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Nanosuspension: A Novel Approach for Poorly Water Soluble Drugs

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ABSTRACT

During recent drug discovery attempts most of the drugs evolved are hydrophobic having good pharmacokinetic profiles but problems with bioavailability. Many attempts are being made to improve the bioavailability by removing hurdles in their pharmacokinetic parameters. Nanotechnology is the technique by which the size of the drug, chemical, or any substance is brought in the range of nanometres (0.1 nm to 1000 nm). This can be achieved using constantly improving sophisticated technologies which led to its widespread use in various facets of health care. Nanocrystals are the outcome of applying modern/novel techniques to formulate different formulations including colloidal dispersion. Nano-suspension is the easiest and cost-effective technique for solving problems like poor entrapment, variability in absorption, polymer toxicity, biocompatibility & stability, high crystal energy with reduced toxicity of the drug. This review summarizes the development of nano-suspension of various BCSCLASS Ⅱ drugs including some examples of excipients, preparatory techniques, and formulation considerations. It also gives brief information regarding applications, advantages, and disadvantages of nano-suspensions along with evaluation parameters-their methods.

INTRODUCTION:

Approximately 40% of drug candidates currently available for the therapeutic purpose are hydrophobic which affects the bioavailability of such type drug molecules. Many techniques are employed to overcome this problem, out of which most important are size reduction to nano-size (Formation of Nanocrystals), pH adjustment, use of salt and co-solvents, surfactant, and preparation of lipid formulation. [1]

Crystals are defined as the presence of a high degree of order with a three-dimensional periodicity in a position of atoms or ions in a molecule, with a configurational periodicity of molecules that form the crystal. All chemical entities including drug molecules can possess different crystalline forms called polymorphic form, which have the same molecular formula, but arranged in different configurations and showing different physical properties [2]. Specific polymorphic forms are often considered as important quality-relevant attributes of a drug substance. Polymorphic forms exhibit different dissolution rates, solubility, flow properties, hygroscopicity, and behavior under mechanical stress encountered during milling, tableting, agglomeration, etc. [3]. (Amorphous molecule shows molecular level disorder in configuration, having high internal energy (Chemical potential) i.e. thermodynamically unstable. These compounds possess higher solubility in the aqueous phase as compared to crystalline compounds that possess low internal energy i.e. highly thermodynamically stable with lower solubility[4]. Various techniques are used to enhance the solubility of crystalline drugs which include structural modification by physical and chemical methods and other methods like particle size reduction (Micronization / Nanonization), crystal engineering, solid dispersion, use of surfactant, salt formation, and complexation. [5]

Biopharmaceutics Classification System (BCS) was developed to segregate various drug molecules based on their solubility, dissolution, and permeability properties which categorizes the drugs in four classes as shown in figure number 1. [6]

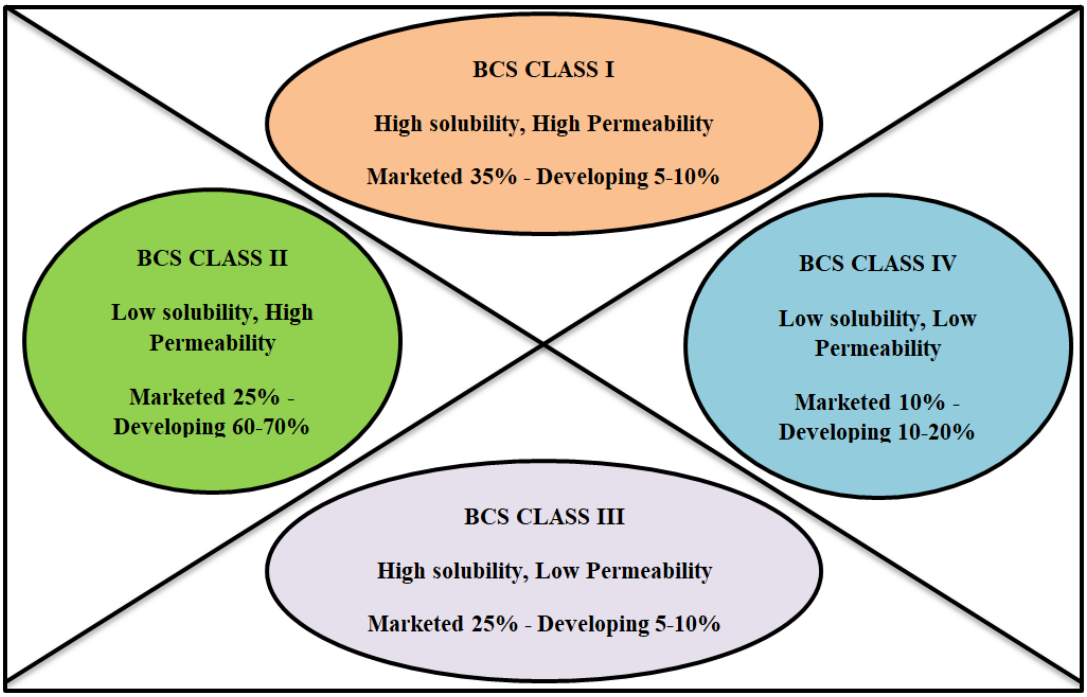

Figure No. 1: Class wise distribution of various marketed drugs & probable drug candidates based on BCS classification. [7]

