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Review Article

PARENTERAL SUSPENSION: AN OVERVIEW

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ABSTRACT

Many conventional dosage forms are available to treat disease ailments. Parental suspension is useful dosage form for administering insoluble or poorly soluble drugs and it also provide drug stability. The larger surface area of disperse drug may help ensure a high degree of avaibilty for absorption.Suspension offer some advantages over other conventional dosage form, as it gives ease of absorption, bioavailability and fast onset of action. Parental suspension provides more prolonged release from the injection site than comparable to solution.

Keywords: Stability, Parenteral suspension, Syringebility

INTRODUCTION

Advances have been made in the area of various conventional drug delivery systems which controlled the release of drug, but there are number of possible loopholes in this area of research includes difficulty in establishing a relationship between *in vivo* and *in vitro* data, unpredictable performance of conventional dosage forms under different dietary conditions, thereby rendering accurate pharmacokinetic prediction difficult and often unpredictable absorption characteristics in different regions of the gastrointestinal tract [GIT][1]. Due to these problems, parenteral controlled release systems have been investigated[1]. Parenteral suspensions are dispersed, heterogeneous systems containing insoluble drug particles which, when are to be resuspended in either aqueous or vegetable oil vehicles before administering to a patient[2,3]. To obtain a pharmaceutically acceptable suspension it should fulfill the below mentioned characteristics.

- They should be sterile, pyrogen free, stable, re-suspendable, syringeable, injectable, isotonic & non-irritating.
- Because of above requirements injectable suspensions are one of the most difficult dosage forms to develop in terms of their stability, manufacture & usage.
- The parenteral suspensions may be formulated as a ready to use injection or require a reconstitution step prior to use.
- They are usually administered by either subcutaneous (S.C.) or intramuscular (I.M.) route.
- Newer suspension delivery system containing drug in microparticulate or nanoparticle can be injected by intravenously or subcutaneously.
- These suspensions usually contain between 0.5% and 5.0% solids & should have particle size less than 5 micrometer for I.M. or S.C. administration.
- Certain antibiotic preparations (For example procaine Penicillin G) may contain up to 30% solids.

These days many suspensions are supplied as dry powders which are converted into suspensions by assign the specified amount of a vehicle before used to ensure the stability of suspension.

Ex : (insulin zinc suspension (amorphous)

(Insulin zinc suspension (crystalline).

Parental suspension is useful dosage from for administering insoluble or poorly soluble drugs. The larger surface area of disperse drug may help ensure a high degree of avaibilty for absorption. Parental suspension provides more prolonged release from the injection site than comparable to solution.

Advantages of Parental suspension[3]

- It is better for the therapeutic use of drugs that are insoluble in convention solvents.
- In this dosage from there is increased resistance to hydrolysis & oxidation as drug is present in the solid from.
- Formulation of controlled released drug is possible in this dosage form.
- There is elimination of hepatic first pass effect.

Disadvantages of Parental suspension [2,3]

- Difficulty in formulation: Parenteral suspensions limit the formulator in selecting the ingredients, which are parenterally acceptable as suspending agent, viscosity inducing agent, wetting agent, stabilizers and preservative.
- Difficulty in manufacturing: Special facilities are required to maintain aseptic condition for manufacturing processes such as : crystallization, particle size reduction, wetting, sterilization
- The stabilization of suspensions for the period between manufacture & use present a number of problems. e.g. solids gradually settle & may cake, causing difficulty in redispersion prior to use.
- Maintenance of physical stability is very difficult in this dosage form.
- There may be chances of non-uniformity of dose at the time of administration.

Parenteral suspensions are developed due to following reasons[4]

- The drugs, which are insoluble and are difficult to be formulated as a solution.
- For the drug which are more stable when suspended than in solution form.
- When there is a need to develop dosage forms having retarded or controlled release of drug.

Ideal characteristics of parental suspension [2,5,6]

- The suspensions are manufactured and tested for microbial contamination. So as to maintain its sterility during its storage & use.
- It should be easily drawn into a syringe (Syringeability) and readily ejected from the syringe (Injectability). The syringeability & injectability of a suspension are closely related to viscosity & particle characteristics.

- Particle size should be small & uniform.
- Re- suspension of drug particles should occur easily with mild shaking.
- The dispersed particles do not settle rapidly after shaking.
- Re-suspension should result in homogeneous mixing of drug particles in such a manner that same concentration of drug can be removed repeatedly.
- Cake formation shouldn't occur during its shelf life.
- The suspensions should maintain its stability and elegance during its shelf life.
- It should be isotonic & non-irritating.

FORMULATION CONSIDERATION OF PARENTERAL SUSPENSION

Following parameters should be taken in consideration while formulating parenteral suspension

- Interfacial properties:[3, 7]

Interfacial properties of dispersed particles such as the increase in the specific surface area with reduction in particle size and the presence of electrical charge on the surface of particles play an important role in the stability of suspensions.

$$\Delta G = \chi_{s/u} \Delta A \quad \text{.....eq.1}$$

where,

ΔG= change in surface free energy in ergs

$\chi_{s/u}$= interfacial tension in dyne /cm^2 between dispersed particles and dispersed medium

ΔA= change in surface area in cm^2.

Equation 1 Illustrates the principle that as the interfacial tension and the surface area approaches zero, the surface free energy is minimum.

Generally particle size of solids is reduced in suspension to prevent settling of dispersed particles however this result in clumping of particles in an attempt to reduce the surface free energy.In order to formulate a thermodynamically stable system the interfacial tensions is minimized by use of surface active agents.

