circulation time, and target specific tissues or cells.
Nanoparticles	Particles ranging from 1 to 100 nanometers in size that can encapsulate drugs. Nanoparticles can enhance drug.Solubility, bioavailability, and provide targeted drug delivery.

Sterile drug manufacturing is critical aspect of parenteral drug production. It involves maintaining aseptic conditions throughout the manufacturing process to prevent contamination and ensure product sterility. Technologies such as separator, restricted access barrier systems (RABS), and clean rooms are employed to minimize the risk of microbial

contamination and particulate matter.[2] Packaging materials should be inert with the dosage form, maintain sterility, and reassure product integrity and stability during storage and transportation. Advances in packaging technology have led to the development of pre-filled syringes, vials, and other innovative delivery systems that enhance ease of use, dosage accuracy, and patient convenience. Manufacturing technology in the parenteral drug delivery field is continually evolving to meet the increasing demands of the pharmaceutical industry and regulatory authorities. Quality control measures, adherence to Good Manufacturing Practices (GMP) and compliance with regulatory guidelines are of utmost importance to guarantee product safety and efficacy. Parenteral formulations can be classified based on the volume of the formulation being administered.[3]

Classification of parenterals

Small Volume Parenterals (SVP): Small Volume Parenterals are typically defined as parenteral formulations with a volume of 100 mL or less. They are often supplied in vials, ampoules, or prefilled syringes. SVPs are commonly used for immediate drug administration, such as bolus injections, intravenous push, or intermittent infusion.[4]

Large Volume Parenterals (LVP): Large Volume Parenterals are parenteral formulations with a volume greater than 100 mL. They are generally administered through intravenous infusion, providing a continuous flow of the drug over an extended period. LVPs are commonly supplied in IV bags or bottles and may require the use of an infusion pump.[5]

Microdose parenterals: Microdose parenterals refer to parenteral formulations with an extremely small volume, typically less than 1 mL. These formulations are often used for highly potent drugs or drugs that require precise dosing, such as certain biologics or specialized therapies.

Total Parenteral Nutrition (TPN): Total Parenteral Nutrition refers to parenteral formulations that provide complete nutrition, including macronutrients, micronutrients, vitamins, and minerals. TPN formulations are administered intravenously to patients who cannot consume food orally or through other routes. These formulations are usually provided in large volume bags and require careful monitoring and customization based on the patient's nutritional needs.[6]

Advantages of parenteral drug delivery

Rapid onset of action: Parenteral administration allows drugs to directly enter the bloodstream, by passing absorption barriers in the gastrointestinal tract. This leads to faster drug delivery and rapid onset of action, making it suitable for emergency situations or when immediate therapeutic effects are needed.[7]

High bioavailability: Parenteral routes often provide higher bioavailability compared to oral administration.

Precise drug delivery: Parenteral routes allow for accurate and precise drug dosing. Healthcare professionals can administer specific doses based on the patient's condition. Suitable for Patients with Gastrointestinal Issues: Parenteral administration is particularly useful when patients have gastrointestinal disorders, such as nausea, vomiting, or malabsorption, which may impair oral drug absorption or cause adverse effects.

Disadvantages of parenteral drug delivery

Invasive route: Parenteral administration requires puncturing the skin and underlying tissues, which can be uncomfortable and may cause pain or discomfort.

Increased risk of infection: The invasive nature of parenteral routes poses a risk of infection. Strict aseptic techniques and clean environments are necessary during drug preparation, administration, and handling to minimize the chances of contamination.

Professional Administration Required: Parenteral administration typically necessitates the involvement of healthcare professionals due to the specialized skills and knowledge required.

Higher Cost and Complexity: The manufacturing, packaging, and quality control processes for parenteral products are also more complex, requiring specialized facilities and expertise, which can contribute to higher costs.

Limited Self-Administration: Unlike oral medications that patients can easily self-administer at home, many parenteral routes require professional administration, making it less convenient for patients to manage their treatment independently. The following ingredients are included in the preparation of parenteral products to create a stable mixture and the outcomes have been patented as shown in table2.

Table 2: Accessed patentable data of parenteral formulations with active medicament.

S. No.	Delivery Route	Patent No.	Country of filling WIPO	Active Medicament	Outcomes	Year of publication
1	Parenteral	WO018596	United States	Docetaxel	It reduced the hypersensitivity and fluid retention thereby preventing premedication in Docetaxel delivery	2010
2	Parenteral	US0015266	Canada	Model drugs		2011
3	Parenteral	CA2848163	WIPO	Respiratory syncytial Vaccine	Controlled drug transport and Improved balance the use of solidified NE for parenteral route	2013
4	Parenteral	WO101749	Unitedstate	Glucagon	It improves the bodily and chemical balance of Glucagon the use of nanoemulsion	2013
5	Parenteral	US0256828 A1	Unitedstate	Isoflurane /sevoflurane	It is unhazardous composition with minimal infection on administration and environment friendly vaccine delivery based totally systems. It has quicker distribution in talent tissues ensuing in diminished time for induction of anesthesia and improvedtreatment efficiency	2014