The drugs classified under BCS class II & IV reported having problems in their solubility, stability, and compatibility which affects their bioavailability and formulation aspects, which can be overcome by making nanocrystals, nanosuspension during their formulations [8]. Nano-suspension is a biphasic colloidal system, prepared by dispersing solid drug particles of nano-size range (200–400nm) into suitable dispersion media. This can be used to formulate different dosage forms such as tablets, capsules, parenteral, ophthalmic, and nasal preparations. The nanosuspension based drug delivery system (DDS) was developed first time in 1994 [9] thereafter there is continuous growth in the interest. The formulation of nano-suspension requires the use of surfactants and polymers without the need for any matrix materials tabulated in table number 1. Nanosuspension based dosage forms can be administered by almost any route of administration. [10]

Table No. 1: Category wise list of excipients required during the formulation of nanosuspensions, with their functions [11].

Excipient	Function	Example
Stabilizer	Prevent Ostwald's ripening, agglomeration of Nano-suspensions, and enhance the shelf half-life.	Lecithins, polysorbate, Cellulosics, Poloxamers, Povidone, and its derivatives.
Co-surfactant	Increase the wettability of solid particles, and also influence in phase behavior when microemulsions are used to formulate nano-suspensions	Dipotassium Glycyrrhizinate, Bile salts, Transcutol, Glycofurol, Ethanol, isopropanol.
Organic solvent	Organic solvents are used to dissolve hydrophobic drug compounds or excipients.	Methanol, Ethanol, Chloroform, Butyl lactate, Ethyl Formate, Isopropanol, ethyl acetate, Triacetin, Propylene carbonate, and Benzyl alcohol.
Other Additives	Used to enhance formulation compliance and to ease and suitable for the formulation method.	Cryoprotectant, Salts, Buffers, Polyols, and Osmogens, etc.

1.1 ADVANTAGES OF NANOSUSPENSION [12]

1. Improves the bioavailability pattern of drugs by reducing particle size at nanosize.
2. The frequency of dose administration can be minimized.
3. Nanosuspension improves saturation solubility which directly enhances bioavailability.
4. Can improve the chemical & physical stability of drugs.
5. Drug targeting can be achieved with a passive process.
6. Can be used as targeted drug delivery.
7. Wide range applicability.

8. The formulation procedure of nanosuspension is simple, economical, and applicable for all drugs.

9. Nanosuspension can be administered by different routes of administration such as oral, parenteral, mucoadhesive, topical, ocular, and nasal due to advantages of reduced particle size.