- Flocculation and Deflocculation [3]

- The charge at the shear plane associated with the particle surface is described as the zeta potential.
- When zeta potential is high the electrostatic repulsive forces between two particles exceeds attractive London force, resulting in deflocculated particles.
- Deflocculated particles settle at slow rate and they form a hard cake on settling which cannot be easily redispersed.
- Flocculating agents are added to reduce the electrical force of repulsion at a certain concentration resulting in predominance of the attractive force causing the formation of loose aggregates. These aggregates settle quickly, and are not bound tightly with each other and are thus easily redispersible.
- Flocculated suspension are the more common type of parenteral suspension because most injectable suspension contain low concentration of solids,
- Additionally they are easier to formulate, less viscous and have a less potential to produce stability problems.
- The deflocculated approach is use for oleaginous suspensions and for suspensions containing relatively high concentration of solids e.g. procaine penicillin G.
- Electrolytes act as flocculating agents by reducing the electric barrier between the particles, as evidenced by decreased in zeta potential & formation of bridge between adjacent particles so as to link them together in a loosely arranged structure.
- Surfactants, both ionic & nonionic have been used to bring about function of suspended particles.
- Polymers are long chain compounds and act as a flocculating agents because part of the chain is absorbed on the particle surface with the remaining parts projecting out in to the despension medium. Bridge between this latter portion leads to the formation of flocs.
- The controlled flocculation approach is capable to fulfill the desired physical chemical requisites of a pharmaceutical suspension, the product can look unsightly if F, the sedimentation volume is not close or equal to 1.
- If the volume of sediment in a flocculated suspension equals the original volume of suspension, than F=1, such product is said to be in "flocculation equilibrium "& show no clear supernant on standing.

- Stock's Law [3, 8] : (eq. 2) indicated that an increase in viscosity of liquids or by decreasing particle size minimizes sedimentation rate and thus enhance the physical stability of suspension.

$$S = d^2 (P_s - P_1) g / 18 \eta \quad \text{..... eq.2}$$

Where, S = Sedimentation rate in cm/sec

d = Diameter of particles in cm

P_S = Density of the dispersed phase

P_1 = Density of the dispersed medium

g = Gravity constant

η = Viscosity of dispersion medium in poise.

- Crystal Growth [2]

The following factors affect the potential for crystal growth in suspension.

A) Partical size distribution.

B) Dissolution and recrystallization.

C) Changes in PH and temperature.

D) Polymorphism and solvate formation.

The effect of particle size and dissolution of crystal in vehicle is given by the Oswald Freundlich equation.

$$\ln C_1/C_2 = 2MV/PRT * 1/R_1 - 1/R_2 \quad \text{.... Eq. 3}$$

Where,

C_1 and C_2 are the solubilities of particles of radius R_1 and R_2 respectively.

M is the molecular weight

V is the surface energy of the solid in contact with solution

P is the density of the solid

R is the gas constant

T is the absolute temperature.

- Smaller particle (R1) has higher solubility (C1) than the solubility (C2) of larger particle (R_2).
- A suspension will have a normal distribution of particle size.
- Variable particle size distribution result from various factor including:

(A) Preparation of suspension by precipitation methods where the degree of super saturation and rate of nucleation are greatest at the beginning of the process resulting in large particle formation initially and smaller particle formation subsequently.

(B) Changes in pH caused due to drug decomposition.

(C) Temperature changes.

With time the smaller particles will disappear and larger particles will grow.

To prevent crystal growth, viscosity inducing agents are included in formulation as increasing viscosity minimizes the probability of crystal growth according to eq. 4

$$Kcr = Ae^{-\alpha n + \beta} \quad \text{..... eq. 4}$$

- It is well known that certain hydrophilic gums like gelatin, polyvinyl pyrolidon, polysorbates will absorb at particle surface and retard crystal growth.
- Crystal growth also occurs as the result of dissolution and recrystallization phenomenon along with polymorphism, solvate formation and temperature fluctuations.
- The use of polymorphic form other than the most thermodynamically stable form could lead to dissolution of the more stable crystal form followed by recrystallization and conversion to more stable form resulting in crystal growth and problem in resuspending the drug in the vehicle.
- Solvate formation can occur when an anhydrous drug is suspended in a solvent and when it is suspended in an aqueous vehicle and a hydrate is formed. The hydrate form, being more energetic is more likely to develop large crystals.
- Temperature fluctuation can cause crystal to be subjected to unsaturated condition for a while then to saturated condition and so forth. Not only will small crystals disappear and large crystals grow but also chemical instability of the drug may occur.
- Thus to minimize crystal growth the formulator must understand the theory behind the formation of large particles, know the particle size distribution of the drug to be suspended and viscosity inducing agents, use the right drug polymorph and solvent form and conduct meaningful temperature cycling studies to evaluate the rate and the extent of temperature effects on physical as well as chemical stability of suspension.
- Caking
- The inability to re-suspend drug particles upon caking usually result from particles setting as a hardened sediment call a "cake" it will occur when attractive forces among drug particle are greater than forces between solids particles and the suspension vehicle.

- Crystal growth and extremes in flocculated deflocculated suspension can lead to caking.
- Deflocculated system by their definition will settle slowly as individual particles which will become closely packed sediments. Thus complete dispersion of small narrow ranged particles with appropriate amount of wetting agent and /or there agents increase zeta potential will minimize the tendency of these particles to agglomerate and form a hard cake. (Fig. 1.)

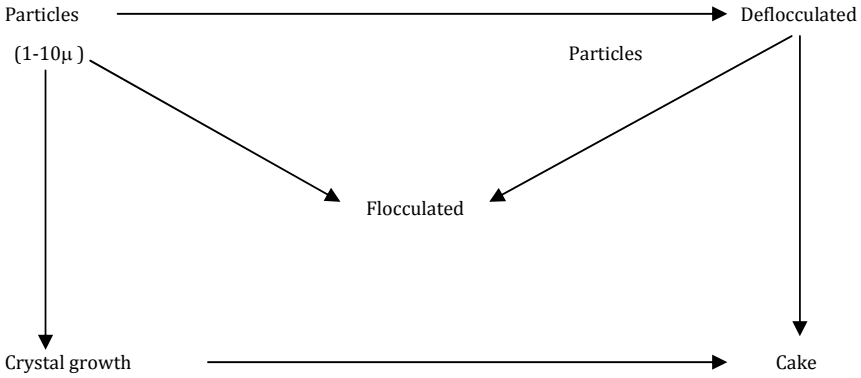

Fig. 1: Schematic representation of formation of cake

Factors affecting in design of parenteral suspension.[3, 9]

