International Journal of Scientific Research and Engineering Development-– Volume X Issue X, 2022

Available at www.ijsred.com

REVIEW ARTICLE OPEN ACCESS

Emulsion and Suspension Development for Parenteral Drug Delivery System

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Abstract:

The recommended delivery form for administering insoluble medications is parenteral emulsions and suspensions. This could be a substantial challenge for formulators due to some of the physicochemical characteristics that need to be taken into account in order to produce a consistent formulation, such as Hydrophilic Lipophilic Balance (HLB), Zeta potential, and particle size distribution. Additionally, certain preparations may have undesirable features like stability issues or microbial growth susceptibility, as well as some adverse effects, including discomfort at the injection site and anaphylactic hypersensitivity reactions in patients. On the other hand, this market is more protected from generic production because of the difficult procedure and necessary expenditure. In order for lipid injectable emulsions to be beneficial as drug delivery vehicles, formulation components and process factors must be adequately incorporated into formulation development methods. When choosing such delivery vehicles, careful consideration must be given to the physicochemical characteristics of active therapeutic agents because they have a major impact on the pharmacokinetics and tissue disposition after intravenous injection of drug-containing lipid emulsion. Targeted treatments, poorly soluble APIs and cancer drugs have a large amount of space for innovative suspension and emulsion development.

Keywords — Suspension, Emulsion, Parenteral, Parenteral suspension and emulsion, Method of preparation and Evaluations.

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I. INTRODUCTION

Designing and developing, efficient medicinal medicines has benefited from a structure-activity-based logical approach. The limited aqueous solubility of many of these really promising agents causes them to be removed from the development pipeline. Injectable suspensions and emulsions, a heterogeneous system in which one phase is disseminated as droplets in an aqueous phase and stabilised by suspending or emulsifying agents, have begun to develop as a feasible approach for delivering hydrophobic molecules in recent years. In this, a brief overview of the parenterals, suspension and emulsion and the various facts in the development of injectable suspensions and emulsions for drug delivery have been discussed below.

Different types of liquid dosage forms are mentioned below:

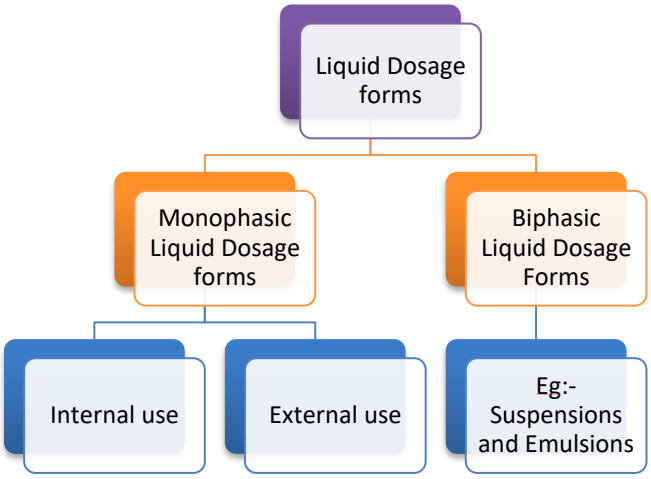

FIG. 1. TYPES OF LIQUUID DOSAGE FORM

II. SUSPENSION

A Pharmaceutical suspension is a biphasic dosage forms in which internal phase (therapeutically active ingredient) is dispersed uniformly throughout the external phase. Because of their intrinsic structural instability, complications associated manufacturing and packing, and significance as a form of pharmaceutical formulation, suspensions pose several difficulties for those responsible for formula development. Suspensions may be intended for parenteral use, external application, or oral delivery. The continuous phase of them is made up of a finely split solid (individual particles range in size from 0.5 to 5.0) suspended in a liquid or semi-solid medium. Nowadays, a lot of suspensions are sold as dry powders that must be "constituted" before usage by adding a specific quantity of a vehicle. Such suspensions are created mostly due to stability issues. While formulating a suspension, the particle size of the dispersion phase is crucial. Small particle size should be used in suspensions intended for topical treatment to prevent a gritty feeling during application and to maximize coverage and protection for the region being treated. If the solid substance is intended to penetrate the skin, its small size will hasten disintegration and penetration. Particle sizes in suspensions intended for ocular cavity introduction should not exceed 10. If the suspension is larger than this, the patient may experience pain or discomfort. Below this size, the patient does not feel any pain. Particles in injectable suspensions should be small enough to fit through a syringe needle with ease. The needle-shaped particles often have a prolonged action and are thus preferred in products of the "depot" form.