1. STRATEGIES FOR THE PREPARATION OF NANOSUSPENSION:-

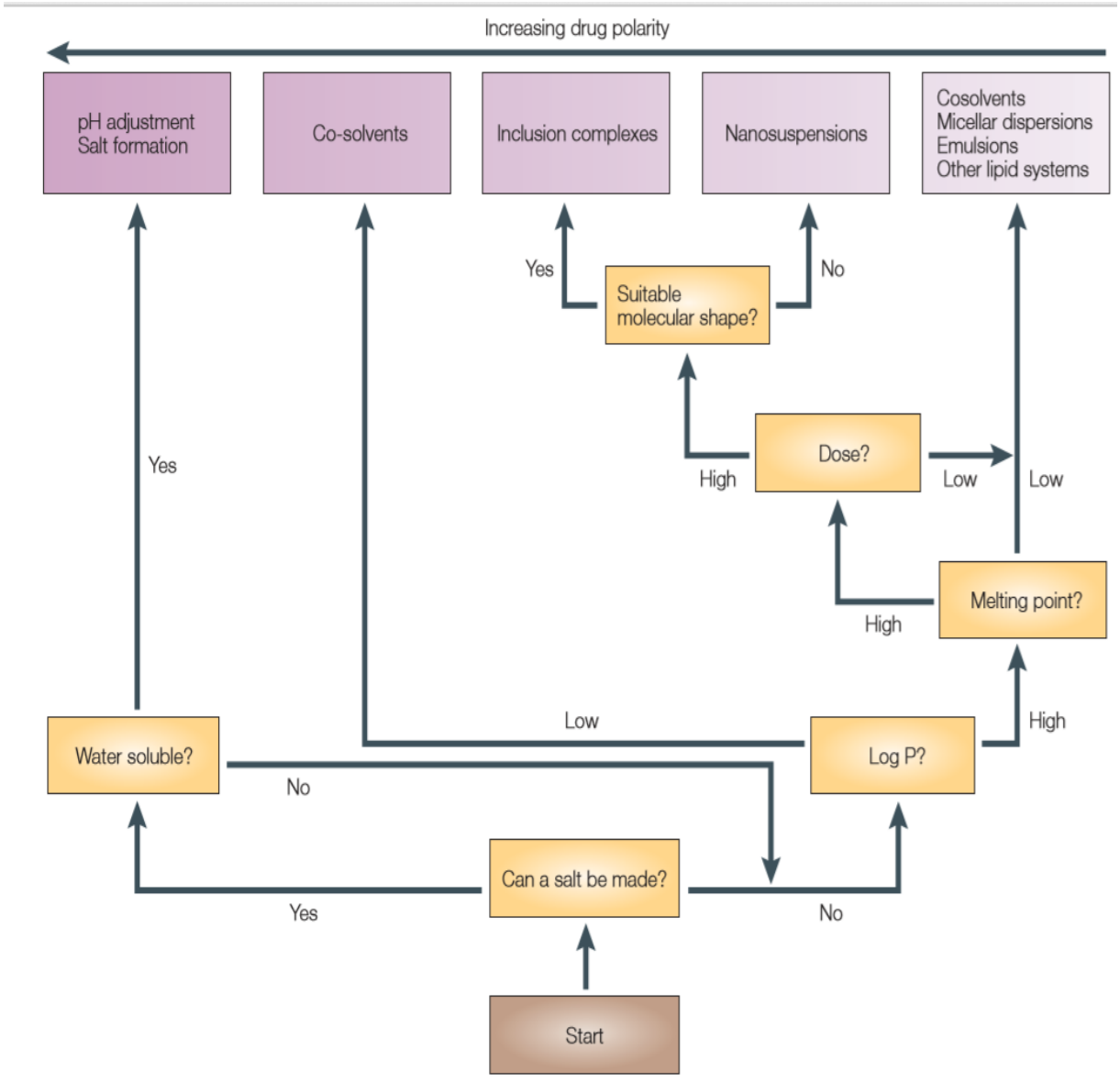

Figure No. 2: Nanosuspension development strategies for different types of drug molecules. [13]

2. METHOD OF PREPARATION OF NANOSUSPENSION:

A stable nanosuspension can be prepared by using different methods. Nanosuspension preparation methods are majorly classified into following 3 types. [14, 15, 10]

Figure 3: Different methods of the preparation of the nanosuspension. (Adopted from Increasing Possibilities of Nanosuspension by **Sutradhar. et al. 2013**) [16]

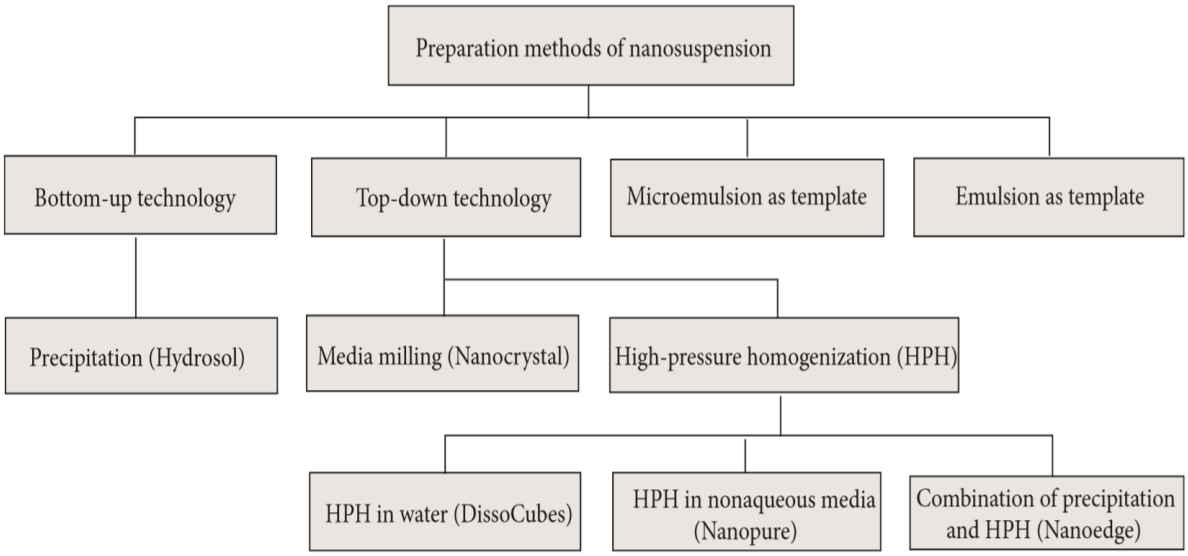

Figure No. 3: Different methods of the preparation of the nanosuspension. (Adopted from Increasing Possibilities of Nanosuspension by Sutradhar et al. 2013) [16]

(3.1) Top-down approach. [10]

The top-down approach involves the breakdown (disintegrate) of larger particles into the nano-range by using external force/energy therefore this method also called disintegration method. In the top-down approach, energy-dependent processes are used to formulate a nanosuspension high energy process called High-Pressure Homogenization and a low-energy process called Media Milling, both methods are used to develop nanosuspension.