Formulation considerations

The principles of parenteral formulation evaluates the formulated product is safe, effective, and appropriate for the intended route of administration. Manufacturing and quality control processes are implemented to adhere regulatory guidelines and Good Manufacturing Practices (GMP) to maintain product quality, safety and efficacy.[8] The primary goal of each individual parenteral dosage form is to achieve proper excipient compatibility (i.e., to prevent the development of new contaminants through either drug substance degradation or the creation of a new chemical entity between the drug and the excipient). Additionally, the compatibility of the preparations with the primary container (no leaching or adsorption to the

container) is important. Formulation of parenteral products involves the development and preparation of a drug formulation that is suitable for administration through parenteral routes such as intravenous (IV), intramuscular (IM), subcutaneous (SC), intradermal (ID), or intrathecal (IT) routes. The formulation process flollows certain principles to ensure the safety, efficacy, and stability of the product (ICH Q8. The drug must be completely dissolved to achieve uniform distribution and accurate dosing upon administration. Compatibility studies are performed to evaluate the interaction between the drug and the excipients used in the formulation, ensuring they do not adversely affect each other. The formulation process includes the use of sterile ingredients, equipment, and aseptic techniques. Sterilization methods such as filtration, heat, or irradiation may be employed to ensure the final product's sterility. Pyrogens are substances that can cause fever when introduced into the body. Pyrogen testing is conducted to ensure that the parenteral formulation is free from pyrogens, as their presence can lead to severe adverse reactions in patients.[9] The pH of the parenteral formulation should be within an acceptable range to prevent irritation at the injection site and ensure stability of the drug. Tonicity refers to the osmotic pressure of the formulation, which should be similar to physiological conditions to minimize discomfort and tissue damage upon injection. Parenteral formulations must maintain the drug's potency, purity, and physical characteristics over the intended shelf life. Stability studies are conducted to assess the formulation's stability under various conditions such as temperature, light, and humidity. These studies help to determine appropriate storage conditions and establish the product's expiration date. It is important to ensure that the drug is uniformly distributed throughout the formulation to achieve consistent dosing. The concentration and volume of the drug in the formulation should be accurately labeled to facilitate correct administration.[10]

Extended release technology

Microspheres: Microspheres, also known as microcapsules or microspheres are small spherical particles typically ranging in size from 1 to 1000 micrometers. They are composed of biodegradable or non-biodegradable materials and can be used in various applications, including drug delivery, imaging agents, cell encapsulation, and controlled release systems.

The drug can be released through diffusion, degradation of the microsphere matrix, or a combination of both.[11] Microspheres offer advantages such as prolonged drug release, reduced dosing frequency, and protection of the drug from degradation, and targeting specific sites in the body. Microspheres can be made from biodegradable or non-biodegradable

materials. Biodegradable microspheres are designed to degrade over time, eliminating the need for their removal after drug release. Common biodegradable materials include polymers such as poly(lactic-co- glycolic acid) (PLGA), poly(lactic acid) (PLA), and gelatin. Non-biodegradable microspheres, such as polystyrene or polyacrylates, are typically used as carriers for sustained drug release or as imaging agents. The size of microspheres is an important parameter that affects their behavior and application. Microspheres can range from nanoscale particles (nanospheres) to micrometer-sized particles (microspheres). Microspheres can be surface- modified to enhance their functionality or target specific sites.[12] Surface modification techniques include surface coating, conjugation with ligands or antibodies, and incorporation of targeting moieties. They can be used as imaging agents, where imaging dyes or contrast agents are encapsulated within the microsphere matrix to enhance visualization and diagnostics. Microspheres are also used for cell encapsulation, creating protective microenvironments for cells in tissue engineering, regenerative medicine, or cell-based therapies. Microspheres used in parenteral drug delivery are the product called Zoladex® (goserelin acetate) Depot. Zoladex is a widely used medication for the treatment of prostate cancer, breast cancer, and certain gynecological conditions. The preparation methodology and depot release criteria is as shown in figure2.