- The formulation of stable suspension mainly involves use of high solid content and /or increased viscosity of the system.
- However most parenteral suspensions are usually dilute and have particles limitation for viscosity because of syringeability and injectability constraints.
- The limited numbers of parenteral acceptable excipients further accentuates the challenge to formulate an injectable suspension.
- In addition the above mentioned limitations the factor affecting the release of drug from the suspension and absorption from the intramuscular or subcutaneous injection site should be considered while developing suspension formulation.
- The rate of drug release from suspension can be affected by different steps involved in the process.
- These include dissolution of drug particles, perfusion of the area by blood, oil water partition co-efficient and diffusion through the highly viscous adipose layer to the vascular system. The specific histological structure of the muscle & adipose tissue & the difference in their lipoidal character also influence the lipid solubility, protein binding & release rate of the drug in addition, the injection depth is an important variable because the mean absorption times are considerably longer when the drugs are shallowly injected in the adipose layer.

Important Properties of the parental suspension for the formulation development

- Solubility of drug in biological fluids at the injection site.
- Lipid solubility and oil water partition coefficient of the drug.
- Pka of the drug.
- Dissolution rate of the solid drug from its dosage from.

- pH of the vehicle & tonicity of suspension.
- Particle size of the drug in suspension.
- Compatibility of other ingredients in the dosage from.

Typical excipients used in parenteral suspensions include following

1. Flocculating \ suspending agents.
2. Wetting agents.
3. Solvent systems
4. Preservatives
5. Antioxidants
6. Cheating agents
7. Buffering agents
8. Tonicity agents

1. Flocculating \ suspending agents.[3]

There are basically three techniques used to formulate a suspension.

(a) Controlled flocculation

(b) Structured vehicle

(c) Combination of a & b

The choice depends on whether the particles in a suspension are to remain flocculated or deflocculated.

(a) The controlled flocculation approach uses a flocculating agents(s) to from loosely bound aggregate or flocs in a controlled manner that settles rapidly but redisperses easily upon agitation.

An appropriate amount or flocculating agent is added that result in maximum sedimentation volume & prevents cake formation. Electrolytes, surfactant and hydrophilic colloids have been typically used as flocculating agents.

Electrolytes & surfactants reduce the electrical forces of repulsion between particles & allow the flocs to form, which in turn is influenced by the surface charge on the particles.

E.g. Electrolytes used in Parenteral Suspensions.

Potassium \ sodium chloride

Potassium \ sodium citrate

Potassium \ sodium acetate

The surface charge of the system can be measured by the zeta potential. The zeta potential must be controlled so as to lie within a range (generally less than 25 mV) to obtain a flocculated, noncaking suspension with maximum sedimentation.

Hydrophilic colloids (generally negatively charged) not only affect the repulsive force but also provide mechanical barrier to the particles.

For e.g. a 25% PVP solution is used in combination with polysorbate 80(2%) acts as a stabilizer to provide a stable injectable 30% aqueous powder suspension.

(b) Structured vehicles approach is used to keep the dispersed particles in the suspension in a deflocculated state. These agents function as viscosity imparting agent & reduce the rate of sedimentation of the dispersed particles.

Various hydrophilic colloids are used as structured vehicles. Ideally, these form pseudo-plastic or plastic system that undergoes sheer thinning with some degree of thixotropy. However the high viscocity & poor syringeability of such system limit their use in parenteral suspension.

Some viscosity building agents used in formulation of injectable suspension.[3]

Sodium carboxymethyl cellulose

Acacia

Gelatin

Methyl cellulose

Polyvinyl pyrrolidone

The deflocculated approach is used for oleaginous suspension and for suspensions containing relatively high concentration of solid e.g. in the formulation of injectable suspension of procaine penicillin – G.

2. Wetting Agents [3, 10]

Wetting of the suspended ingredient(s) is one of the most important aspects of the injectable suspension because of the hydrophilic powders often suspended in aqueous systems.

Wetting as described by young's equation – illustrates that a θ (contact angle) less than 90 is observed in the case of hydrophobic powders which usually require an adjuvant to aid in their dispersion.

Various nonionic surfactants and non-aqueous solvents like glycerin, alcohol & propylene glycol are types of wetting agents commonly used in injectable suspensions.

Wetting agents reduce the contact angle between the surface of the particle & the wetting liquid to obtain maximum wetting efficiency; surfactants with hydrophilic lipophilic balance (HLB) value in the range of 7 to 9 should be selected. The usual concentration of surfactants varies from 0.05% to 0.5% depending on the solid contents of the suspension. Care should be taken in terms of the amount used; excessive amounts may cause foaming or caking or provide an undesirable taste/odor to the product.

Surfactants (wetting agent)

Lecithin, Polysorbate 20, Polysorbate 80, Pluronic F-68, Sorbitan trioleate(span 85) for e.g. in the preparation of a non-aqueous suspension of cefazolin sodium in peanut oil, addition of polysorbate 80 at concentration greater than 0.17% resulted in deflocculated suspension which was difficult to redisperse. Microscopic examination revealed extensive agglomeration and crystal growth of cefazolin sodium in the presence of polysorbate 80.

3. Solvent system [3, 11]

Solvent system used in parenteral suspension are classified as either aqueous or nonaqeous vehicles. Choice of a typical solvent system depends on solubility, stability & desired release characteristics of the drug.

Non-aqueous vehicles include both water miscible and water immiscible vehicles.

- Water for injection is generally the preferred solvent system. However, non-aqueous water miscible agents are used as co solvents with water for injection to promote the solubility & stability in parenteral preparation. Examples of water miscible nonaqueous vehicles include ethanol, glycerin, propylene glycol & n–lactamide.
- The used of water miscible cosolvents can lead to undesirable side effect for e.g. intramuscular injection of propylene glycol-water, ethyl alcohol-water & polyethylene glycol (PEG) 400 water mixtures was found to cause muscle damage as measured by in vitro release of creatinine kinase from isolated rat skeletal muscle.
- At moderate concentration (20% t0 40%V/V) organic cosolvents PEG 400 is less myotoxic than propylene glycol & ethanol. Myotoxicity was not correlated exclusively to a single physicochemical property of the cosolvent-water mixtures such as dielectric constants, apparent pH, surface tension, viscosity or a combination of these for a series of cosolvents. Based on this result it was suggested that biochemical interaction between organic

cosolvents & skeletal muscle fibers may be involved in the cosolvents induced toxicity.