(3.1.1) High Pressure Homogenization (HPH) [17,18].

Principle:- Particle size reduction is carried out by particle-particle collision at high shear and high pressure by using a homogenizer. Particle size reduction is achieved by controlling two factors i.e. Pressure up to 100mPaand number of homogenization cycles. Particle size, polydispersibility index, and wetting of solid particles in nanosuspension are achieved by

incorporating the surfactants. Viscosity enhancers are necessary to increase the viscosity, which also maintains the rate of sedimentation of the solid particles. The high-pressure homogenization method is classified into two types based on the involvement of solvent as water or without water that is.

3.1.1.1) Dissocubes (Homogenization in aqueous media) &

3.1.1.2) Nanopure (Homogenization in non-aqueous media).

Albendazole, Amphotericin-B, Omeprazole, Fenofibrate, Azithromycin, Budesonide, Buparvaquone, and Clofazimine are the drugs formulated into nanosuspension by high-pressure homogenization technique. [19,17]

3.1.1.1) Dissocubes:-

This technique is used to prepare the nanosuspension by utilizing aqueous media, which includes primarily the following three steps/stages [20].

1) Preparation of pre-suspension by dispersing API into the aqueous media.

2) Passing of pre-suspension through a small orifice.

3) Homogenization of pre-suspension by using initially low and finally high pressure (1,500-2000bar) up to the formation of nanosuspension.

Dissocubes were invented by Muller & co-workers with the help of piston gap homogenizer. (e.g. APV Gaulin/ Rammie homogenizers).In the Dissocube method, the desired particle size, and stability of nanosuspension achieved by using jet milling technique and high-speed stirrer. Jet milling is also used to reduce the particle size at about 25 um for various crystalline drug compounds. Pre-suspension is prepared by adding solid drug compound into an aqueous surfactant solution with the help of high-speed stirrer [21,20]. After preparation of the pre-nanosuspension at high velocity then pass through the small orifice (5-25um) of the piston under high pressure (1500 – 2000 bar), which results in an increase in dynamic pressure and decrease in the static pressure below the vapour pressure of water. Consequently, the boiling of water at room temperature results in the generation of bubbles which creates homogenization space (cavitation) in the liquid due to collapsing of water bubbles. Finally, nanosuspension is obtained at high pressure (1500 bar), and homogenization

cycles (15-20 cycles) [22, 14]**.** Depending upon the hardness of drug, homogenization pressure, and several homogenization cycles, the mean size of bulk is obtained. The selection of a suitable and appropriate surfactant is an important factor that may directly affect stability (physical/chemical) or solubility of the nanosuspension. Various types of surfactants are available for the different types of dosage forms. In the following table number 2 best few examples of surfactants are given which are suitable according to different types of nanosuspension.

Advantages of Dissocube technique [23]

Dissocube is the safest technique for the preparation of nanosuspension with low and high concentrations.

1) It can detect metal contamination (less than 1ppm) during the running process. The instrument is very costly so formulation cost also increases.

Dissocube technique is also having drawbacks. It may require many numbers of homogenization cycles (time-consuming), and pre-treatment is necessary for particle size reduction before homogenization.

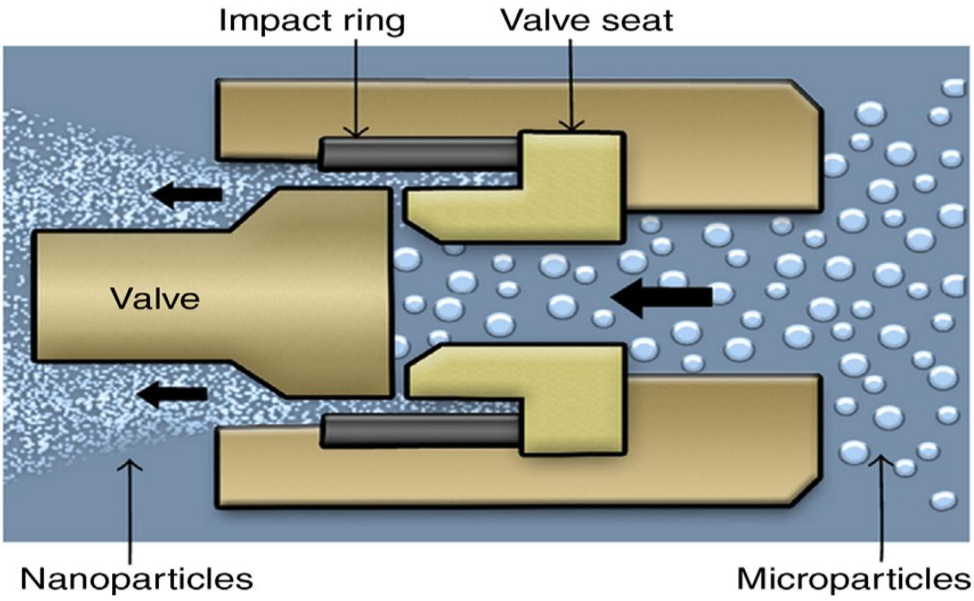

Figure No. 4:- Mechanism of the High-Pressure Homogenisation process. (Adopted from NANOSUSPENSION DRUG DELIVERY SYSTEM: By- Zhang et al. 2017. Page No: 416). [10]

