International Journal of Scientific Research in Engineering and Management (IJSREM)
Volume: 09 Issue: 10 | Oct - 2025 SJIF Rating: 8.586 ISSN: 2582-3930

Injectable Drug Product Formulation

Nilesh Prajapati

Abstract:

This study has been undertaken to investigate the Parenteral Formulations are sterile, pyrogen-free, administered by injection through skin layers. This review highlights all the aspects regarding parenteral products advantages, disadvantages, routes of administration, additives, preparation, types of containers and quality control tests for evaluation. They are required, like any pharmaceutical dosage forms, to meet the pharmaceutical quality standards as described in pharma-copeias and to be safe for the intended purpose of use. Sterility can be achieved by different processes of sterilization that should be appropriate to the formulations, while the pyrogen-free aspect will require, if no depyrogenation process is used during the preparation of the sterile drug products, the use of pyrogen-free pharmaceutical ingredients; drug substances or API (Active Pharmaceutical Ingredient) and excipients. Keywords: Parenteral Formulations, Antimicrobial Agents, Needle.

I. INTRODUCTION

Parenteral preparations are sterile, pyrogen-free pharmaceutical dosage forms intended for administration by injection, infusion, or implantation into the body. These formulations may be in the form of solutions, emulsions, suspensions, or sterile solids, and are packaged in either single-dose or multi-dose containers.

Unlike oral or topical routes, parenteral administration bypasses the body's natural protective barriers, such as the skin and mucous membranes. As a result, parenteral drug delivery allows for rapid and targeted therapeutic effects by introducing the drug directly into the bloodstream (intravenous), muscle tissue (intramuscular), under the skin (subcutaneous), or more specialized sites such as the spinal cord (intrathecal).

Due to their direct entry into systemic circulation and the risk of contamination, parenteral preparations must meet strict standards of sterility and purity.

II. DEFINITION

Parenteral preparations are sterile pharmaceutical dosage forms intended for administration by injection or infusion. They include solutions, suspensions, emulsions, powders reconstituted for injection or infusion, and injectable gels. These preparations are designed to be introduced directly into the systemic circulation of humans or animals, bypassing the gastrointestinal tract.

Due to their route of administration, parenteral products must be free from microbial contamination and pyrogens, ensuring safety and efficacy in clinical use.

III. ADVANTAGES AND DISADVANTAGES OF PARENTERAL FORMULATIONS

3.1 Advantages

1. **Rapid Onset of Action**: Parenteral administration, especially via the intravenous (IV) route, provides a rapid clinical response, making it highly effective in emergency situations such as epilepsy, asthma, cardiac arrest, and hypertensive crises.

2. **Alternative for Non-Oral Administration**: It serves as a valuable route for patients who are unconscious, vomiting, or unable to swallow.

3. **Prolonged Drug Action**: Some parenteral formulations offer sustained release, reducing the frequency of administration. For example, intramuscular (IM) injection of benzathine penicillin-G can provide therapeutic levels for up to a month.