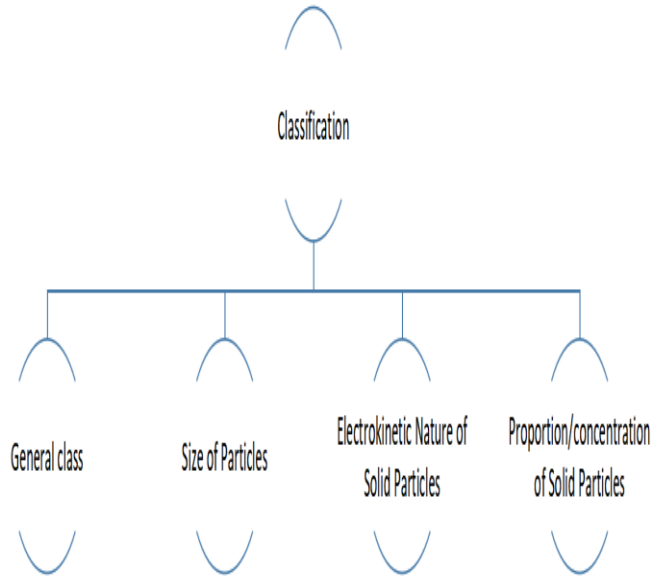

Fig. 2. Classification of Suspension

A. Theories for suspension

1. **Sedimentation:** Sedimentation is the process of allowing particles suspended in liquid to separate as a consequence of gravity. The sedimentary particles that form from the suspension during the collection and treatment process are known as sludge.
2. **Brownian Motion:** Brownian motion is the zigzag or irregular motion that minute particles of matter display when suspended in a liquid. The effect has been demonstrated in solid-in-liquid, liquid-in-liquid, gas-in-liquid, solid-in-gas, and liquid-in-gas colloidal suspensions (see colloid).
3. **Zeta potential and electrical double layer:** When most surfaces come into contact with aqueous surfaces, they develop a surface electric charge. When in contact with an aqueous medium, a solid charged surface has both positive and negative charges. The Stokes equation shows that sedimentation occurs more quickly for bigger particles. The viscosity of the dispersion medium has an inverse relationship with the sedimentation rate.

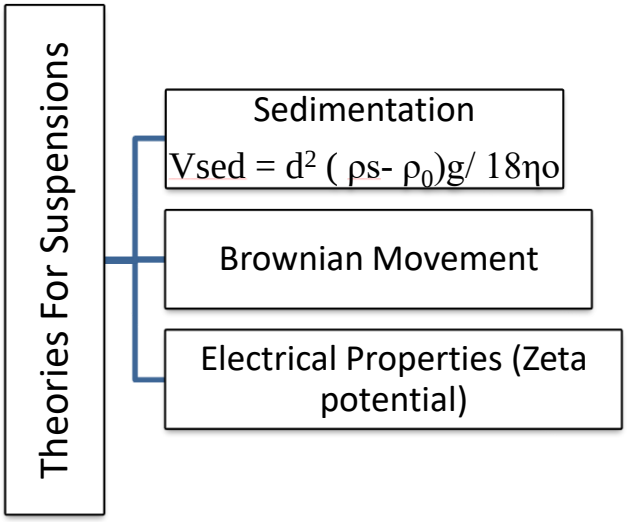

Fig. 3. Theories of Suspension

B. List of Ingregients used for preparation of Suspension:

Excipient used	Examples
Suspending agents- help the active pharmaceutical ingredients stay suspended in the formulation and prevent caking at the bottom of the container	CMC, gums , sodium alginate
Wetting agent- used to reduce the surface tension of water and thus help the water-based solutions to spread	Polysorbate 80 , acacia , tracaganth
Flavoring/ Sweetening agents- gives pleasant odour and palatible	Mint flavor, Fructose,sucrose
Coloring agent- to make suspensions look pleasant and good	Amaranth , Titanium dioxide
Humectants- ability to retain moisture while also preserving the overall properties of the product	Propylene glycol glycerol
Buffers and pH adjusting agents- necessary to adjust and maintain the pH	Phosphate , and carbonate buffers
Osmotic agents- increase the blood's oncotic pressure, which draws water from tissues and significantly increases blood volume. Renin release will be inhibited by the increased blood volume, thus increasing renal blood flow..	Dextrose , mannitol , sorbitol
Preservatives- to protect against microorganisms	Disodium EDTA, Butyl paraben , propylene glycol
Antioxidants- to protect against radicals	Butylated hydroxy anisole(BHA), Butylated hydroxytoluene (BHT)

C. Method of Preparation:

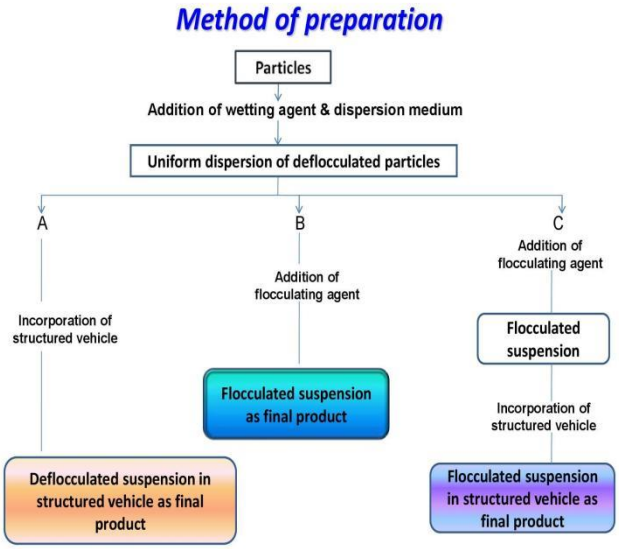

FIG. 4. METHOD OF PREPARATION FOR SUSPENSION

D. Advantages of Suspension:

1. In comparison to solid dose forms, the medicine in suspension has a higher rate of bioavailability.
2. Suspension, capsule, compressed tablet, coated tablet: the order of the treatment.
3. Suspension can increase a drug's chemical stability.
4. Controlled release of drugs
5. Suspension can cover up a drug's harsh or bitter taste.
6. Administration convenience.