3.1.1.2) Nanopure method:- Nanopure process is operated at a low temperature hence also called a "deep-freeze" method. The primarily piston-gap homogenizer is used to achieve the desired particle size of suspension in homogenized nonaqueous media like melted PEG, propylene glycol, oils, or reduced water media (e.g. glycerol-water, ethanol-water mixtures). This process operated under very low temperature (Freezing temperature i.e. 0°to -20°C). Oils or oily fatty acids having low vapor pressure and high boiling points, so a decrease in pressure is not sufficient for the cavitation hence deep freezing requires. Nanosuspension separated by the cooling and may compress into a tablet or may fill into the capsule. Aggregation may occur in melted nonaqueous media at the time of release from dosage form which is directly correlated with the bioavailability; it is decreasing as aggregation increases. Generally, the Nanopure method is used for thermo labile compounds. [18, 24, 25]

(3.1.2) Low-energy process / Media milling process.

This technique involves the application of mechanical energy to reduce the particle size, and discovered & reported by Liversidge (1992) [26]. The media milling technique is mostly used to produce the micronization or nanonization of drugs to improve the bioavailability of poorly soluble materials [27]. Nanosuspension prepared by applying high shear and energy to reduce the particle size under controlled temperature. Based on the physicochemical properties of a drug, different types of mills are used according to suitability such as Roller mills, Cutter mills, mortar-pestles, and runner mills. In these milling operations, the dried crude drug cut by utilizing sharp blades (cutter mill), impacted by hammers or crushed/compressed by the application of pressure (roller mill, pestle, and mortar) [28]. Use of different mills is based on their principles such as compaction, attrition, and both compaction and attrition. The milling medium involves various components such as glass, zirconium oxide, or highly cross-linked polystyrene resin. Milling chamber is feed with the media, drugs, water, stabilizer, excipients, and surfactant [29]. Media milling also distinguished into two class i.e. Wet milling and Dry milling. Wet milling is an environmentally isolated system and requires less energy and time. RetschGmbh recommended that a combination of planetary ball milling, dry milling, and pearl millings can be used in a wet milling technique. [27]

Table No. 2: Some examples of nanosuspensions prepared by the Media milling technique (Table adopted from the Yadollahi. et al. 2015) [17].

Trade Name	drug	Indication	Dosage form	Company	Status
Rapamune	Sirolimus	Immuno-suppressant	Oral Suspension/ Tablet 1-2 mg	Wyeth	Marketed in 2000
Tricor	Fenofibrate	Hypercholesterolemia	Oral Tablet 48-145 mg	Abbott	Marketed in 2004
Emend	Aprepitant	Antiemetics	Oral capsule	Merck	Marketed in 2003
Megace ES	Megastrol	Antianorexia	Oral Suspension 125 mg	Par Pharmaceutical	Marketed in 2005

(3.2) Bottom-up approach. [31, 32]

Principle: - In the bottom-up approach, precipitation of solid drug particle is prepared by dissolving the drug into an organic solvent and anti-solvent, which is stabilized by adding stabilizer.

A bottom-up approach is used for the preparation of nanosuspension based on precipitation of supersaturated solutions, therefore this technique also called a precipitation method. This method involves various pharmaceutical processes such as solvent-anti-solvent technique, supercritical fluid processing, and emulsion solvent evaporation [33]. The bottom-up approach gives the production of mono-disperse particles in narrow size range distribution of particles. It can be operated at low energy and low processing temperature for the thermolabile compounds. It is the economical process &no need for advanced equipment.

Different types of precipitation methods are used are as given below.

Solvent-anti-solvent, Simple mixing methods, Modified methods, Sono-precipitation, High gravity precipitation, Evaporative precipitation techniques, Precipitation in a supercritical fluid, Rapid expansion of supercritical fluid (RESS), Supercritical anti-solvent (SAS) Methods based on solvent removal processes, Conventional solvent removal techniques, Flash nano-precipitation, ultra-sonication, Precipitation using special freezing techniques and Precipitation coupled with high energy processes this method also used for the precipitation [34]. From the above-given methods, Solvent-anti-solvent, Sono-precipitation, Supercritical fluid, ultra-sonication, and evaporative precipitation methods are commonly used.