- Additionally lysis of human red blood cells in the presence of cosolvents such a propylene glycol, glycerol, PEG 200,300 & 400& ethanol have been reported.

In the presence of 0.9% to 2.7% sodium chloride cosolvents other than PEG 300 & 400 were less hemolytic than when mixed with water.

- Hemolysis caused by cosolvents may be releted to their possible binding with the red blood cell membranes. Hemolytic potential of ethyl alcohol, PEG 400 is low whereas propylene glycol has a high hemolytic potential.

- Nonaqueous water-immiscible vehicles used in parenteral suspensions include fixed oil as ethyl oleate isopropyl myristate and benzyl benzoate.

Fixed oil must be fluid at room temperature and vegetable in origin & should have good thermal stability at both high & low temperatures; generally an antioxidant is needed to ensure the stability of fixed oil over the shelf life of the drug product.

E.g. of various fixed oils used in suspension formulations include sesame oil, peanut oil &castor oil. Some other oils being studied in the development of parenteral suspensions include almond oil, sunflower oil, iodinated poppy seed oil, cotton seed oil & corn oil. Excessive unsaturation of oil can cause tissue irritation. Some patients may have allergic reaction to the vegetable oil; hence specific oil used in the product should be listed on the product label. The type of oil & its volume have been found to affect the release of the drug from the suspensions for e.g. the androgenic activity of testosterone andosterone in oleaginous solution is dependent on the type of oil vehicle used. Additionally the subcutaneous activity of testosterone depends on volume of oil injected for the same amount of testosterone by forming a long acting ester such as testosterone propionate, the androgenic activity is greatly enhanced and is further increased by three times if the injection volume is increased from 0.2 to 0.8 ml.

4. Tonicity Agents [3, 12]

Isotonicity of the parenteral preparation for subcutaneous or intramuscular administration is desired to prevent pain; irritation and tissue damage at the site of administration, the aqueous solution of tonicity agents used in parenteral suspensions include dextrose & various electrolytes.

5. Preservatives [3, 13]

Antimicrobial agents are required for parenteral products that are intended for multiple dosing, in order to protect the product from accidental microbial contamination during clinical usage & maintain sterility.

Similarly, preservatives should be added to formulations aseptically packaged in signal dose vials if the active ingredient(s) does not have bactericidal or bacteriostatic properties or is growth promoting. A growth promoting study should be conducted to determine the microbiological properties of the preservative free formulation.

Some typical preservative used in parenteral suspensions and their commonly used concentrations are as follows.

- Benzyl alcohol (0.9% to 1.5%)
- Methylparaben (0.18%to0.2%)
- Propylparaben (0.02%)
- Benzalkonium chloride (0.01% to 0.02%)
- Thimerosal (0.001% to 0.01%)
- Benzalkonium chloride is used in ophthalmic dosage forms & not in injectable dosage forms.
- Propyl and methyl parabens are referred to chemically as propyl and methyl esters of p-hydroxy benzoic acids. Because of the inherent chemically reactive nature of preservatives, stability & compatibility problems of preservative need to be evaluated for their usage in the final formulation.

The low aqueous solubility of parabens and a decrease in stability with increasing pH complicates their use in the parenteral formulation.

Generally parabens are solubilized by adding them to alcohol UPS or small volume of water heated to approximately 80˚C. The heated solution requires further dilution to prevent precipitation at parabens before it cools significantly. Parabens are sensitive to excessive light exposure and are incompatible with alkaline excipients and polysorbate 80. Benzyl alcohol can cause convulsions in neonates so it should be avoided in certain drug product with neonatal indications.

- Most antimicrobial preservatives & antioxidants are known to volatilize or adsorb to rubber closures & can cause loss of sterility & stability & potential problems with flocculation & resuspendability of the product.
- A USP antimicrobial preservative effectiveness test should be conducted on preparations formulated with, for example 90%,75% and 50% of the initial preservative concentration to determine the minimally effective concentration of the preservative over the shelf life of the drug product.

6. Antioxidants/chelating agents [3, 14]

- Oxidation can lead to unacceptable discoloration of the drug product without necessarily causing significant potency loss.
- Drug formulated in the reduced form have low oxidation potential and are susceptible to oxidation.
- Oxidative degradation of drug in solution is mediated either by free redicals or by molecular oxygen and can be catalyzed by metals, heat, light, and hydrogen ions.
- Antioxidants are added in the formulation to minimize this degradation by preferentially undergoing oxidation as the result of their lower oxidation potential or by terminating the propagation step in the free redical oxidation mechanism.
- Antioxidants are either used alone or in combination with a chelating agent or other antioxidants.
- Certain compounds (ascorbic acid of citric acid) have been found to act as synergists & increase the effectiveness of antioxidants that block oxidative reaction.
- Chelating agents sequester heavy metals, thereby preventing the catalysis of oxidation reaction e.g. of suitable antioxidants & chelating agents & their typical concentration for injectable dosage forms are listed in Table 1.

Table 1: Typical antioxidants/chelating agents for parenteral preparations

Compound	Typical concentration
1. Ascorbic acid	0.02-0.1
2. Sodium bisulfite	0.1-0.15
3. Sodium meta bisulfite	0.1-0.15
4. Sodium formaldihydesulfoxylate	0.1-0.15
5. Thiourea	0.005
Antioxidants (propagation termination oil soluble)	
1. Ascorbic acid ester	0.01-0.15
2. Butylated hydroxy toluene	0.005-0.02
3. Tocopherols	0.05-0.075
Chelating agent	
1. Ethylene diamine tetraacetic acid salt	0.01-0.075

Auto –oxidation is defined as oxidative degradation by molecular oxygen. In such cases the exposure of active ingredient to oxygen during the manufacturing process should be avoided. This can be accomplished by the following processes.