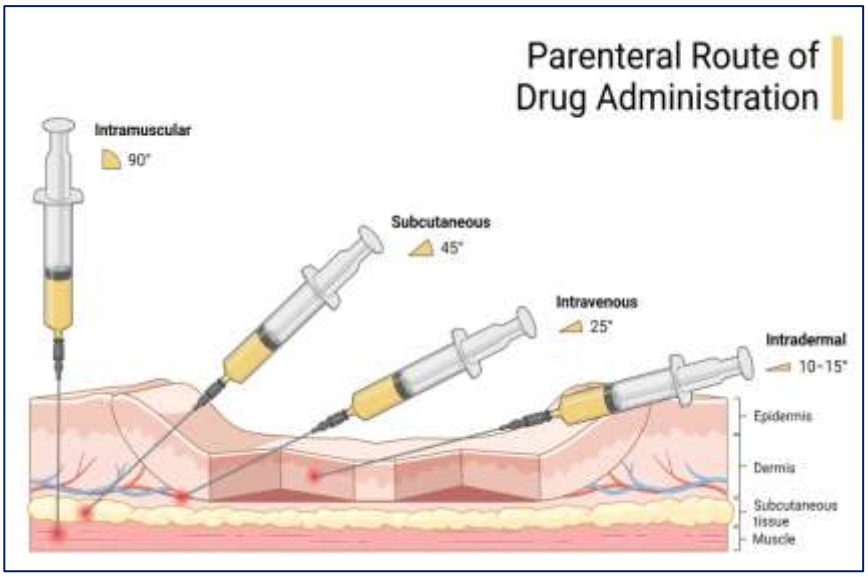
3.2 Disadvantages

- **Irreversibility**: Once administered, parenteral drugs cannot be easily removed from the body in cases of overdose or adverse reactions.
- **Local Reactions**: Needle insertion may cause pain, irritation, or tissue damage at the injection site.
- **High Production Costs**: Manufacturing parenteral products requires strict aseptic conditions, making production more complex and expensive.
- **Risk of Improper Administration**: Incorrect technique or dosing can lead to complications, including infection, embolism, or injury.

IV. ROUTES OF ADMINISTRATION OF PARENTERAL PRODUCTS

Parenteral drugs can be administered through several different routes, depending on the desired onset, duration, and site of action. The most common parenteral routes include:

- **Intradermal (ID) Route**
- **Subcutaneous (SC) Route**
- **Intramuscular (IM) Route**
- **Intravenous (IV) Route**



4.1 Intradermal (ID) Route

This is a **superficial injection** into the layers of the skin — specifically between the epidermis and dermis — commonly administered on the anterior surface of the forearm.

Uses:

- Diagnostic testing, e.g., for susceptibility to bacterial diseases like **tuberculosis** (Mantoux test) and **diphtheria**.
- **BCG vaccine** administration (for immunization against tuberculosis).

Volume administered: Approximately **0.1 mL**

4.2 Subcutaneous (SC) Route

In this method, the drug is injected into the **subcutaneous tissue** located beneath the dermis. Common sites include the **upper arm, thigh**, or **lower abdomen**.

Volume administered: Typically **not more than 1 mL**

Note: Larger volumes may be given if the enzyme **hyaluronidase** is co-administered. This enzyme breaks down hyaluronic acid, increasing subcutaneous tissue permeability and allowing greater drug dispersion.

Advantages:

- Faster absorption than the ID route due to:
  - A larger surface area.
  - Richer vascular (blood) supply in the SC region.

Examples of drugs administered via SC route:

- **All insulin preparations**
- Some vaccines, e.g., **rabies**, **cholera**

4.3 Intramuscular (IM) Route

Here, the drug is injected deeply into **skeletal muscle**, typically in the **deltoid muscle (upper arm)** or the **gluteal muscle (buttocks)**.

Advantages over ID and SC routes:

- **Highly vascular** with a **larger surface area**, allowing administration of:
  - **2–5 mL** in the deltoid
  - Up to **5 mL** in the gluteal muscle
-
- Suitable for:
  - **Aqueous and oily solutions**
  - **Aqueous suspensions**

Examples:

- **Oily solutions:**
  - *Depo-testosterone* (testosterone propionate in sesame oil)
- **Aqueous suspensions:**
  - *Depo-medrol* (methylprednisolone in water) – provides **prolonged action** due to slow dissolution.
- **Vaccines:**
  - *Cholera*, *diphtheria*, *influenza*

4.4 Intravenous (IV) Route

This route involves injecting the drug **directly into the bloodstream**, usually through the **median basilic vein** on the inner forearm. It is used for both **small and large volumes** of drug solutions.

Advantages:

- **Immediate onset of action**, making it ideal for **emergency situations** (e.g., cardiac arrest, shock, or severe infections).