3.2.1 Antisolvent precipitation method

In this method nanosuspension prepared by introducing drug compounds into the solution containing organic compounds as a solvent and water as an antisolvent by rapid mixing, which generates highly supersaturation leads to causes fast nucleation rates. Oswald ripening leads to cause the growth of particles which can be avoided by rapid drying (desolvation) of hydrophobic drug compounds. Number of stabilizers can be used to stabilize nanosuspension, such as polymers or surfactants which are given in table number 3. Stabilizer inhibits the growth of the particle by being absorbed on the surface of the particle. The antisolvent precipitation method is an effective and easiest method for the preparation of nanosuspension as compare to other methods. [33, 35, 36]

Table No. 3: Some examples of stabilizers used in the preparation of Nano suspension by different methods

Sr. No.	Name of Stabilizer	Nano suspension Method	Reference
1	**Sodium Lauryl Sulphate and PVP K30**	Prepared Efavirenz Nano suspension by media milling technique	[37]
2	Lutrol F127, Poloxamer 407 & HPMC E15	Prepared Nevirapine nanosuspension by using nano edge method	[38]
3	Polyvinyl alcohol	Prepared Nitrendipine & Furosemide nanosuspension by using precipitation–ultrasonication method. PVA sterically stabilizes the nanosuspension and improved bioavailability and Pharmacodynamic profile.	[39,40]
4	α-Tocopherol succinate (Co-surfactant)	Prepared carvedilol nanosuspension through anti-solvent precipitation–ultrasonication method.	[36]
5	Tween 80	Prepared Ezetimibe nanosuspension by solvent-antisolvent precipitation technique which increased the saturation solubility. of drug.	[41]
6	Poloxamer 188 & Poloxamer 407	Prepared Esmoprazole nanosuspension by the evaporative-precipitation-ultrasonication method.	[42]
7	HPMC E5, Sod. CMC, Polysorbate 80, Poloxamer 188 & PVA	Prepared Clarithromycin nanosuspension by sonoprecipitation method.	[43]

3.2.2 Precipitation by Ultra-sonication method.

Principle: - Disintegration of the solid compound at critical size prepared by the periodical compression and refraction of ultrasound when it passing through the medium. Massive micro-bubbles form and collide on the solid surface during this process. [44]

In the ultrasound-assisted antisolvent precipitation method, ultrasounds (a bath or a probe sonicator) are used to produce the nanosuspension by introducing the probe of sonicator into the solution containing a drug molecule. Active drug substance which is insoluble in aqueous media is immediately precipitate out by using ultrasonication. Nanosize drug particles are achieved by setting a period of burst time of about 20 min. (on time and off time) and cool conditions maintained throughout processing. Further separation of nanoparticles carried out by the centrifugation and freeze-drying process [44, 46,]. Ultrasonication improves the supersaturation and it is also used to produce crystal. This technique was used in the preparation of aceclofenac nanocrystals with an average size around 112 nm, and a low polydispersity index (PDI) (0.165), obtained crystals are assessed for in-vitro and in-vivo, which showed a great enhancement of the dissolution rate and increase in the drug bioavailability. [47]

3.2.3 Flash Nanoprecipitation (FNP)

Principle: - Confined impinging jet mixers (CIJMs) and Multi-Inlet Vortex Mixers (MIVMs) are used for mixing of all components of the nano-suspension; it produces the nanoparticles by rapid precipitation and higher super-saturation of solid particles. FNP accelerates the rate of formation of nanoparticles. [48]

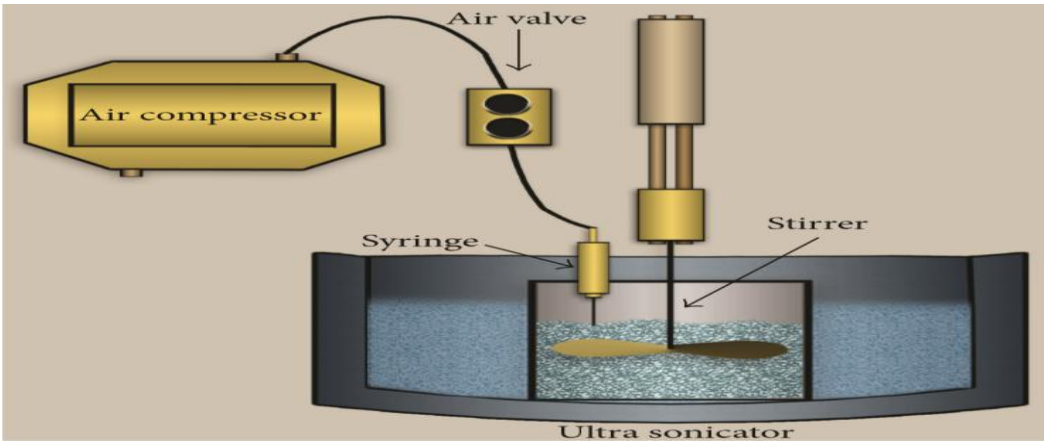

Figure No. 5: Size reduction (Nano suspension) by ultrasonication method. [10]

The particle nucleation is an important step in the FNP supersaturation and these are carried out by fast mixing of a stream containing molecularly dissolved solute and stabilizing molecules with an opposing stream containing a miscible solvent, which acts as a non-solvent for the solute and stabilizer. The mixing occurs at the high energy and provides supersaturation conditions, however, it required for simultaneous precipitation of solute and stabilizers. Block copolymer is also used for the inhibition of growth of the solute particles and for steric stabilization but, which results in the poor drug encapsulation efficiencies and loading contents [49].