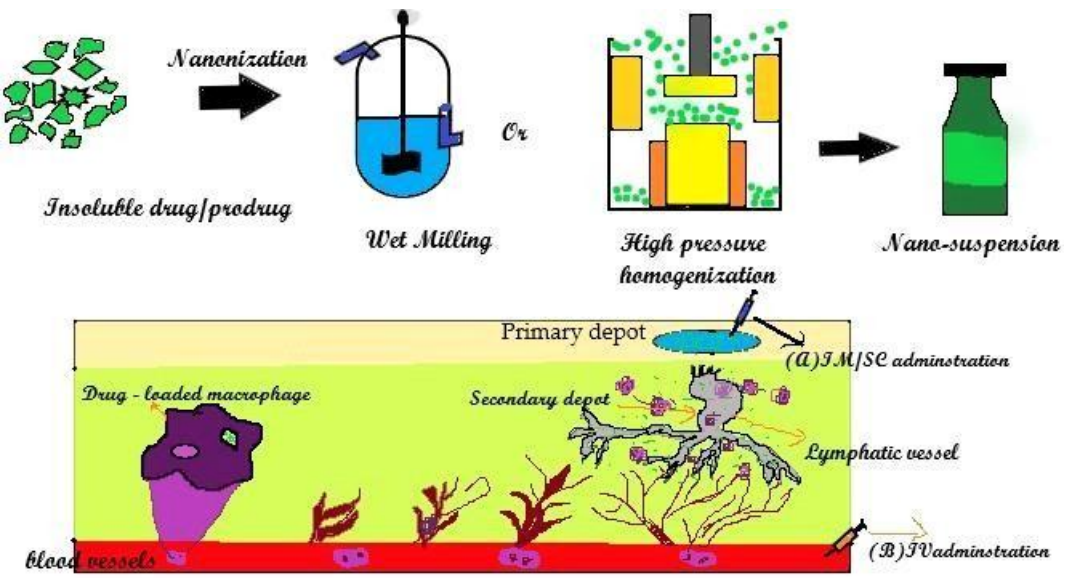

Fig. 2: Methodology and Mechanism of drug release of parenteral formulations.

Liposomes: These are lipid-based vesicles that can be used in parenteral drug delivery to encapsulate and deliver drugs to target sites in the body. They consist of a phospholipid bilayer structure with an aqueous core, providing a versatile platform for encapsulating both hydrophilic and hydrophobic drugs. Liposomes can encapsulate broad variety of drugs,

consisting of small molecules, peptides, proteins, and nucleic acids. Hydrophilic capsules can be encapsulated inside the aqueous core, whilst hydrophobic capsules can be included into the lipid bilayer. Liposomes can be designed to provide controlled release of drugs. By altering the lipid composition and membrane properties, the release kinetics of the encapsulated drug can be modulated.[13] This allows for sustained drug release, reducing the frequency of administration and maintaining therapeutic levels over an extended period. Liposomes can be surface altered with targeting ligands, such as antibodies or peptides to selectively deliver drugs to specific cells or tissues. Liposomes are generally biocompatible and biodegradable. Many liposome formulations use phospholipids that are naturally occurring in the body, reducing the risk of immunogenicity or toxicity.[14] Liposomes can contain drugs of different solubilities; hydrophobic drugs outperform hydrophilic drugs, and phospholipid bilayers become entangled in the aqueous depression. Doxil's introduction in 1995 for the treatment of patients with ovarian threats and AIDS-related Kaposi's sarcoma was the fundamentally defining moment in liposome- based products.[15]

Surgical implants

The term "implant" refers to a device or substance that is inserted or joined into the physique for prosthetic, beneficial, symptomatic, or experimental purposes. The dosage kinds used to reap worthwhile concentrations for a prolonged time are implants. In retaining with this, the foundational resources used in implants ought to be biocompatible. As a base material, polymers both biodegradable and not are frequently used. After the drug is consumed, non-biodegradable polymers must be surgically removed, which is painful and burdensome for the patients. Biodegradable polymers can be used to create surgical implants through carefully controlled manufacturing techniques like extrusion, injection moulding, and compression molding. The release profiles of these devices are typically highly reproducible.

Injectable gels

As parenteral depot systems, biodegradable injectable in situ gel-forming drug transport constructions are a achievable preference to microspheres and implants. It is made up of dissolvable, biodegradable polymers in a biocompatible service. The liquid polymer system solidifies upon contact with aqueous body fluids to form a solid implant when it is injected into the body using conventional needles and syringes.[16] If a drug is added to the polymer solution, it will become trapped inside the matrix as the polymer solidifies. As the polymer degrades over time, the drug is released. These designs choose polyhydroxyacids,

polyanhydrides, polyorthoesters, polyesteramides, and different biodegradable polymers. As additional proteins lose their patent security in the near future, their extent will enhance. For the delivery of drugs, biodegradable injectable in situ warehouse shaping designs are a legitimate trade for inserts. A steady terminal assortment at the infusion page after subcutaneous or intramuscular. In situ controlled release of bioactive macromolecules has a number of advantages, including easy in administration, simple formulation procedures, and effortless manufacturing conditions for delicate drug molecules. 'Infusion-like' plasma level time profiles are the most significant advantage of these systems, along with reduced dose and dosing frequency, improved patient compliance, and reduced dose.[17]

Nanoparticles

Nanoparticles have a small particle size, which allows for improved drug solubility, increased drug loading capacity, and better tissue penetration. Nanoparticles can encapsulate a wide range of drugs, including hydrophilic and hydrophobic compounds, peptides, proteins, and nucleic acids. The drug is encapsulated within the nanoparticle matrix or adsorbed onto the particle surface.[18] This encapsulation provides protection to the drug, improves its stability, and enables controlled release, leading to sustained drug levels and reduced dosing frequency. Nanoparticles can be surface-altered with ligands, antibodies, or peptides that specifically recognize and bind to receptors or markers on target cells or tissues. This allows for targeted drug delivery, enhancing therapeutic efficacy while minimizing off-target effects and reducing systemic toxicity. Nanoparticles can improve the bioavailability of poorly soluble drugs by increasing their solubility and dissolution rate.[19] The small particle size and large surface area-to-volume ratio of nanoparticles facilitate drug absorption, distribution, and cellular uptake. Nanoparticles can protect drugs from enzymatic degradation and rapid clearance from the bloodstream. Surface modifications with hydrophilic polymers, such as polyethylene glycol (PEGylation), can confer stealth properties to nanoparticles, preventing recognition and clearance by the immune system. This results in prolonged circulation time, allowing for improved drug delivery to target sites. Various techniques are employed to fabricate nanoparticles for parenteral drug delivery, including nanoprecipitation, emulsion/solvent evaporation, solvent displacement, and self-assembly methods. These techniques control particle size, drug loading, and surface properties to achieve desired characteristics.[20]