Disadvantages:

- Once administered, the drug **cannot be retrieved**, making it risky in cases of **overdose or toxicity**.

Form of Drug Given via Intravenous (IV) Route

Parenteral drugs administered through the IV route are typically formulated as:

- **Aqueous solutions**:
  - The most common form for IV administration due to immediate compatibility with blood plasma.
- **Emulsions of very fine droplets**:
  - Example: *Phytonadione* (Vitamin K_1) — used to manage bleeding disorders and reverse the effects of anticoagulants.
- **Large volume solutions**:
  - Administered **slowly via IV infusion** (often over several hours).
  - Volumes can be up to **1000 mL**, commonly used in **replacement therapy** and **fluid resuscitation**.

Examples of IV fluids used in replacement therapy:

- **Ringer's solution**: Contains *sodium chloride (NaCl), potassium chloride (KCl), and calcium chloride ($CaCl_2$)* — used to restore electrolyte balance.
- **Dextrose solutions**: Provide fluids and calories in patients unable to eat or drink.

V. GENERAL PROCEDURE FOR THE PREPARATION OF PARENTERAL PRODUCTS

Parenteral products must be **sterile**, **pyrogen-free**, and **free from particulate matter**, as they are introduced directly into the body's internal environment. To ensure this, preparation must occur in a highly controlled environment designed to prevent contamination.

Aseptic Conditions and Environmental Controls

To achieve a sterile environment, the following measures are implemented:

- **Laminar Air Flow (LAF) Systems**:
  - These systems create a continuous flow of **HEPA-filtered air**, which removes dust particles and airborne microorganisms.
  - Often integrated with **UV radiation**, which helps kill any remaining microorganisms.
- **Sterile and Clean Work Surfaces**:
  - **Room walls, benches, and equipment** are routinely cleaned with **antimicrobial agents** (e.g., alcohol-based disinfectants) to prevent microbial growth.
- **Protective Clothing for Personnel**:
  - Personnel involved in the preparation must wear:
    - **Sterilized gowns or coveralls**
    - **Disinfected gloves**
    - **Face masks** (to cover the mouth and nose)

- **Sterile caps or head covers**
- **Protective eyewear** or **plastic glasses** to shield the eyes from UV exposure

These strict aseptic procedures ensure that parenteral preparations remain safe and free from contaminants throughout the manufacturing process

VI. STEPS INVOLVED IN THE PREPARATION OF PARENTERAL PRODUCTS

The preparation of parenteral products involves multiple critical steps to ensure sterility, safety, and efficacy. Each step must be carried out under strictly controlled conditions, in compliance with Good Manufacturing Practices (GMP).

1. Cleaning and Sterilization of Equipment and Containers

- All equipment and containers used must be thoroughly **cleaned** using **automatic washing and rinsing machines**.
- After cleaning, they are **sterilized** using:
  - **Dry heat** (e.g., hot air ovens), or
  - **Moist heat** (e.g., autoclaving).

2. Ensuring Purity of Ingredients

- All raw materials including **active pharmaceutical ingredients (APIs), solvents**, and **excipients** must be of high purity.
- When water is used as a vehicle, **Water for Injection (WFI)** is mandatory.

3. Compounding the Preparation

- The drug formulation is compounded in aseptic conditions.
- **Small volumes** of solvent are added initially to dissolve the active ingredient, followed by gradual addition of larger volumes to reach the final concentration.

4. Filtration

- The solution is filtered to remove microorganisms and particulates.
- For **thermolabile (heat-sensitive)** products, **sterile filtration** is used instead of heat sterilization.
- Commonly used filters: **Millipore membranes** made from **cellulose acetate**.

5. Filling into Final Containers

- The sterile product is transferred into final containers such as:
  - **Glass ampoules**
  - **Vials**
  - **Plastic IV bags**
- **Glass containers** are preferred due to their heat resistance during terminal sterilization.
- **Amber-colored glass** is used for **light-sensitive (photolabile)** drugs, although it can hinder visual inspection for particulate matter.