- Purging the solvent system (i.e. water for injection USP) and bulk drug product with filtered (0.22μm)nitrogen during the manufacturing process by controlling the mixing speed and the nitrogen flow rate , rate of oxygen can be improved.
- Blanketing the bulk drug product with filtered (0.22μm) nitrogen /argon during the filling operation
- Displacing oxygen from the head space of the filled container with filtered (0.22μm) nitrogen.

7. Other stabilizers.[3, 15]

- Various other stabilizers have been used in different specific parenteral suspensions of drugs. For e.g. sugar such as sorbitol, sucrose or fructose have been associated with enhanced stability of procaine benzyl penicillin and sodium benzyl penicillin parenteral suspensions.
- Oil based injectable suspensions of tetracycline in miglyol are stabilized by the addition at maleic acid or a maleate salt.
- D-Glucose, polyethylene glycol or adenine inhibits the aggregation of aqueous suspension of nitrozepam during freezing & defrost to allow smooth passage through the syringe needle.
- Aluminum monosterate is water repellant used mostly in long acting parenteral suspensions it acts by reducing the interfacial tension.
- Collodial polymeric particles made from biodegradable materials such as polyhydroxy butyrate (PHB) are possible carrier system for controlled delivery of drug.These PHB carries possess low zeta potential and that is further reduced by incorporation of oppositely charged drugs.
- Antiflocculants such as sodium pyrophosphate, sodium citrate and sodium dihydrogen phosphate adsorb in on the suspension particles & the electrostatic repulsions of the similarly charged particles enhance the physical stability by increasing the zeta potential. The antiflocculants should be selected by considering the effect of pH shifts, maximum net charge increase, and their toxicological acceptance.

METHODS FOR PREPAPARATION OF PARENTERAL SUSPENSION[3]

Two basic methods are used to prepare parenteral suspensions:

(a) Aseptically combining sterile powder and vehicle. This method involves aseptically dispersing the sterile, milled active ingredient(s) into a sterile vehicle system (solvent plus necessary exipients); aseptically milling the resulting suspension as required, and aseptically filling the milled suspension into suitable containers. For example, this process is used for preparation of parenteral procaine penicillin G suspension.A schematic diagram is shown in Fig. 2.

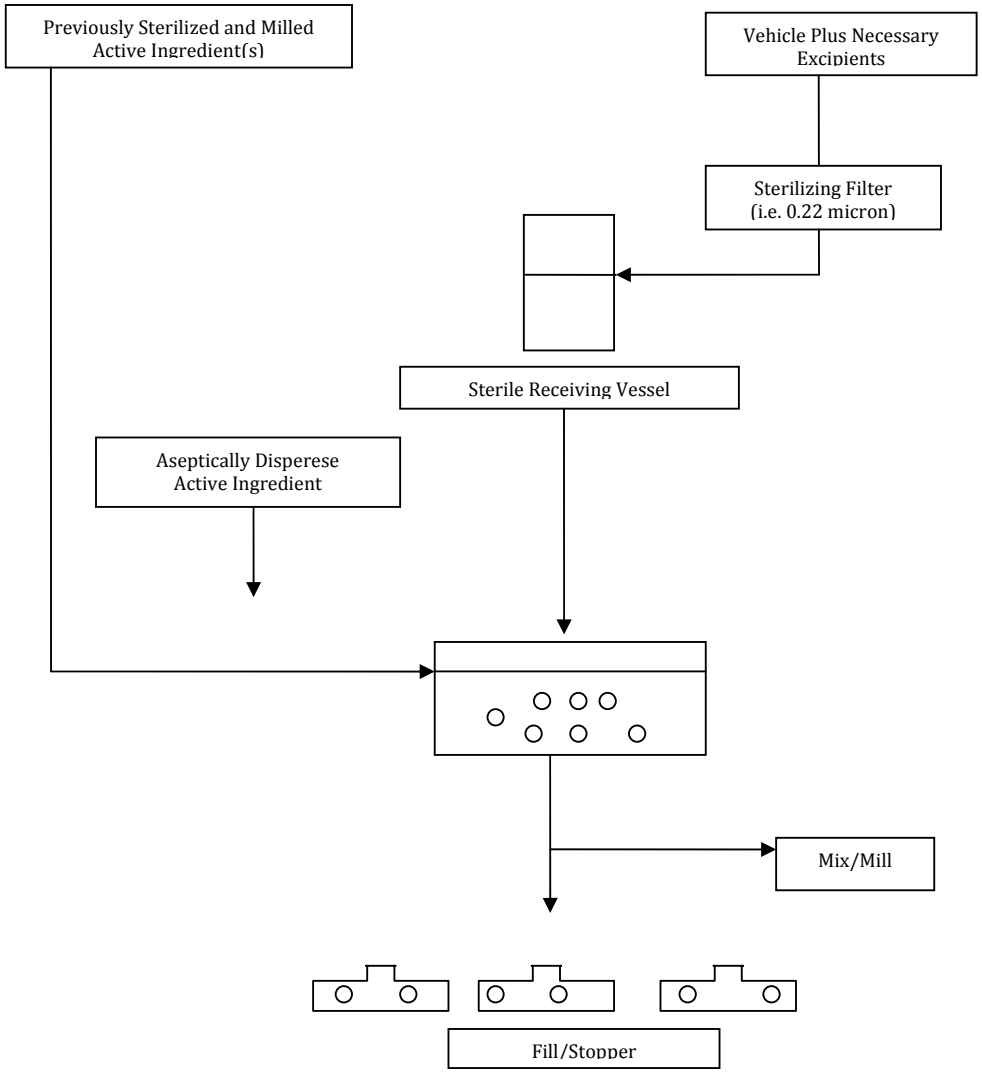

Fig.2: Schematic diagram of sterile manufacturing of injectable suspensions using aseptic technique