E. Disadvantages for Suspension:

1.Problems can be brought on by physical instability, sedimentation, and compaction.
2.Due to its size, it must be handled and transported with proper care.
3. It is challenging to formulate.
4. If the suspension is not packaged in unit dosage form, it will be impossible to ensure uniform and exact dosage.

III. EMULSION

AN EMULSION CONSISTS OF TWO IMMISCIBLE LIQUIDS ONE OF WHICH IS UNIFORMLY DISPERSED AS DROPLETS.

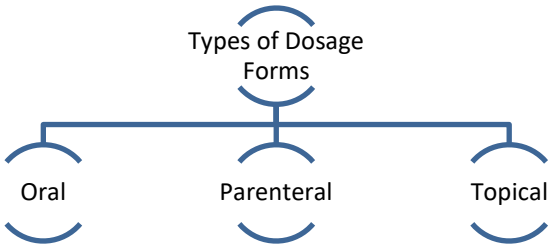

Fig. 5. Types of dosage form for Emulsion

A. Theories of Emulsion:

1. **Surface tension theory:** According to the surface tension hypothesis of emulsification, surface-active substances lower the interfacial tension between two immiscible liquids, lowering the repelling force between them as well as the attraction of each liquid to its own molecules. Surfactants are employed as surface-active agents. Surfactants assist in breaking up large globules into smaller ones, which are less likely to rejoin or agglomerate and can disperse more readily.
2. **Oriented Wedge Emulsification Theory:** A common illustration of a diluted emulsion is soap, which emulsifies two to four percent oil in water without the use of an emulsifying ingredient. The oriented wedge theory of soap molecules at an oil-water interface states that the hydrocarbon radical points toward oil and the Na+ radical points toward water. Ends that are non-polar or "oily" turn toward oil, whereas ends that are polar or "liquid" turn toward polar liquid. According to the oriented wedge theory of emulsions, water droplets develop when the polar end of the emulsifying agent's molecule shrinks, but oil in water emulsions (or the typical type) form when the nonpolar end of the molecule shrinks. Because the stray field of the molecule is asymmetrical, fluids and solids must have a different orientation of the field axes than pure substances where all molecules are aligned in a random fashion in order to have a distinct surface layer from their internal mass.
3. **The Theory of Emulsification via Interfacial Film:** According to this hypothesis, the emulsifying agent's encircling droplets of the internal phase are shielded from collision and the coalescence of the dispersion phase by a thin layer that has been adsorbed to their surface. The o/w and w/o emulsions have a direct association with water-soluble substances.