6. Closing and Sealing

- Containers are securely closed and sealed:
  - Ampoules: sealed by melting the glass tip.

- Vials: sealed with rubber stoppers and aluminum caps.
- IV bags: sealed using heat or mechanical systems.

7. Final Sterilization

- The filled and sealed containers are subjected to **terminal sterilization** (if applicable), using heat or radiation, depending on the product's stability.

8. Labeling

Each container must be labeled with:

- **Product name**
- **Concentration and quantity of ingredients**
- **Storage conditions**
- **Batch number**
- **Manufacturing and expiry dates**

VI. STERILIZATION OF PARENTERAL PRODUCTS

Sterilization:
The process of killing or removing all living microorganisms from a certain preparation or material.

Essential methods of sterilization:

- Dry heat
- Moist heat or steam
- Filtration

VII. QUALITY CONTROL (OR EVALUATION) OF PARENTERAL PREPARATIONS

To ensure parenteral products meet the required standards of **safety** and **effectiveness**, the following tests are performed:

- **Sterility test** — to confirm the absence of viable microorganisms
- **Clarity test** — to check the solution for particulate matter or cloudiness
- **Pyrogen test** — to detect fever-causing substances (endotoxins)
- **Leaker test** — to ensure the container is properly sealed and leak-free

7.1 STERILITY TEST

Purpose:
All parenteral products must be sterile. The sterility test is performed on randomly selected samples to confirm this.

Principle of the Test

- A sample of the product is transferred into suitable liquid culture media.
- Different culture media support the growth of different types of microorganisms.
- The inoculated media are incubated for specified periods and temperatures to detect microbial growth.

Culture Media and Conditions:

Medium	Organisms Detected	Incubation Time	Temperature
Thioglycolate liquid medium	Anaerobic organisms	7 days	35 - 37°C
Soybean-casein liquid medium	Aerobic organisms	7 days	35 - 37°C
Sabouraud liquid medium	Fungi	7-10 days	25 - 27°C

Controls

I) Positive Controls (10 days):

- **Thioglycolate medium:** inoculated with *Clostridium supergenes* (anaerobic bacterium), incubated 7 days at 35-37°C
- **Soybean-casein medium:** inoculated with *Staphylococcus aurous* (aerobic bacterium), incubated 7 days at 35-37°C
- **Sabouraud medium:** inoculated with *Candida alb cans* (fungus), incubated 10 days at 25-27°C

These confirm the fertility (ability to support growth) of the media.

II) Negative Controls:

- Culture media without any microorganisms or samples, incubated at the same conditions, ensure that the media themselves are sterile.

Special Notes:

- If the sample contains antimicrobial agents, they must be neutralized or diluted to prevent false-negative results.
- Example: Phenyl mercuric nitrate is inactivated by thioglycolic acid.

Observations of the Sterility Test

- **Tested material is considered sterile if:**
  - **No growth or turbidity** is observed in samples **a, b, c, g**
  - **Growth is observed** in control samples **d, e, f**
- **If growth is observed in samples a, b, c, g** (which should be sterile)

OR

No growth is observed in controls d, e, f (which should show growth),
Then the test must be **repeated with a fresh sample**.

- If, upon repeat testing, **growth is still observed in test samples**,

The preparation is considered **unsterile and rejected**.

Basically:

- No growth in test samples + growth in controls = sterile
- Growth in test samples or no growth in controls = inconclusive or unsterile → repeat test

- Persistent growth in test samples after repeat = reject product

7.2 PYROGEN TEST

What are Pyrogens?

- Metabolic products produced by microorganisms, mainly from their **cell walls**.
- Composed of **lipopolysaccharides**.
- Characteristics: water-soluble, filterable, thermostable.
- Cause **febrile reactions** (fever, headache, backache) in humans.