Nanosuspensions

Pharmaceutical nanosuspension consists of drug particles that are nanometers in size and are dispersed finely in an aqueous medium for either pulmonary and parenteral administration or oral and topical use. Nanosuspensions are typically less than 1 micron and between 100 and 200 nanometers in size.[21] The many advantages of nanosuspensions make them suitable for a wide range of applications. This system improves the drug's saturation solubility and dissolution rate, which increases the drug's bioavailability for poorly soluble or hydrophobic drugs. The creation of a stable nanosuspension for the delivery of vitamin B-12 was patented. The stable nanosuspension is created by first forming a nanofluidizable mixture with vitamin B-12 and then processing it through a nanofluidization process. It can then be administered through transmucosal membranes or other suitable routes of administration.

Nanoemulsion

Oil and water are mixed to form a liquid dispersion that is homogeneous, transparent, and thermodynamically stable. This is accomplished by adding copious amounts of surfactant and cosurfactant, which have droplet diameters ranging from 100 to 1000 microns.[22] Oil-in-water (o/w) or water-in-oil systems called nanoemulsions are transparent or translucent and have mean droplet diameters between 100 and 500 nm. Mini- emulsions and sub-micron emulsions are terms used interchangeably to describe them. Emulsifiers are used to stabilise two immiscible phases into a single phase in these thermodynamically stable systems. The primary issues with macroemulsions, such as creaming, flocculation, coalescence, and sedimentation, are not present in the system. On the basis of the energy required, nanoemulsion production techniques can be classified. Low-energy methods include spontaneous emulsification, the solvent diffusion method, and phase inversion temperature (PIT), whereas high-energy methods include high-pressure homogenization, microfluidization, and ultrasonification. The carrier approaches used in parenteral drug delivery system is as shown in figure 3.

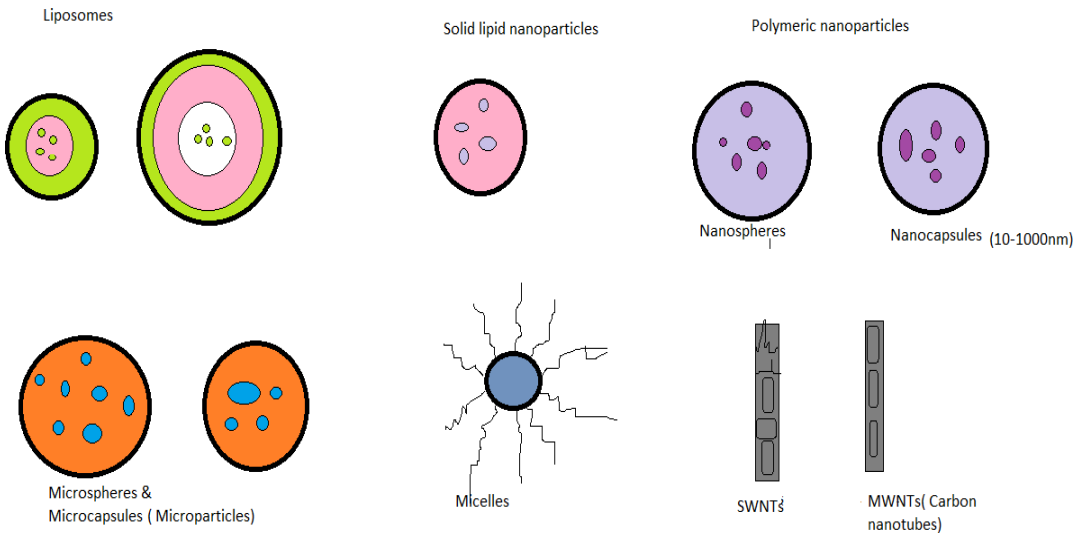

Fig. 3: Carrier systems used in parenteral products.

Manufacturing technologies

A complex exercise is carried out to ensure product quality within the general guidelines of the FDA, WHO, ISO, and good manufacturing practises in the pharmaceutical industry. The principle of design, facility design, and building a clean room are examples of this. The design of the room, the sterile processing area, the air handling system, the environmental contamination control system like the HVAC system, RTRH, aerosol behaviour, ventilation, entry, and exit, and their design methodology, as well as equipment like the High Efficiency Particulate Air (HEPA) filter and Laminar Air Flow (LAF) Systems—a combination of HEPA filters and laminar air flow—are all important factors in the design process. Controlling contamination and cross- contamination in the parenteral industry requires careful design.[23]

Design and Layout for parenteral production

The design layout of a parenteral product refers to the arrangement and organization of components and elements involved in the production of parenteral pharmaceuticals. The layout should optimize workflow, ensure product quality, and comply with regulatory requirements. The layout should reflect a logical and efficient flow of the manufacturing process, from raw material handling to final product packaging. This includes the sequence of activities, such as formulation, sterilization, filling, labeling, inspection, and packaging. The layout should minimize cross contamination risks and ensure smooth movement of materials and personnel. Parenteral products require aseptic manufacturing, typically carried out in cleanrooms with controlled environmental conditions.[24] The design and strategy for product development is as shown in fig4.