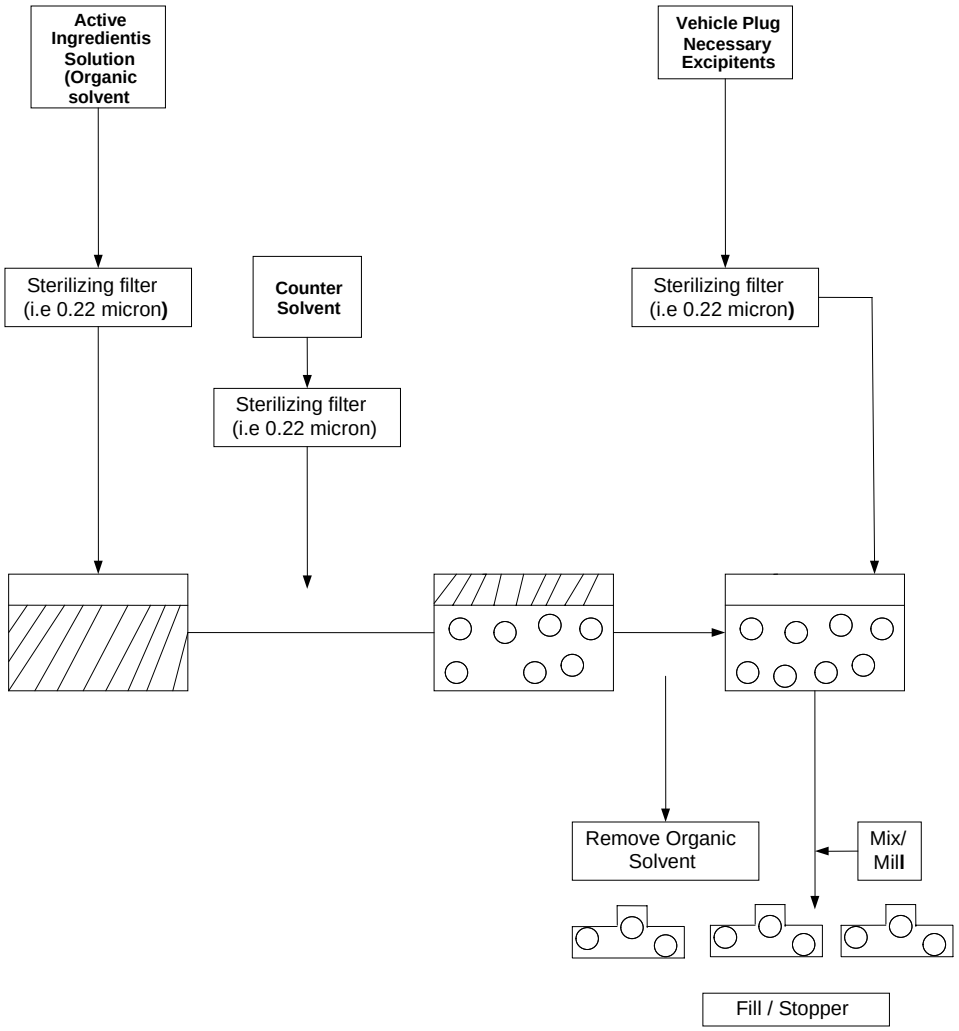

Fig. 3: Schematic diagram of sterile recrystallization process for the manufacturing of injectable suspension.

(b) In situ crystal formation by combining sterile solutions. A schematic is shown in Fig.3 In this method active ingredient(s) are solubilized in a suitable solvent system, a sterile vehicle system or counter solvent is added that causes the active ingredient to crystallize, the organic solvent is aseptically removed, the resulting suspension is aseptically milled as necessary, and then filled into suitable containers. For example, this process is used for testosterone and insulin parenteral suspensions.

In addition, several other methods are described for preparation of specific parenteral suspensions. Lyophilization of the product or direct fill of the dry powder in the final package can be used for parenteral suspension. Another approach is described for preparing an injectable suspension of allow melting compound, butyl-p-aminobenzoate, which forms solid lumps on cooling after dry heat sterilization. The drug particles are dispersed in a solvent containing polysorbate 80 and normal saline. The suspension is then sterilized for 20 min at 120°C without cooling. The suspension is cooled while being shaken vigorously and than frozen to-18°C. Special milling procedures involving frequent defrosting/shaking of the frozen suspension are used to obtain acceptable particle size.

In another example, monodisperse insulin suspensions is prepared by seeding the swine insulin solutions with insulin crystals of 3 to 5 um and allowing it to crystallize till 70:30 crystal/amorphous ratio is obtained. At this point an aqueous solution containing $ZnCl_2$ and methylparaben is added and the pH is adjusted to 7.1 to 7.3.

STABILITY AND EVALUATION OF PARENTERAL SUSPENSION [3, 19]

Because suspensions are thermodynamically unstable system, physical stability of suspensions becomes as important as the chemical and biological stability. In addition, injectable suspensions require evaluation of characteristics such as syringeability, injectability, isotonicity, sterility and preservative effectiveness. Rhelological properties of an injectable suspension can provide some formidable challenge in their administration and delivery.

Therefore, flow properties such as syringeability and injectability are necessary to evaluate and control.