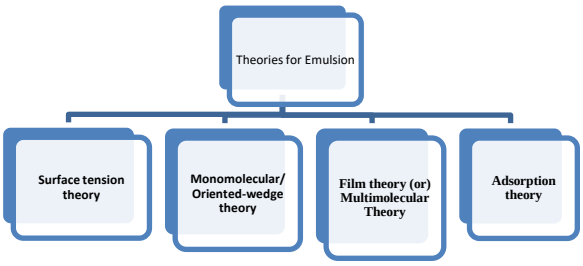

Fig. 6. Theories for Emulsion

B. Physical instabilities of Emulsion

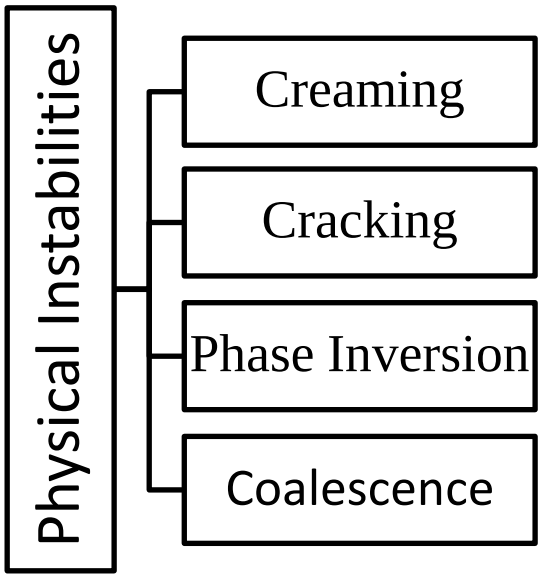

Fig. 7. Types of Physical instabilities

1. **Creaming and Sedimentation:** This process is the result of outside forces, usually centrifugal or gravitational. When these forces are greater than the Brownian motion of the droplets, a concentration gradient forms in the system, with the larger droplets migrating more quickly to the top of the container (if their density is lower than the medium's) or the bottom (if their density is higher than the medium's). In the most extreme situations, the droplets may form a compact (random or ordered) array at the top or bottom of the system, with the continuous liquid phase occupying the remaining space.
2. **Coalescence:** This is the process of the liquid film between the droplets thinned and disrupted, leading to the fusion of two or more droplets into bigger ones. Complete separation of the emulsion into two different liquid phases is the limiting scenario for coalescence. Surface or film variations that cause close approach of the droplets and strong van der Waals forces that keep them from separating are what cause coalescence.
3. **Phase inversion:** This refers to the procedure through which the disperse phase and the medium will interchange. For example, an O/W emulsion may become a W/O emulsion over time or with a change in conditions. Phase inversion usually goes through a transition state where several emulsions are created.

Excipients	Examples
Emulsifying agents- help the active pharmaceutical ingredients stay suspended in the formulation and prevent caking at the bottom of the container	1. Natural: Gum acacia, tragacanth, agar, starch, pectin,wool fat, gelatin. 2. Semi synthetic: Methyl cellulose, Na CMC 3. Synthetic: a. Anionic, Sodium Lauryl Sulphate (sls) b. Cationic. Cetrimide, benzalkonium chloride. c. Non-ionic: Glyceryl ester- glycerol monoesters etc. 4. Inorganic: Milk of magnesia, Magnesium oxide, Magnesium trioxide etc. 5. Alcohols : cholesterol and lecithin.
Antioxidants- to prevent against free radicals	Gallic acid, Propyl gallate , Ascorbic acid, Sulphites, L-tocopherol
Preservatives- to prevent against microorganisms	1.Acids and acid derivatives - Benzoic acid - Antifungal agent 2.Aldehydes – Formaldehyde – Broad spectrum 3.Phenolics – Phenol, Cresol, Propyl p-hydroxy benzoate

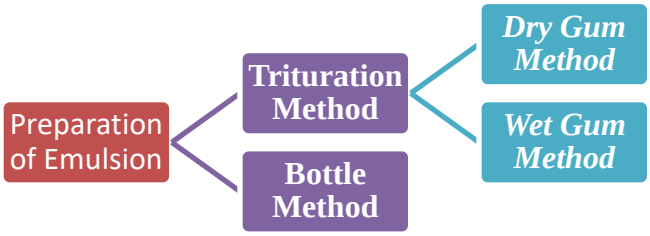

Fig. 8. Preparation of Emulsion

1. Dry Gum Method: In this technique, the primary emulsion is produced by first triturating the oil with gum and a small amount of water. Continue triturating until a distinctive "clicking" sound is produced and a thick white cream forms. The final emulsion is created by gradually adding the remaining water after the primary emulsion has been developed.

2. **Wet Gum Method:** As the names indicate, the first step in this process is the trituration of gum and water to produce a mucilage. To form the primary emulsion, the needed amount of oil is then slowly added in small quantities while being thoroughly triturated. The remaining amount of water is added after the primary emulsion has been created to create the final emulsion.

3. **Bottle technique:** The bottle method is useful for the extemporaneous preparation of emulsions from volatile oils or oleaginous substances with low viscosities. The powdered acacia is placed in a dry bottle, and two parts of oil are added. The mixture is thoroughly shaken before being sealed.

D. Advantages of Emulsion:

1. Drugs that are hydrophobic in nature but easily soluble in oils can be delivered via pharmaceutical emulsions.
2. Pharmaceutical emulsions, in which the substance is dispersed in the internal phase of an o/w emulsion, may be used to disguise the bitter taste and odor of medications.
3. Drugs that exhibit better stability in an emulsion pharmaceutical formulations are those that are more durable in an oily phase compared to an aqueous phase.
4. Emulsions, especially semisolid emulsions, can be employed to delay the release of the medication and provide prolonged release action.

E. Disadvantages of Emulsion:

1. Pharmaceutical emulsions must be developed to stabilise the emulsion from the separation of the two phases because they are thermodynamically unstable.
2. 2. The production of pharmaceutical emulsions could be challenging.
3. 3. Storage circumstances may impact stability.
4. 4. Bulky, challenging to transport, and susceptible to container damage.
5. prone to microbial deterioration, which may produce cracking.

F. Packaging, Labeling and Storage of Suspension & Emulsions:-

- Pharmaceutical Suspensions and Emulsions are typically packaged in wide mouth containers for oral administration. Glass ampoules or glass vials are used to package parenteral solutions and emulsion.
- Amber coloured bottles are used to contain items that are sensitive to light.

IV. Parenterals

Parenterally delivered injections offer sterile, pyrogen-free formulations.