3.3 COMBINATION TECHNOLOGY (Nano-edge)

Combination technology involves micro-precipitation by high-pressure homogenization called a Nano-edge technique. The nano-edge technique undergoes the bottom-up process (precipitation) which also combines with the top-down process (HPH). This technique was reported by the Kipp et.al and patented by Baxter Inc. [50] the conversion of a drug molecule from the unstable form to stable crystalline form by using the annealing process. Annealing is the process in which thermodynamically conversion of molecule/ matter into stable form (lower energy state) by applying direct heat or mechanical energy. During the precipitation formation of crystal growth and long term, stability is the drawbacks that are encountered by nano edge method.

Procedure:-

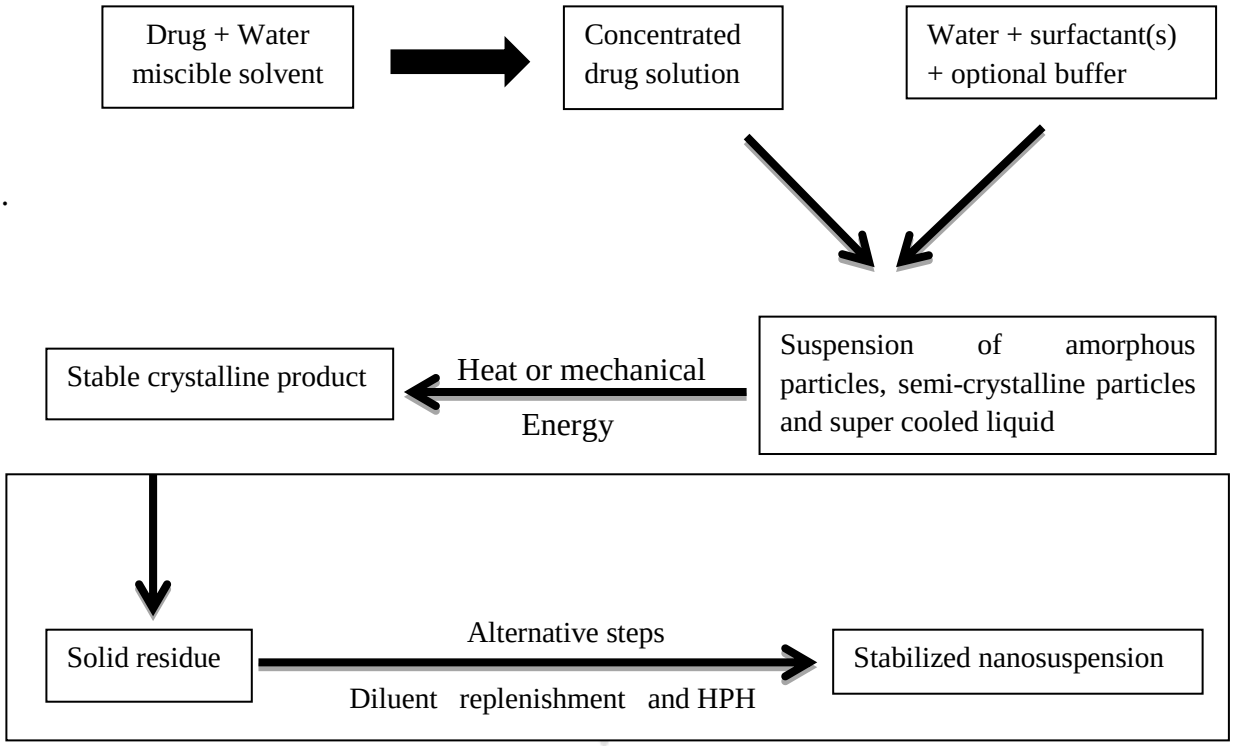

Figure No. 6: Procedure for the preparation of nanosuspension by combination method.

Melt Emulsification method is generally used for the preparation of the Solid-Lipid nanoparticles. This method is discovered and reported by Kipp and coworkers for the preparation of nanosuspension of ibuprofen [12]. The emulsion is prepared by mixing drugs in the aqueous solution containing stabilizer and solution pass through HPH by maintaining the temperature (below the melting point of the drug) during the overall process. Finally, emulsion precipitate out and particle separation by centrifugation. Various parameters are important to take into consideration for the stability and particle size of suspensions such as the concentration of drug, stabilizers and its type, cooling temperature and homogenization process, the effect of high energy processes during precipitation. [34, 52]

Table No. 4: Advantages and disadvantages of the various preparation methods [53, 54].