Major Source:

- **Water** used as a vehicle in parenteral preparations is the main source of pyrogens.

Removal of Pyrogens:

Adding oxidizing agents like **potassium permanganate + small quantity of barium** to oxidize pyrogens into non-volatile organic solids that can be filtered out.

PYROGEN TEST (In Vivo)

- Performed on all **aqueous parenteral preparations**.
- Uses **rabbits** because their febrile response to pyrogens is similar to humans.

Principle:

- Measure the **rise in rectal temperature** after intravenous injection of the test sample.

Procedure:

- Dose: **10 ml/kg** of sample injected into ear vein of **8 rabbits**.
- Temperature recorded before injection and at 1, 2, and 3 hours after injection.
- The **rectal temperature increase should NOT exceed 0.6°C** above the normal baseline.

Recently: In Vitro Pyrogen Test

- The test solution is added to a **lysate solution** (e.g., Limulus Amebocyte Lysate test).
- If pyrogens are present, **a gel forms**.
- If no pyrogens, the solution remains **clear**.
- This method is more **sensitive, rapid**, and avoids animal use compared to in vivo testing.

7.3 CLARITY TEST

- **Definition:**

Clarity refers to the absence of any foreign matter or visible particles in parenteral preparations.

- **Procedure:**

The solution is visually inspected under **strong light** to check for any cloudiness, turbidity, or particulate matter

7.4 LEAKER TEST

Purpose:
To ensure ampoules are effectively sealed and free from leaks.

Procedure:

1. **Immersion:**

Ampoules are submerged in a tank containing **1% methylene blue dye solution**.

2. **Vacuum Application:**

The tank is sealed and air inside is evacuated to create **negative pressure** (vacuum).

- This increases pressure on any weak points in the ampoule seals.
- The vacuum also helps the dye penetrate any leaks.

3. **Inspection:**

Ampoules are removed and washed.

- Any ampoule containing **blue dye inside** indicates a leak and is **rejected**.

VIII. ADDED SUBSTANCES (OR ADDITIVES)

Additives, also known as excipients, are substances incorporated into pharmaceutical formulations for various purposes, including:

- **Maintaining the solubility** of the active drug substance.
- **Enhancing the stability** of the formulation during storage and use.
- **Ensuring isotonicity** of the product, particularly for parenteral, ophthalmic, and nasal preparations.
- **Facilitating administration** by improving taste, texture, or ease of delivery.

ADDITIVES USED TO MAINTAIN THE SOLUBILITY OF THE DRUG

To enhance the solubility of **poorly water-soluble drugs**, the following approaches can be adopted:

. Use of Water-Miscible Solvents

Adding one or more **water-miscible solvents** to hydrophobic drugs improves solubility. **Examples of Water-Miscible Solvents:**

- **Polyethylene glycol (PEG)**
- **Propylene glycol (PG)**
- **Glycerol**
- **Ethanol**

2. Complex Formation

Some drugs form **water-soluble complexes** with certain agents, which enhances their solubility.

Example:

- **Sodium benzoate** is used to solubilize **caffeine** by forming a **highly water-soluble complex**.

3. Use of Surface Active Agents (Surfactants)

Surface-active agents reduce surface tension and **increase the solubility** of hydrophobic substances.

Examples of Surfactants:

- **Tweens** (e.g., Tween 80)
- **Spans**

Uses of Surface Active Agents:

- Enhance the solubility of **oil-soluble drugs** such as vitamins A, D, E, and K.
- Improve **wettability** and promote **dispersion** of solids in **parenteral suspensions**.
- Prevent the formation of **foams** during preparation or administration.

4. Use of Suspending Agents

Suspending agents help keep **solid particles evenly dispersed** in suspensions by reducing their rate of sedimentation.