A. Advantages:

1. Beneficial for individuals who are unable to take pills orally
2. Rapid of the action
3. Beneficial in emergency situations4. Providing sustained drug delivery (implants, depot injection)
5. Avoids first pass metabolism resulting in maximum bioavailability
6. Can inject drug directly in to a tissue (target drug delivery)
7. Useful for delivering fluids, electrolytes, or nutrients (TPN)

B. *Disadvantages of Parenterals:*

1.Pain on injection
2. Difficult to undo the effects of a drug administered.
3. An allergic or sensitive reaction at the injection site.
4. Demands higher sterility and non-pyrogenicity controls than other formulations.
5. A trained person is required.
6. Costly to produce.

C. *Routes of Administration:*

- It is feasible to inject drugs into practically any organ or bodily part.
- Major routes:
  vein (intravenous, IV),
  muscle (intramuscular, IM),
  under the skin (subcutaneous, SC)
- Other routes:
  Joint fluid area (intra-synovial),
  spinal cord (intra-spinal),
  spinal fluid (intra-thecal),
  arteries (intra-arterial), and in an emergency,
  even the heart (intra-cardiac).
  skin (intradermal, intra-cutaneous)

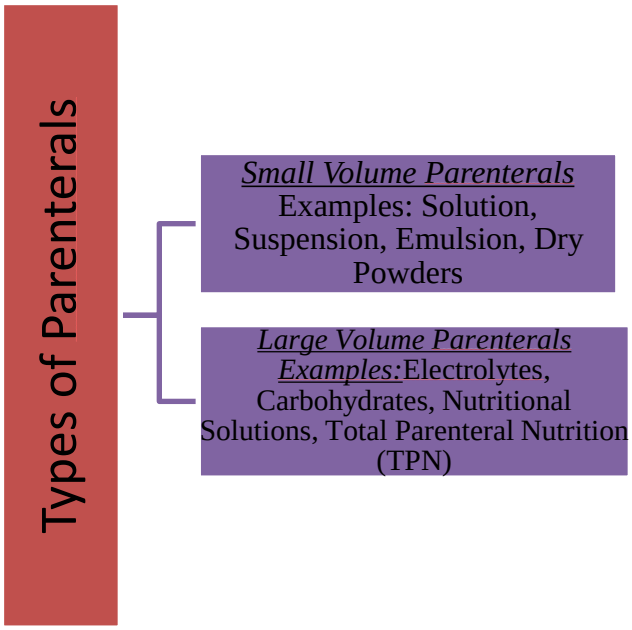

Fig. 9. Types of Parenterals

D. Formulation of Parenteral Products:

Excipients Used	**Examples**
Antimicrobial agents- to prevent against microorganism	Phenol, benzyl alcohol
Antioxidants- prevent against pree radicals	ascorbic acid and sodium bisulfite
Tonicity agents- to adjust and maintain pH	sodium chloride, potassium chloride, dextrose, mannitol, sorbitol
Suspending agents- help the active pharmaceutical ingredients stay suspended in the formulation and prevent caking at the bottom of the container	Gelatin and PVP
Emulsifying agents- adsorbs at the newly formed oil–water interface during emulsion preparation, and it protects the newly formed droplets against immediate recoalescence.	SLS
Chelating agents- effective means of inhibiting metal-ion-catalyzed lipid oxidation	EDTA, disodium edetate, tetra sodium edetate
Co-solvents- to increase solubility and stability	ethanol, PEG, glycerin
Vehicles	Aqueous vehicle: Water for Injection (WFI), Bacteriostatic Water for Injection (BWFI), Sterile Water for Injection (SWFI), USP Non-aqueous vehicle

E.Steps Involved:

The standard process for producing parenterals includes -

a) Cleaning and washing of containers, closures and equipments.
b) Collection of high purity raw material
c) Preparation of parenteral products
d) Filtration
e) Filling in Final Container
f) Sealing
g) Terminal Sterilization
h) Evaluations
i) Labelling and Packaging

And After Every Step IPQC is Performed

F.Sterilization Methods for Parenterals:-

Sterilization - For destruction of all living organisms and their spores or their complete removal from the parenteral preparation before final packing thereby to ensure the sterility of product.

1) STEAM (MOIST HEAT) STERILIZATION:

Different condition of sterilization are:
10-lb pressure (115.5°C, or 240°F) for 30 minutes
15-lb pressure (121.5°C, or 250°F) for 20 minutes
20-lb pressure (126.5°C, or 260°F) for 15 minutes

USED FOR STERILISATION:- Solutions in ampoules or other sealed containers. Unless there is a tiny amount of water present, sealed empty vials. glassware, surgical dressings, equipment, and bulk solutions.

CANNOT USED FOR:- Oils, fats, oleaginous preparations and other preparations which are not penetrated by moisture Exposed powders that may be damaged by the moisture.

2) Dry Heat Sterilization

Carried out in ovens designed for this purpose it which it may be heated either by gas or electricity and are generally thermostatically controlled.

Mechanism of killing of microorganisms through oxidation.

Dry heat is less effective (due to less penetration power) in killing microorganisms than in moist heat so higher temperatures and longer periods of exposure are required

Usually conducted at 150°C to 170°C for not less than 2 hours.