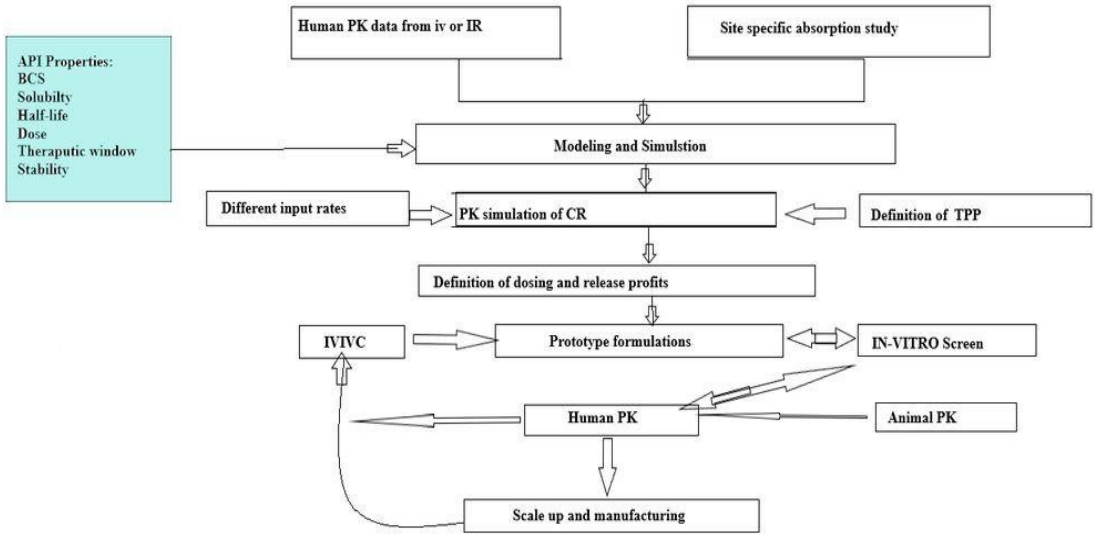

Fig. 4: Strategy for product development during preformulation- study Design and Production.

Cleanrooms are classified based on the level of cleanliness required for specific manufacturing processes. The classification is determined by the maximum allowable number of particles of a specified size per cubic meter of air.[25] While the ISO cleanroom classification system is widely used, there are also other classification systems utilized in different industries.

Class 10: Allows a maximum particle count of 10 particles of 0.5 micrometers or larger per cubic foot of air. This classification is also common in microelectronics and semiconductor industries.

Class 100: Allows a maximum particle count of 100 particles of 0.5 micrometers or larger per cubic foot of air. This classification is used in industries such as pharmaceutical manufacturing, medical device manufacturing, and biotechnology.

Class 1,000: Allows a maximum particle count of 1,000 particles of 0.5 micrometers or larger per cubic foot of air. This classification is used in industries such as pharmaceutical manufacturing, medical device operating, and biotechnology.

Class 10,000: Allows a maximum particle count of 10,000 particles of 0.5 micrometers or larger per cubic foot of air. This classification is commonly found in industries such as electronics assembly, optics, and automotive manufacturing.

Class 100,000: Allows a maximum particle count of 100,000 particles of 0.5 micrometers or larger per cubic foot of air. This classification is used in industries such as food processing, packaging, and general manufacturing. The list of clean room with details are enumaerated in table 3.

Table 3: List of ISO class cleanroom with descriptive features.

Clean room	Maximum Particle	Description
Class	Count (Particles ≥0.1 micrometers) per Cubic Meter of Air	
ISO Class 1	≤10	Ultra-clean environments required for critical processes, such as microelectronics manufacturing and nanotechnology research.
ISO Class 2	≤100	Highly controlled environments used in advanced electronics manufacturing and precision Optics applications.
ISO Class 3	≤1,000	Clean environments necessary for pharmaceutical manufacturing, sterilecompounding, and some electronics assembly.
ISO Class 4	≤10,000	Controlled environments used in general manufacturing, medical device assembly, and automotive industry.
ISO Class 5	≤100,000	Less stringent cleanliness requirements found in packaging areas, food processing, and non-Critical assembly operations.

Environmental control

In parenteral production, environmental control zones are established to ensure the appropriate control of environmental conditions, such as temperature, humidity, air cleanliness, and air pressure differentials. These zones are designed to maintain sterility, prevent contamination, and meet regulatory requirements (IES-RP-CC018.2). The commonly recognized environmental control zones in parenteral production.