Examples of Suspending Agents:

- **Sodium carboxymethyl cellulose**
- **Methyl cellulose**
- **Polyvinyl pyrrolidone (PVP)**

Note:

- Suspending agents are used to **reduce the sedimentation rate** in parenteral suspensions.
- They should not be used in **high concentrations**, as excessive viscosity may hinder injection.

Table 1: Additives for Solubility Enhancement

Method	Additives/Examples	Function
Water-miscible solvents	PEG, PG, Glycerol, Ethanol	Improve solubility of hydrophobic drugs
Complex formation	Sodium benzoate + Caffeine	Form water-soluble complexes
Surface active agents	Tweens, Spans	Solubilize oil-soluble drugs, improve dispersion, prevent foaming
Suspending agents	Sodium CMC, Methyl cellulose, PVP	Maintain suspension stability, reduce sedimentation

Conclusion

- **Parenteral formulations** are among the most critical drug delivery systems in the pharmaceutical industry due to their rapid and direct therapeutic action.
- Because they are administered directly into body tissues or cavities, ensuring their **sterility** and **formulation stability** is essential.
- Based on the route of administration, parenteral products can take various forms such as **injections, infusions, and implants**.
- All parenteral products must be prepared under **aseptic conditions** to avoid contamination and ensure patient safety.
- The **physical and chemical properties** of all components used in parenteral preparations must be thoroughly evaluated to ensure **safety, efficacy, and compatibility**.

REFERENCE

1) Remington, Science And Practice Pharmacy,Parental Preparation, 20th Edition.Philadelphia: Ise Publication 1 (2000)

2) Ford Jl. "Parent Products". In: Aulton Me, (Ed.)Pharmacy:Science Measurement Form Design. New York; Longman (1988).

3) Ansel HC., Et al. "Drug dosage forms and drug delivery system, program 7". Lippincott Williams and Wilkins: Philadelphia (1999).

4) Colombo G., et al. "Stable aqueous suspension for use by parents". US6495534 (2002).

5) Beecher P. "Encyclopedia of emulsion technology, basic theory". Marcel Dekker: New York 1 (1983).

6) Collins Gold LC., Et al. "Parental emulsions for drug delivery". Advanced Drug DeliveryReview 5 (1990): 189-208.

7) Singh M and Ravin L. “Parent emulsions as drug management systems”. Journal of Parenteral Science and Technology 40 (1986): 34- 44.

8) Brazeau GA., Et al. "Volume Forms: Parents". To: Swarbrick James (Ed.). Encyclopedia of Pharmaceutical Technology. 3rd edition. Informa Healthcare USA, Inc: New York 1 (2007): 1001-1011.

9) United States Pharmacopeia, National Formulary. US Pharmacopeial Convention, Rockville, MD (1995): 1775-1777.

10) Groves MJ. "Parental drug delivery system". To: Mathiowitz Edith (Ed.). Encyclopedia of regulated releases. John Wiley and Sons, Inc: New York 1-2 (1952): 743-777.

11) Chien YW. "Parental drug delivery and delivery programs". In: New Drug Delivery Program, 2nd ed. 50. Marcel Dekker: New York 1992): 382-385.

12) Avis KE., Et al. "Dosage forms: Parenting". Marcel Dekker: New York 1992; 1.

13) JC Boylan and AL Fites. Parental Products, in Modern Pharmaceutics, G.L. Bankerand C.T. Rhodes, Ed. (Marcel Dekker Inc. New York, NY), (1979): 445

14) PP DeLuca and JC Boylan. Parental Formation for Small Volume Doses Forms: Pediatric Drugs, K.E. Avis et al., Ed. (Marcel) Dekker Inc., New York, NY), (1992): 215.

15) RJ Harwood., Et al. "Processing of Young Parental Parents and Related Introductory Products" in Medication Dosage Forms: Parental Medicine 2 (1993): 61.

16) Gadzag M., et al. "Stable songs of parents of vinblastine or vincristine". US5397784 (1995).