Higher temperatures permit shorter exposure while Lower Temperature require longer exposure times.

USED FOR: Substances that moist heat cannot adequately sterilise and are not stable. Glycerin and fixed oils. a variety of petroleum products, including paraffin, liquid petrolatum (mineral oil), and petrolatum, as well as a number of heat-stable powders, including zinc oxide. glasses and surgical devices.

3) ***STERILIZATION BY FILTRATION:*** Used for heat liable/sensitive preparation. Useful for heat-sensitive solutions, it relies on the physical removal of microorganisms through adsorption on the filter medium or by a sieving mechanism.

ADVANTAGES:Faster filtration of small quantities of solution, Can sterilize thermolabile materials, Relatively inexpensive equipment required,and Complete removal of living and dead microorganism and other particulate matter from the solution.

DISADVANTAGES: grow-through and multiplication of microorganisms, tendency of the filter components to slow down during line surges and retention of some liquid in the filter

4) *Gaseous sterilization:-* Used for Heat-sensitive and moisture-sensitive materials By exposure to ethylene oxide gas (highly flammable when mixed with air but can be employed safely when properly diluted with an inert gas such as carbon dioxide or a suitable fluorinated hydrocarbon). Requires specialized equipment resembling an autoclave.

G.Validation required for Sterile Parenteral Process and Equipements:

Reductions in processing time can be achieved with no loss in sterility assurance and resulting in fewer rejections. Reduction in Utility Costs , fewer Complaints. Equipment validation and qualification can expedite equipment installation and problems. Expanding from Development is simpler The

achievement of quantiative validation criteria provides a clear target for the scaling-up of activities. Equipment Maintenance Seems to be Easier The qualification report's extensive information can hasten equipment repairs. The automation of processes is significantly easier when there is a defined, understood, and acceptable procedure available through validation.

V. Parenteral Suspension

Parenteral suspensions are dispersed, heterogeneous systems containing insoluble drug particles which, when are to be resuspended in either aqueous or oil vehicles before administering to a patient. They are administered by either subcutaneous (S.C.) or intramuscular (I.M.) route.
For Example: procaine Penicillin G.

A. Pre-Formulation Consideration:- Compatibility with ingredient (Drug-Excipient, Excipient-Excipient compatibility), Dissolution, pH stability

B.Formulation Consideration: Solubility of Drug in biological fluids at injection sites, Lipid solubility and oil-water partition, coefficient of the drug, pKa of the drug, Dissolution rate of solid from its dosage form, Particle size of the of drug in suspension.

C.Method Of Preparation:- Individual ingredients are sterilized separately by different methods of sterilization.
Sterilization of the vehicle by filtration and collection into a second vehicle, under aseptic condition.
Disperse the (sterile) therapeutic agent into the sterile vehicle containing an antimicrobial preservative, a surfactant (for wetting, a dispersing or suspending agent), and a buffer or salt. If required the particle size of the disperse phase may be reduced by passing through a ball mill, micronizer, colloid mill, or other appropriate equipment (whose contents and packing material are both sterile). Then formulation may be filled into the final container, followed by sealing. If the suspension is stable for heat sterilization, it may be manufactured and filled into the final container.