Controlled Non-sterile Area (CNSA): This area is designated for activities that do not require aseptic conditions but still need control over environmental parameters. It may include activities such as raw material storage, weighing, and non-sterile component preparation.

Aseptic Processing Area (APA): The APA is the core area of parenteral production where aseptic operations take place, such as formulation, filling, and sterilization. It is designed to maintain a high level of cleanliness and sterility. The APA includes clean rooms with

appropriate air filtration, temperature, humidity, and pressure differentials. Stringent procedures, including proper gowning, cleaning, and disinfection, are implemented to minimize contamination risks (ISO 14644-1). Primary Engineering Control (PEC): This is the critical component within the APA where aseptic manipulations, such as filling or compounding, occur. Examples of PECs include laminar airflow workbenches, isolators, or restricted access barrier systems (RABS). The PEC provides a localized environment with high-efficiency particulate air (HEPA) filtration to maintain sterility during aseptic operations.

Secondary Engineering Control (SEC): The SEC refers to the surrounding environment of the PEC and includes the entire cleanroom area. The SEC supports the PEC by providing additional control over temperature, humidity, air quality, and pressure differentials to ensure the integrity of the aseptic environment.[26]

Support areas: These areas are ancillary spaces that support the main production activities. They include gowning rooms, material and equipment preparation areas, equipment washing areas, quality control laboratories, and storage areas for components, materials, and finished products.

Process optimization for parenteral products using quality by design (Qbd)

The essential goal of cycle plan and streamlining is to guarantee that assembling activities are done in the most ideal circumstances during the underlying stages, stage III clinical preliminaries, and furthermore at the business level, consequently affirming that the determinations have been met to the actual edge of the characterized plan space. Hese significant focuses should be covered in the procedure sketch report, which moreover comprises of records on the conveniences and climate, the gear, the assembling factors, and any necessities for it.[27] For the reason for working with the customary programming of the QbD norms and the ICH Q8 (R2) (drug improvement), Q9 (Quality gamble the executives), Q10 (Drug quality frameworks), and Q11 (Improvement and production of medication substances) hints in the drug fabricating industry, the criticality mission bunch inside the ISPE item quality lifecycle execution (PQLI) drive has presented a succinct, rational, and normal technique for criticality assurance. When used within the design space, the process validation ensures that it will produce a product of acceptable quality, and the smaller-scale systems used in R&D to create the design space mimic how the process will perform at the commercial production scale.[28] Process streamlining for parenteral product the utilization of

Value by means of Plan (QbD) is an orderly system that objectives to make specific item extraordinary through planning and controlling the assembling system. Here are the key advances stressed in enhancing parenteral product the utilization of QbD. Define Target Product Profile (TPP) and Critical Quality Attributes (CQAs): TPP describes the desired characteristics and performance of the parenteral product, while CQAs are the measurable attributes that directly impact the product's quality, efficacy, and safety. Identifying the TPP and CQAs is crucial for process optimization. Design of Experiments (DoE): DoE includes systematically various manner parameters and measuring their influence on CQAs. It helps become aware of crucial system parameters (CPPs) that drastically have an impact on the product's pleasant. DoE studies can be conducted at laboratory or pilot scale to determine the optimal process conditions. Risk Assessment: Conducting a risk assessment helps identify potential risks associated with CPPs and their impact on product quality.

Process Analytical Technology (PAT): Implementing PAT involves using real-time monitoring, measurement, and control of process parameters to ensure product quality. This can include technologies such as spectroscopy, chromatography, and particle sizing techniques.[29] PAT allows for continuous process monitoring and adjustment, reducing the risk of batch failures and improving process efficiency. The design space defines the range of process parameters within which the product consistently meets its desired quality attributes. It is established based on the knowledge gained from DoE and risk assessments.

Continuous Process Verification (CPV): CPV involves ongoing monitoring of the manufacturing process to ensure it remains within the established design space. It includes collecting and analyzing data, assessing process performance, and implementing appropriate corrective and preventive actions as needed. Process Validation: Once the optimized process is established, process validation confirms its ability to consistently produce products of the desired quality.[30]

Preformulation studies are conducted as the first step in the product development process in order to screen the excipients or packaging components and choose those that are compatible with the candidate drug using accelerated stress-testing techniques. To ultimately choose the best product variant, stability data must be generated for one or more of the variants. Although product and process design and optimization are portrayed in the development framework as separate stages, they are actually closely related in practice.[31] The compiled list of patentable parenteral formulations are described in table 4.

Table 4: List of patentable products of parenteral technology.