17) Brahmankar DM and Jaiswal SB. "Drug absorption". In: Biopharmaceutics and pharmacokinetics manual. Vallabh Prakashan: Delhi (2006).

18) Patel RM. "Parent suspension: View all". International Journal of Current Medicine Research 2.3 (2010): 4-13.

19) Chang HC., Et al. "Types of continuous parental doses of dog butorphanol". International Journal of Current Pharmaceutical Research 176 (1999): 147-56 .

20) KE Avis., Et al. Forms: Parental Medicine. Ed. (Marcel Dekker Inc., New York, NY) (1993): 61.

21) United States Pharmacopeia, National Formulary. US Pharmacopoeial Convention, Rockville, MD, 1995; 1775-7. Encyclopedia of regulated releases. John Wiley and Sons, Inc: New York 1-2 (1952): 743-77.

22) Singh M and Ravin L. “Parent emulsions as drug management systems”. Journal of Parental Science and Technology 40 (1986): 34-44.

23) Day AA., Et al. "Parent microemulsions: Overview". International Journal of Medicine355 (2008): 19-30.

24) JK Haleblian. "Specification of Practices and Crystal Modification of Solid Materials and Their Applications for Medicines". Journal of Pharmaceutical Science 64.8 (1975): 1269-1288

25) S Byrn., Et al. "Solid Drug Components: A Strategic Controls for Management". Medical Research 12.7 (1995): 945-954.

26) K Ashizawa. Et al. "Solid-State Stability and Preformulation Study of New Parenteral Cephalosporin Antibiotic (E1040)". Yakugaku Zasshi 110.3 (1990): 191-201.

27) (2000) Physician desk index, system 54. Medical Economics Company, Inc. Montvale, New Jersey, pp. 888–889.

28) Strickley RG. Solubilizing excipients in oral formulation and injections. Pharm Res. 2004; 21: 201–230. doi: 10.1023 / B:PHAM.0000016235.32639.23.

29) Darwish IA, Florence AT, Saleh AM. Effects of hydrotropic agents on melting, saturating, and binding to eoposide proteins. J Pharm Sci. 1989; 78: 577–581. doi: 10.1002 / jps.2600780714.

30) Day AA, Nagarsenker MS. Parent microemulsions: an overview. Int J Pharm. 2008; 355: 19–30. doi: 10.1016 / j.ijpharm.2008.01.004.

31) Rowe RC, Sheskey PJ, Weller PJ (eds) (2003) Pharmacological resources, fourth edition. Pharmaceutical Press, London / American Pharmaceutical Association, Washington .

32) Panaggio A, Rhodes CT, Worthen LR. Possible use of autoclaving microemulsion for sterilization. Drug Dev Ind Pharm. 1979; 5:169– 173. doi: 10.3109 /03639047909055670 .

33) Prince LM. In: Microemulsions: theory and practice. Prince LM, editor. London:Education; 1977. pages 1-20.

34) Attwood D. Microemulsions. In: Kreuter J, editor. Colloidal drug delivery systems, vol. 66. New York: Marcel Dekker; 1994. pp. 31-71 .

35) Block LH. Medicinal emulsions and microemulsions. In: Lieberman HA, Rieger MM, editors. Forms of drug dosage: dispersing systems, vol. 2. New York: Marcel Dekker; 1996. pp. 47-109.

36) Bock TK, Muller BW. Novel tests to determine the hemolytic activity of drugs incorporated into colloidal carriers systems. Pharm Res. 1994; 11: 589–591. doi: 10.1023 / A: 1018987120738 .

37) Tian L, He H, Tang X. Stabilization and degradation kinetics of etoposide-loaded parenteral lipid emulsion. J Pharm Sci. 2007; 96 (7): 1719–1728. doi: 10.1002 / jps.20830.

38) Panaggio A, Rhodes CT, Worthen LR. Possible use of autoclaving microemulsion for sterilization. Drug Dev Ind Pharm. 1979; 5:169–173. doi: 10.3109 /03639047909055670.