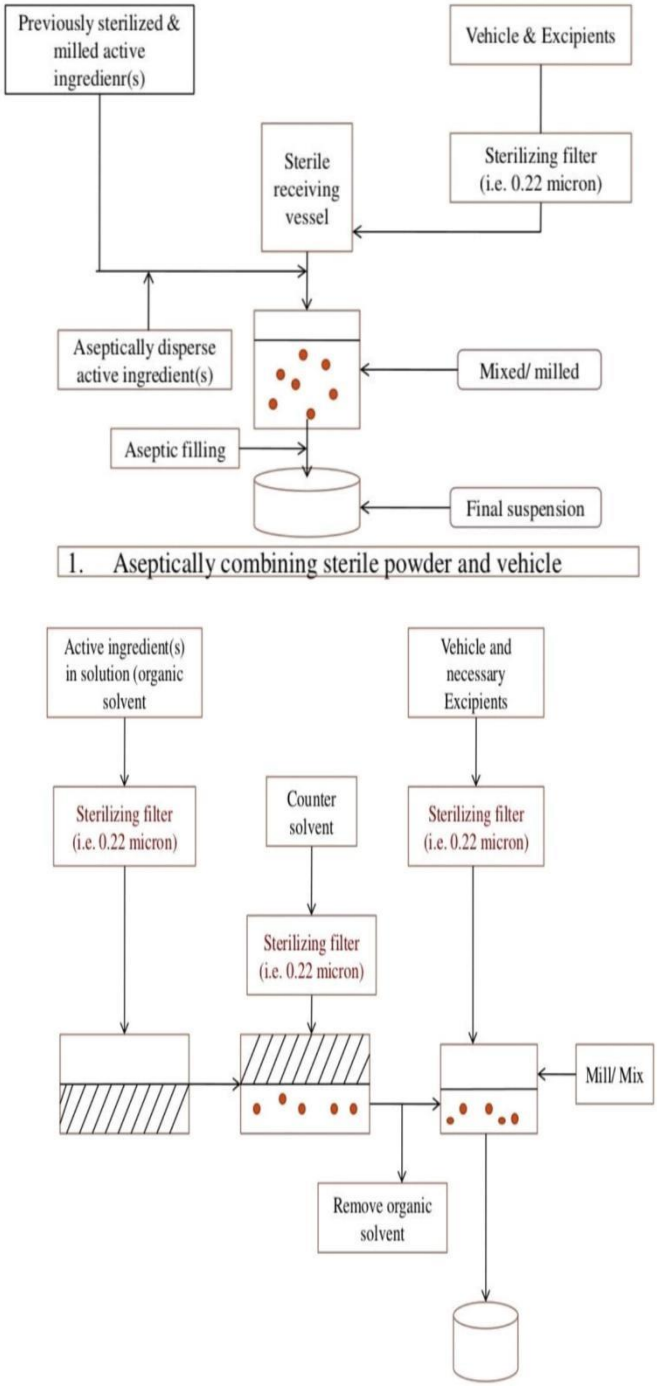

Fig. 10. Method of Preparation For Parenteral Suspension

D. Evaluations:
Physical Evaluations:

1. **Syringeability**: ease of withdrawal from container to syringe, with accuracy of dose and without clogging.
2. **Injectability**: pressure or force required for injection, giving evenness of flow and free from clogging.
3. **Resuspendibility/ Sedimentation Rate:** ease of redisersion by moderate shaking.

4. Particle size measurement-

Methods

• Visual method: Against black and white board
• Coulter counter method: Increase in resistance is observed between two electrodes as the particle approaches and passes through the orifice.
• Filtration method: Filter and analyze the particles.
• Light blockage method: Blocks the path of light.

Methods for identification of particles: Microscopy, X-ray powder diffraction, mass microscopy, polarised light microscopy, SEM

Biological Evaluations:

A} Sterility Testing: It is a testing procedure applied to products intended to be sterile before marketing, to check that these products are free from all living microorganisms. Sterility tests must be conducted under aseptic circumstances in order to prevent unintentional product contamination during use. They are conducted on random samples from the batch. If microorganisms are found in the test samples, their growth is typically monitored by incubation over designated culture media at designated temperatures for designated periods of time.

B} Pyrogen Testing: Pyrogen testing defines a process used by drug manufacturers to determine if bacterial toxins are present in vaccines and drugs that might cause fever when used on humans.

1. Sham test
2. Limulus Amebocyte Lysate test (New method, In-vitro test)

1. Sham test: It is performed to select the proper animals for the main test
i.e Rabbit method.
2.LAL Test

C} Product-Packaging Interaction - Leak test: It is desirable that all the parenteral preparation which are filled in ampoules must be hermetically sealed. The ampoules are immersed in 1% methylene blue solution in a vaccum chamber under negative pressure. When the vaccum is released the coloured solution will enter those ampoules having defective sealing. The presence of dye in the ampoule confirms the leakage and hence rejected.

E. Examples of Marketed Parenteral Suspension: Sterile ampicillin suspension , Tetanus toxoid adsorbed , Betamethasone acetate suspension , Insulin Zinc suspension , Procaine penicillin G suspension.

VI. Parenteral Emulsions

Parenteral emulsion are not preferred due to stability problem- cracking.

A. **Method of preparation**: Homogenization and particle size reduction The emulsifier osmotic agent and preservatives are is usually the dissolved or dispersed in the Aqueous phase .The phospholipids antioxidants and any lipophilic drugs to be Incorporated are usually dissolved or dispersed in the oil phase. Both the faces are then heated to 70 to 80 degree Celsius with agitation The course emulsion is formed by vigorous stirring of mixing (filtration- membrane filters) . Final pH of formulation is adjusted. Terminal Sterilization (if possible by autoclave)

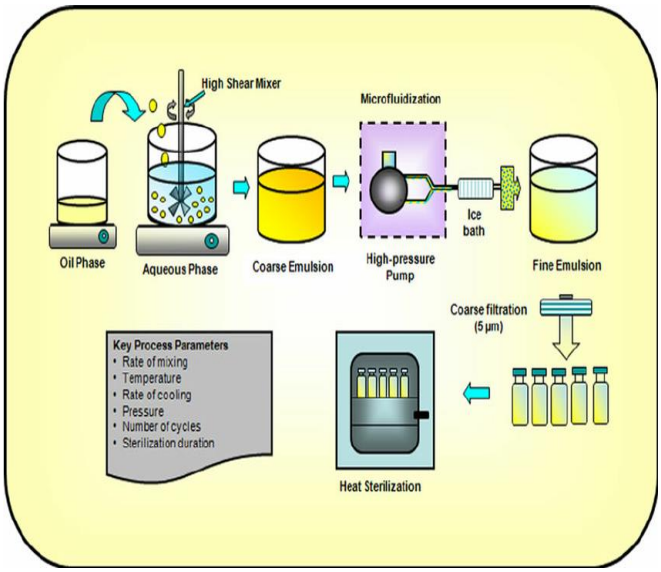

Fig. 11. Method of Preparation of Parenteral Emulsion

B. Evaluations:

1) Physical examination: Visual observation of creaming, coalescence, and oil separation.
2) Chemical analysis: Identification and characterization of the excipients, comprising free fatty acids and oxidation degradation products, as well as the drug ingredient, oil, phosphatide, and other oils that are present.
3) pH determination.
4) Sterility test.
5) Pyrogen test.