Patent No.	Contents	Ref. No.
US20100098735(2010)	Injectable depot compositions and its process of preparation	[32]
US20090156670 (2009)	Non aqueous liquid parenteral aceclofenac formulation	[33]
US20090181101 (2010)	Mucoadhesive nanoparticles for cancer treatment	[34]
US20090233951 (2009)	Parenteral solutions containing metolazone	[35]
US007638558 (2009)	Polymeric micelles for drug delivery	[36]
US20080119408 (2008)	PTH formulations for intranasal delivery	[37]
US20080213177 (2008)	Nanoparticles comprising RNA ligands to impart targeting characteristics for delivery of RNA for targeting cells and imaging purposes	[38]
US20070265190 (2007)	Opoid depot formulations	[39]
US7125909 (2006)	Sterile parenteral nutrition compositions comprising oil-in-water emulsions	[40]
US20020081336 (2002)	Parenterally administered microparticles	[41]
US20020110587 (2002)	Liposomal compositions and methods of using	[42]
US6495534 (2002)	liposomal compositions to treat dislipidemias Stabilized aqueous suspensions for parenteral use	[43]
US20100272639 (2010)	Polysaccharide nanoparticles useful in drug delivery, tissue specific targeting, for medical imaging and diagnosis	[44]

Preservatives in parenteral products

Preservatives are substances, either natural or synthetic, that are added to products like food, medicine, paint, biological samples, wood, etc. Preservatives must be added to such products, especially those with a higher water content, in order to prevent microbial alterations and degradation during storage. They are phenoxyethanol, benzyl alcohol, chlorobutanol, m-cresol, methylparaben, propylparaben, thimerosal, and chlorobutanol. Preservatives are used in a relatively low dose, ranging from 0.002 to 1%, although in some parenteral formulations, preservatives are used in a dose above 1%. Some preservatives have minimum inhibitory concentrations (MIC) that are less than or equal to 5000 mg/mL. Preservatives included in the diluent for lyophilized parenteral products are also excluded from coverage.[45] Other widely used preservatives include phenyl mercuric nitrate, benzalkonium chloride, and benzethonium chloride.[33] Preservatives are often used in parenteral products to prevent

microbial growth and maintain product stability throughout the shelf life.[46] Here are some commonly used preservatives in parenteral products along with examples.

Phenol: Phenol is another commonly employed preservative in parenteral products. It has strong antimicrobial properties and is effective against a wide range of microorganisms.

Methylparaben and Propylparaben: Methylparaben and propylparaben are paraben-based preservatives that are often used in combination. They have antimicrobial properties and can inhibit the growth of bacteria and fungi. Sorbic Acid and Sodium Benzoate: Sorbic acid and sodium benzoate are preservatives that are sometimes used together in parenteral products. These preservatives can be found in certain injectable formulations and ophthalmic solutions. Various generic and brand products are enlisted in table5.

Table 5: Preservatives used in parenterals.

Generic product Name	Product brand Name	Manufacturer	Preservative	Preservative concentration
Diptheria and tetanus toxoids and acellular	DAPTACEL	Sanofi pasture	Phenoxy ethanol	0.6%
pertusis adsorbed	PEDIARIX			0.5%<12.5mg
Diphtheria and tetanus toxoids and acellular pertusis absorbed		Glaxo smithkline	Phenoxy etanol thimerosal	mercury per 0.5 ml dose
hepatitis B (recombinant)and inactivated poliovirus vaccine combined	INFANRIX	Glaxo smithkline	Phenoxy ethanol	0.5%(2.5 mg in 0.5 ml)
Diphtheria and tetanus toxoids and acellular pertusis vaccine adsorbed	HAVRIX TWINRIX	Glaxo smithkline Glaxo smithkline	Phenoxy etanol	0.5%
Hepatitis A vaccine inactivated	ENGERIX-B	Glaxo smithkline	Phenoxy ethanol	0.5%
Hepatits A Inactivated and hepatitis B (Recombinant) vaccine Hepatitis B Vaccine (RECOMBINANT) PNEUMOCOCCAL vaccine polyvalent	PNEUMOVAX	Merck	Thimersoal Phenol	<0.5 mcg mercury(0.5 ml pediatric and1.0ml adult dose) 0.25%

Solubilizers

Solubilizing agents are substances that help in the dissolution of drugs or increase their solubility in a formulation; they can be generally divided into surfactants and co-solvents. Solubilizers are employed to preserve and stabilize the weakly water-soluble medicines aqueous solubility like the solubilizers tweens and polysorbate. The surface tension of the drug compounds is decreased by the surfactants, which increases the dissolution. Solubilizers are used in parenteral drug delivery to improve the solubility and bioavailability of poorly water-soluble drugs. They enhance the drug's dissolution in the formulation, allowing for better absorption and systemic delivery.[47]

Ethanol: Ethanol is a commonly used co-solvent in parenteral formulations to enhance drug solubility. It can improve the solubility of both hydrophilic and lipophilic drugs.[48]

Polyethylene Glycol (PEG): It is often used as a solubilizer in parenteral formulations, particularly in injectable solutions and suspensions.

Propylene glycol: Propylene glycol is a solvent and solubilizer commonly used in parenteral drug delivery. The solubilizers commonly used in parenteral drug delivery along with examples are shown in table 6.

Table 6: Enumerated solubilizers in parenteral formulations.