- Syringeability describes the ability of the suspensions to pass easily through hypodermic needle on transfer from the vial prior to injection. It includes characteristics such as the ease of withdraw, clogging and foaming tendencies and accuracy of dose measurements. Increase in the viscosity, density, particle size and concentration of solids in suspension hinders the syringeability of suspension. A suitable test is to ensure that the entire suspension passes through a 25-gauge needle of internal 0.3 mm.
- Injectability refers to the performance of suspension during injection and includes factors such as pressure or force required for injection. Evenness of flow, aspiration qualities, and freedom from clogging. The syringeability and injectability of suspension are closely related to the viscosity and particle characteristics of the suspension. A simple ejection of the suspension into the open, if done very slowly with intermittent application of pressure to the plunger can provide certain information about suspension. Most methods used for injectability are qualitative in nature. A force monitoring device such as instron can be used to determine ejection and injection pressure, and test result can be recorded on a X-Y recorder. Another instrument to assess the injectability of parenterals measures the time required to smoothly inject a solution or suspension into meat under specified pressure from a syringe through a needle. When a test solution is injected through glass and plastic syringes of various sizes, regression equations are obtained of a given syringe type and diameter using needles of various gauge. These equation permit the calculation of the expected injection time for a given syringe needle system and for a given vehicle of a certain viscosity.
- Clogging or blockage or syringe needles while administrating a suspension may occur because of a single large particle or an aggregate that blocks the lumen of the needle or because of a bridging effect of the particles. It is advisable to avoid particles greater than one-third of the internal diameter of the needle to prevent clogging. Clogging, if observed at or near the needle end, is usually caused by restrictions to flow from the suspension and may involve combination of factors such as vehicle, wetting of particles, particle size. Shape and distribution, viscosity, and flow characteristics of the suspension.
- Drainage refers to the ability of the suspension to break cleanly away from the inner walls of the primary container-closure system and is another characteristic of a well-formulated parenteral suspension. Silicone coating of container, vials, and plugs with dimethicone can improve the drainage of slightly over flocculated systems as well as good suspensions.
- Resuspendibility describes the ability of the suspension to uniformly disperse with minimal shaking after it has stood for some time. Qualitatively, light transmittance through the upper solution in a cylinder after it has been spun for about 2 minutes at 75 rpm can be used to detect the redispersion properties of the system. Resuspendibility becomes a problem for suspension that forms cakes on standing due to the deflocculated particles. Caking describes a process by which the particles undergo growth and fusion to form a nondispersible mass of material.
- Sedimentation Volume is a qualitative term used to describe the amount of settling that has occurred in a suspension. The sedimentation volume is defined as the ratio of the final volume, V_u, to the original volume, V_0, of the suspension. The larger the fraction, the better is the suspendibility, Sedimentation volume is used to evaluate the changes in suspension characteristics with time and also to compare different suspension formulations, when the ratios are plotted against time, the more horizontal the slopes, the more flocculated the suspension. Generally, the sedimentation volume is directly proportional to the size of the flocs, and the rate of setting is inversely proportional to the amount of deflocculation.
- Freeze-Thaw cycles are important for determining the ability of the suspension to withstand thermal shock, retard crystal growth, and maintain chemical stability of the active ingredient and overall physical stability. The freeze-thaw cycle promotes particle growth and may predict the result of long term storage at room temperature. A total of three complete cycles with each cycle consisting of 24 hours at 40°C followed by 24 hours at 0°C is suggested, although various cycles are suitable.
- Crystal Growth in suspension is affected by the particle size distribution, changes in pH, temperature, cycle form, and solvate formation and by dissolution and recrystallization of the particle. Crystal growth should be monitored by examining changes in particle size over time and comparing that with the initial particle size distribution. The tendency for crystal growth in a suspension can be diminished by using a narrow particle size range, decreasing interfacial tension (to reduce the free energy of particle), increasing the viscosity of suspending medium (may be difficult with parenteral suspensions as it affects the syringeability and flow), use of hydrophilic gums like polyvinylpyrrolidone, polysorbates (adsorb at particle surface and retard crystal growth), and choosing a different chemical form of the drug.
- Particle Size Measurements- Variable particle size distribution in suspensions results from different factors, including preparation of suspension by precipitation methods where the degree of saturation and rate of nucleation are greatest at the beginning of the process, resulting in large particles initially and smaller particles subsequently; changes in pH caused by drug decomposition; changes in temperature; and changes during processing in several types of equipment and transfer steps. Particle size measurements are useful in that they allow aggregation or crystal growth to be evaluated there are a number of methods used for particle size analysis; microscopic determination are preferred over Andersen pipette or subsieve sizer and turbidimetry. For particle size determination below 1 um, photon correlation spectroscopy may be employed using a Malvern particle size analyzer. For example, Coulter Multisizer and HICA/Royco particulate counter is used for the size characterization of reconstituted, lyophilized, attenuated mycobacterium boves. Bacillus Calmette-Guerin(BCG) vaccine, formulated as suspension. The cumulative size distribution of the suspension fits the log-probit plot, and this information is used to determine the total number of colony-forming units.
- Zeta Potential determinations can be great value in the development of suspensions, particularly if the controlled flocculation approach is used to formulate the suspension. The electrokinetic method measures the migration velocity of suspension particle with respect to the net effective charges on the surface. The zeta meter is a microelectrophoretic mobility apparatus used to characterize flocculated and dispersed suspensions and to follow changes in physical stability with time. The electrophoretic velocity can be measured by laser Doppler anemomentry using a Malvern Zetasizer or by amplitude weighted phase structuration. Visually observed caking can be related to the changes in the zeta potential as well as to the changes upon addition of additives like electrolytes and surfactants.
- Compatibility with diluents and other Parenterals- Parenteral suspension may require dilution prior to use if small concentrations of the drug are needed or may be mixed with local anesthetics to reduce the pain associated with their administration. Even though dilution with water or normal saline will often cause the system to deflocculate, it may be necessarily detrimental in the light of the time frame of suspension administration, because of slow settling of deflocculated particles. However, agglomeration or coagulation of suspension on mixing with other parenterals may cause serious incompatibilities.