39) Lachman Leon; Theory and Practice of Industrial Pharmacy, 3rd edition; Varghese Publishing House; Bombay; 1987

40) Ansel HC., Et al. “Drug dosage forms and drug delivery system, 7th edition Lippincott Williams and Wilkins: Philadelphia (1999).

41) Remington, Science and Pharmacy, Parental Preparation, 20th Philadelphia Edition: ISE publication 2000; 1.

42) E., Coomans, D., Smeyers-Verbeke, J., Massart, D.L., 2002. Combined results models that are not in line for the dissolution profiles. Int J Pharm 240, 37–53.

43) G.L., Lennernäs, H., Shah, V.P., Crison, J.R., 1995. Theoretical basis for the biopharmaceutic drug classification: the integration of product in vitro drug production and the presence of vivo bioavailability. Pharmacy. Res. 12, 413–420

44) J.K.M., Martens, L.C., 2005. Review: The physiology of saliva and the transfer of drugsto the saliva. Forensic Sci. Int.150,119–131. https://doi.org/10.1016/j.forsciint.2004.10.026

45) P., Sharma, S., Garg, S., 2002. Complications of drug intolerance. Drug Discov. Today 7, 967-975.

46) L.Z., Broccatelli, F., Oprea, T.I., 2011. BDCS has been used in more than 900 drugs. AAPS J. 13, 519–547. https://doi.org/10.1208/s12248-011-9290-9

47) Beule, A.G., 2010. Physiology and pathophysiology of the nasal and paranasalrespiratory mucosa sins. GMS Curr. Up. Otorhinolaryngol. Head Neck Surg. 9, dk07.https://www.egms.de/static/en/journals/cto/2011-9/cto000071.shtml

48) Blumenthal, H.P., Fung, H.L., McNiff, E.F., Yap, S.K., 1977. Plasma nitroglycerin levelsafter subcutaneous speech, oral and topical treatment. Br. J. Clin. Pharmacol. 4, 241–242.https://doi.org/10.1111/j.1365-2125.1977.tb00703.x

49) Bodiford, A.B., Kessler, F.O., Fermo, J.D., Ragucci, K.R., 2013. Higher internationalaverage with the use of grapefruit and the use of warfarin. SAGE open Med. case report 1, 2050313X13511602. https://doi.org/10.1177/2050313X13511602

50) Boylan, J., Nail, S., 2002. Parental Products, at: Banker, G.S., Rhodes, C.T. (Eds.),Modern Pharmacy. Marcel Dekker, Inc., New York, pages 576-625

51) Bray brooks, M.P., Barry, B.W., Abbs, E.T., 1975. Effect of mucin on the bioavailability of tetracycline from the abdominal cavity; in vivo, in vitro links. J. Pharm. Pharmacol. 27, 508–515.

52)Sandeep Nema, John D. Third Edition Vol-2p 122-128, 153-157 Indian Pharmacopoeia 2010, Government of the Ministry of Health and Family Welfare of India196-198.

53) Cai, Q., Feng, L., Yap, K.Z., 2018. Systematic review and meta-analysis of reportedadverse events of treatment of long-term intranasal oxytocin for autism spectrum disorder. Psychiatry Clin. Neurosci. 72, 140–151. https://doi.org/10.1111/pcn.12627

54) By Jennifer Le Pharm D MAS, BCPS-ID, FIDSA, FCSHP, SKAGG SCHOOL OF PHARMACY, AND PHARMACEUTICAL SCIENCE, Oct 2020 Sandeep Nema, John D. Third Edition Vol-2p 122-128, 153-157.

55) Kwatra, S., Taneja, G. and Nasa, N. (2012). Other Drug Control Routes - Transdermal,Pulmonary & Parenteral. Indo Global Journal ofPharmaceutical Sciences, 2 (4): 409-426