Solubilizers	Examples of Parenteral Formulations
Cyclodextrins	Hydroxypropyl-beta-cyclodextrin(HPβCD), Sulfobutyl ether-beta-cyclodextrin (SBECD)
Polysorbate 80	Injectable emulsions, microemulsions
Ethanol	Injectable solutions, suspensions
Polyethylene Glycol (PEG)	Injectable solutions, suspensions
Propylene Glycol	Injectable solutions, suspensions

Packing device

There are various container closure systems for parenteral medications that can be used, but they must be carefully planned and selected to meet a number of requirements. In contrast, the plastic vial lacks all these benefits of the glass vial. However, they are not fragile, are light, are cheap, and can be manufactured in precise dimensions and in a variety of shapes. Type I borosilicate glass has a low thermal coefficient of expansion and is remarkably chemically inert. Third, the type III standard soda lime glass is chemically treated to reduce alkali leachables in the type II surface-treated soda lime glass. (Not used for parenteral drug

products). The packaging of parenteral products plays a crucial role in ensuring their safety, efficacy, and integrity throughout their shelf life.[49] Some key aspects of packaging for parenteral products are:

Primary packaging

Glass vials: Glass vials are commonly used for parenteral products, particularly for liquid formulations. They offer excellent barrier properties, chemical compatibility, and visibility. Glass vials may be colorless or amber to protect light-sensitive drugs.

Ampoules: Ampoules are sealed glass containers used for single-dose parenteral products. They provide a hermetic seal and are typically opened by breaking the ampoule neck.

Pre-filled Syringes: Pre-filled syringes are increasingly used for parenteral products. They offer convenient and accurate dosing, reduce the risk of medication errors, and ensure sterility. Pre- filled syringes can be made of glass or plastic, depending on the compatibility with the drug formulation.[50]

Cartridges: Cartridges are cylindrical containers used for multi-dose parenteral products. They are often made of glass or plastic and can be used with a compatible delivery device, such as a pen injector.

Infusion bags: Infusion bags are flexible containers used for large-volume parenteral products, such as intravenous solutions. They are typically made of polyvinyl chloride (PVC) or polyolefin materials.[51]

Closure systems

Rubber stoppers: Rubber stoppers are commonly used to seal vials and ampoules. They provide a secure seal and can be pierced by needles for drug withdrawal or administration.[52]

Flip-Off Caps: Flip-off caps are aluminum caps with a plastic seal used to cover vials. They provide tamper-evidence and help maintain product sterility.

Needle safety devices: Some parenteral products are packaged with needle safety devices, such as needle shields or retractable needles, to prevent needlestick injuries and enhance user safety.[53]

Secondary packaging

Cartons and Labels: Parenteral products are typically packaged in cartons with appropriate labeling, including essential product information, dosage instructions, and warnings.

Protective packaging: Additional protective packaging, such as blister packs or unit-dose packaging, may be used for specific parenteral products to provide additional protection during storage and transportation.[54]

The selection of packaging materials and designs depends on various factors, including the drug formulation, compatibility, stability, and regulatory requirements. Pharmaceutical manufacturers follow Good Manufacturing Practices (GMP) and regulatory guidelines to ensure the appropriate selection, qualification, and testing of packaging materials and systems for parenteral products.[55]

Prefilled syringes

Prefilled syringes are a popular and convenient packaging option for parenteral products. They are designed to contain a premeasured dose of medication and are ready for immediate use without the need for manual filling or dose measurement. Here are some key aspects of prefilled syringes in parenteral packaging: The prefilled syringe serves as the primary container for the parenteral product.[56] The prefilled syringe has a plunger and stopper mechanism. The plunger, usually made of rubber or synthetic material, is used to expel the medication from the syringe barrel. Prefilled syringes may come with an attached needle or with a needleless system. To ensure product safety, prefilled syringes often incorporate tamper- evident features, such as caps or covers, to indicate if the syringe has been tampered with or used previously.[57]

CONCLUSION

Parenteral drug delivery is a critical route of administration for various medications, particularly when oral administration is not feasible or effective. It involves delivering drugs directly into the bloodstream or specific target sites, bypassing the gastrointestinal tract. The manufacturing technology employedin parenteral production plays a crucial role in ensuring the safety, efficacy, and quality of theproducts. It involves formulation development, process optimization, and the use of specialized equipment and facilities. Key considerations in parenteral manufacturing include maintaining sterility, ensuring accurate dosing, achieving appropriate drug solubility and stability and incorporating extended-release technologies

when necessary. Clean room areas and environmental control play a vital role in parenteral production, with specific classification systems in place to ensure adequate control of airborne particles, microbial contamination, and environmental factors. These controlled environments help maintain the quality and sterility of the products during manufacturing and packaging processes. Additionally, various formulation techniques and technologies are utilized in parenteral drug delivery, such as liposomes, microspheres, nanoparticles, and extended- release systems. These approaches aim to enhance drug solubility, improve bioavailability, provide sustained release profiles, and target specific sites of action. The packaging of parenteral products is critical to ensure product integrity, sterility, and patient safety. Prefilled syringes have gained popularity as a convenient and reliable packaging option, offering accurate dosing, ease of use, and reduced risk of contamination. Overall, parenteral drug delivery and manufacturing technology are continuously evolving to enhance therapeutic outcomes, improve patient compliance, and ensure the safe and effective delivery of medications. These advancements contribute to the development of innovative therapies and the overall advancement of healthcare.

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