- Shipping Characteristics of suspensions under various stresses of shipping such as vibration, impaction and shaking determine the suspension's ability to retain its required attributes during transit. Ideally, the test should expose the suspension to both realistic climate and handling conditions. Common laboratory test methods used to evaluate shipping characteristics include vibrator, shakers, and impact devices.
- Product-Package Interactions- Antimicrobial preservatives and antioxidants present in the suspension formulation are known to volatilize or adsorbed by the stopper resulting in the formation of more monodispersed and less resuspendable suspension. Also, the extractables from the rubber clousures are often masked in suspension. Agglomeration of fine particle on the surface of glass is another type of interaction and becomes particularly evident after the shipping test. The probability of particle agglomeration can be reduced by uniform siliconization of the vial, which also promotes efficient drainage of suspension.
- Viscosity describes the resistance to flow with applied stress for a particular system; a more viscous system requires greater force or stress to make it flow at the same rate as a less viscous system. An ideal suspension should exhibit a high viscosity at low shear (agitation and syrigeabiltity). A fluid system will exhibit either Newtonian or non-Newtonian flow based on linear or nonlinear increase in the rate of shear with the shearing stress. The suspension viscosity can change due to concentration of active ingredient(s), particle shape, size, and distribution. In addition, the actual manufacturing process, equipment and the length and type of exposure to mixing and/or homogenization shear can have a profound effect on the final suspension product.
- Structured vehicles used in suspensions exhibit non-Newtonian flow and are plastic, pseudoplastic, or shear-thinning with some thixotropy. For example, sodium carboxymethycellulose (CMC) and methycellulose (MC) methocel, most commonly used in parenteral suspensions, have pseudoplastic properties. Certain grades of CMC at high levels act as pseudoplastic thixotropes. The viscosity of CMC systems is dependent upon temperature, and storage at accelerated temperature may irreversibly degrade CMC. Sodium carboxymethylcellulose is compatible with most water-soluble nonionic and anionic polymers and gums but is incompatible with di-and trivalent salts. Viscosity of MC decreases on exposure to elevated temperatures. High levels of electrolytes and surfactants affect the methocel systems. Methocel is normally used in conjunction with other suspending agents and not as primary suspending agent. For example, MC in combination with CMC is used as a suspending agent in aqueous suspension of desoxycorticosterone pivalate.

OFFICIAL PREPARATIONS OF PARENTERAL SUSPENSION

(1) Sterile ampicillin suspension USP'95 dispense as powder which is to be reconstituted at time of administration.

(2) Sterile Aurothiglucose suspension USP'95 – vegetable oil suspension.

(3) Tetanus toxoid adsorbed USP'95, IP'96 – aq. Suspension.

(4) Betamethasone acetate suspension USP'96 aq. Suspension.

(5) Insulin Zinc suspension USP'95, IP'96 aq. Suspension.

(6) Procaine penicillin suspension IP'96

Insulin suspensions

Extended-acting insulin preparations are microcrystalline suspensions that provide their protracted effects by slow dissolution of the crystals and gradual release of insulin into the blood stream – There are several approaches to formulate extended acting insulin preparations. For Example: ultralente human insulin (UHI) is a zinc insulin suspension composed predominately of small rhombohedral crystals & characterized by an intermediate to long time action profile ultralente is one of a series of insulin zinc suspension that were developed by halls moller & colleagues, they determined that the addition of zinc ions in preparations that had neutral pH & no zinc binding ions (i.e. no phosphate or citrate) led to insulin formulations with protected effects.

- This series of zinc insulin suspension formulation include ultralente (crystalline insulin particles) semilente (amorphous insulin particle & lente (a mixture of amorphous & crystalline insulin particles.) A second approach to making protracted insulin preparation is to depress insulin solubility by adding basic peptides. This approach is exemplified by the product neutral protamine hagedorn insulin (NPH). NPH is an intermediate acting formula prepared by co-crystallization of insulin with the basic peptide protamine. Recently lys^{b28} pro^{b29} human insulin is produced by inventing the native sequence of the B chain Pro^{b28} Lys^{b29} in the C terminal of human insulin.

In the presence of both zinc ions & phenolic ligands lyspro can be assembled in weekly associated hexamer without impacting its pharmacological properties.

Preparation of a micro crystalline suspension formulation of Lys^{b28} Pro^{b29} Human insulin with ultralente properties [20, 21, 22]:

The stock solution was prepared containing 22 mg/ml lyspro. Acidic zinc oxide (10 mg/ml) was supplemented in proper volume and pH adjusted to 2.5 to 3 by 10% HCl.

A buffer solution containing 21.3 mg/ml, Sodium acetate 186.7 mg/ml, sodium chloride & sodium hydroxide solution were added to above solution to make pH 5.5 that resulted in immediate formation of the white flocculent precipitate. The mixer was stirred at 100 RPM. A small amount of human seed crystals were added. Small crystals were visible with in 24 hours.Crystallization is allowed to proceed for 24-96 hours at room temperature. The solution is then diluted to active concentration of 40 units / ml.

The ULP crystals were estimated to have edge size of approximately 5-15 microns. Mean particle size for the crystals was 20 + 1 microns as measured by the coulter particle size technique. This result were in good agreement with the mean particle size of the commercial UHI samples, HPLC analysis revealed that the solid phase contained approximately 40 units/ml of lys-pro, whereas less than 0.05 units/ml of lys-pro was found in the soluble fraction indicating the completeness of crystallization in the final product.

Table 2: Normoglycemic activity and duration of various commercial insulin products

Insulin preparation	Normoglycemic activity		
	Onset	Peak	Duration
Insulin injection IP	0.5-1.0	2-3	6
Semilente Insulin	0.5-1.0	5-7	12.76
Lente Insulin	1.0-1.5	8-12	24
Ultralente Insulin	4-8	16-18	>36
Globin Zn-Insulin Injection USP	~2	8-16	~24
Isophane Insulin suspension USP	1-1.5	8-12	~24
Protamine zn-Insulin suspend USP	4-8	14-20	>36

Table 3: List of official marked parenteral suspension preparations

Drug	Brand Name	Manufacturer
Aurothioglucose	Solganl ®	Schering
Betamethasone Sodium Phosphate And Betamethasone acetate	Celestor®	Schering
Dexamethasone acetate	Decadron-LA®	Merck
Methylprednisone acetate	Depo-Medrol®	Upjohn
Medroxyprogesterone acetate	Depo-Provera®	Upjohn
Penicillin G Benzothine and Penicillin G Procaine	Bicillin® C.R.	Wyeth
Penicillin G Procaine	Bicillin® C-R	Wyeth

CONCLUSION

Suspension is the better choice of dosage form, as it's bioavailability and fast onset of action over the other conventional dosage forms such as tablets and capsules as they facing the problem of first pass metabolism and also in respect to the drug stability, it is an excellent dosage form. Many pharmaceutical manufacturers coming forward to formulate parenteral suspension due to it's beneficial characteristics over other conventional dosage forms.

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