C. Examples of Marketed Preparations*:* Intralipid , Diazemuls, Vitalipid, Diprivan

D. Packaging for Parenteral Suspension and Emulsion:

Injectable suspension and emulsions packed in USP type I and II glass bottles
One can utilise silicone-coated bottles with an inner surface that repels water.
Clothes made of rubber are frequently used.
Closures should not be oxygen permeable or flexible upon contact.

E. Problems while developing Parenteral Suspensions and Emulsions:

Achieving compatibility between the drug substance and excipients is the fundamental obstacle with parenteral dose forms. Sanitation of the product.
The options for formulation are significantly constrained by the small number of stabilisers and emulsifiers available (for example, lecithin for o/w type emulsion).
Colloidal release from in-vitro dispersion.
The use of IV emulsion has also been constrained by unwanted physiological consequences, such as hemolysis and pyrogenic response.

F. To overcome above Problems:

Sterilization by filtering (which requires the emulsion droplet size to be below 200 nm) can be used if the components of the emulsions are heat labile. Toxicity and stability of the emulsion system are directly impacted by droplet size, zeta potential (ionic strength, type, and concentration of emulsifier), and pH, thus it is necessary to optimise these parameters. The release of medication from colloidal dispersions has been measured using a variety of experimental techniques, including the diffusion cell method, dialysis bag method, centrifugal ultrafiltration technique, ultrafiltration at low pressure, continuous flow methods, and in situ flow methods. Antioxidants and preservatives should be used and stored properly.

VII. Conclusions: While suspension and emulsion-based drug delivery is a relatively new field with exciting growth potential, there are several pitfalls to be avoided. Foremost among them is the failure to adequately characterize experimental formulations with respect to emulsion and suspension integrity including droplet size distribution,, minimize toxicity of the carrier system independent of the drug substance, Filtration and stability of the product. Currently, suspension and emulsion technology may be fine-tuned to meet the unique requirements of each drug. Formulation development approach needs to be considered keeping the target product profile in mind.

References:-

1. Howard CA. Introduction of Pharmaceutical Dosage Forms (Lea and Febiger, Philadelphia, PA), 1981, 139- 166. Habib MJ, Mesue R. Development of controlled release formulations of ketoprofen for oral use. Drug Development and Industrial Pharmacy. 1995; 2112:1463- 1472.
2. Kawashima Y, Lwamoto T, Niwa H, Takeuchi H, ltoh Y. Preparation and characterization of new controlled release ibuprofen suspension for improving suspendability. International J of Pharmaceutics. 1991; 75:25-36
3. Mason, T.G. and Bibette, J. (1996) J. Phys. Rev. Lett., 77, 3481. 87.
4. Heinze, J.O. (1955) AICHE J., 1, 289. 88.
5. Vankova, N., Tcholakova, S., Denkov, N.D., Ivanov, I.B., Vulchev, V.D., and Danner, Th. (2007) J. Colloid Interface Sci., 312, 363. 89.
6. Podgorska, W. (2006) Chem. Eng. Sci., 61, 2986.
7. D. Delmas, V. Aires, E. Limagne, P. Dutartre, F. Mazue, F. Ghiringhelli and N. Latruffe, Ann. N. Y. Acad. Sci., 2011, 1215, 48–59.
8. M. Matos, G. Guti´errez, J. Coca and C. Pazos, Colloids Surf., A, 2014, 442, 69–79. 5 Y. Hemar, L. J. Cheng, C. M. Oliver, L. Sanguansri and M. Augustin, Food Biophys., 2010, 5, 120–127
9. Lieberman H.A., Leon L. The Theory and Practice of Industrial Pharmacy. Third edition, Varghese pubhising house, Bombay, pp-639-680.

10. Francoise N., Gilberte M. Pharmaceutical emulsion and suspension. Marcel Dekker,inc, New York, pp- 229-270
11. Remington, The Science and Practice of Pharmacy 21" edition, Volume I, Lippincott Williams & Wilkinss, pp- 802-836.
12. Lieberman H.A., Leon L., Pharmaceutical Dosage forms: Parenteral Medications Volume 1, 2nd Edition, pp- 173-245
13. L.C. Collins-Gold, R.T. Lyons and L.C. Bartholow Parenteral emulsions for drug delivery Advanced Drug Delivery Reviews, pp 189-208, 1990.
14. Rajesh M. Patel; Parenteral suspension: An overview , International Journal of Current Pharmaceutical Research Vol 2, Issue 3, 2010.