Preparation Method	Advantages	Disadvantages
High-pressure homogenization	a) Simple, economical, and applicable to all drugs. b) It can be used to formulate very dilute as well as highly concentrate nanosuspension. c) Aseptic production is possible.	a) More number of homogenization cycles required. b) Presuspension is required. c) Metal ion contamination may occur from the wall of the homogenizer. d) Prerequisite micronized drug particles
Media milling	a) Highly flexible procedure for the very little batch to batch variation in particle size. b) Simple handling for large quantity drugs.	a) It requires more time. b) Erosion may occur through pearl milling. c) Instability of amorphous drugs may occur due to high milling. d) Scale-up is not easy due to mill size and weight.
Precipitation	a) Simple process. b) Requires very low energy. c) Economical production. d) Form a stable product and ease for scale-up.	a) Limitation for the surfactant addition. b) Drugs should be soluble minimum in one solvent. c) Nonaqueous solvent produces toxicity. d) Wide range in the particle size.
Melt emulsion or micro-emulsion	a) Simple preparation method. b) High drug solubilization with long shelf life. c) Large-scale preparation at low-cost may possible.	a) Requires the use of a high amount of surfactant and stabilizers. b) The organic solvent which is unsuitable for human health.
Dry co-grinding	a) Easy process. b) No requires an organic solvent. c) Requires short grinding time.	a) Generation of the residue of milling media

4.1 EVALUATION OF NANOSUSPENSION.

The nanosuspension can be subjected to qualitative and quantitative evaluation for three major parameters that are Chemical, Physical, and Biological parameters which are as follows.[54]

4.1 pH – pH may affect the stability of the nanosuspension particularly the determination of pH is necessary for the drugs having pH-dependent solubility and drugs which are to be

formulated for the ocular, oral and topical routes. pH can be determined by the pH meter at any stage or level. [55,56]

4.2 Viscosity- Viscosity affects the physical stability of the suspension or nanosuspension. Optimum viscosity of formulation prevents the rapid formation of floccules and hard cake during storage condition, and enhances the stability. The minimum viscosity requires to maintain the redispersibility in such a way that nanosuspension should produce a deflocculated system.[51]

4.3 Zeta Potential- Zeta potential is the numerical value of charge (positive and negative) present on the surface of the solid particle, this value indicates the stability of the nanosuspension. For the electrostatic stability of nanosuspension minimum zeta potential of ± 30 mV is required and for steric stability requires ± 20 mV. The polymer used in the formulation decreases the zeta potential as an increase in the concentration of it, due to the adsorption of polymer onto the surface of solid particles. [57] Zeta potential can be adjusted by using the electrostatic agent which maintains the charge present on the surface of the particle and of its surroundings. Electroacoustic technique and delsa nanometer is used to measure zeta potential. [58,59]

4.4 Powder X-ray diffraction (PXRD):-High Pressure homogenization, Ultrasonication may cause the polymorphic changes in the crystalline structure of drug and excipient which may directly affect the stability of nanosuspension. Polymorphic changes can be studied by the Powder X-ray diffraction technique which involves plotting on graph intensity versus the diffraction angle (2θ) it gives the information of the polymorphic form of the API. It gives sharp peaks of crystalline compounds and no sharp peaks for the amorphous compound. [60]

4.5 Differential scanning Calorimetry (DSC):- DSC measure the difference in heat flow between sample and standard (reference compound)as a function of time and temperature at a controlled environment (pressure and purge gas flow). The unit of heat flow is mJ/s. DSC gives complete information regarding the melting point, boiling point, and glass transition temperature. [61] DSC consists of two aluminum pans i.e. nonhermetically sealed aluminum pan called as standard pan & empty aluminum pan called reference pan. Samples that have to investigate are accurately weighed and kept in the standard pan and heat run is set according to the physical properties of a mixture or single compound under a controlled environment.

[62] Difference between the heat flow from the standard and reference sample is described by the following equation.

$$\frac{dQ}{dT} = Cpb + f(T,t)$$

Where dQ/dt is the difference of heat flow, Cp is the heat capacity of the sample, b is the rate of temperature change (dT/dt) and f(T, t) is the heat flow from kinetic processes [63] (**Paul. 2008)**. DSC graph of a pure compound is compared with the graph obtained from the alone or physical mixtures of the compound for qualitative analysis of the material. [62,64] DSC graph of nanosuspension used to detect any changes in the energy level of drug, a mixture of drug and excipient which may interfere in formulation behaviour. [65]

4.6 Particle size and Particle-size distribution. Particle size can be determined by various sophisticated analytical instruments like Delsa instrument, Photon Correlation Spectroscopy (PCS), laser diffraction and coulter current multisizer, etc. [51,56] Particle size distribution and its range (polydispersity index) may affect the physical stability of the nanosuspension and should be low as much possible for the long term stability. A PI (Polydispersibility Index) value of 0.1 to 0.25 shows a slightly narrow size distribution and If PI value more than 0.5 indicates a very broad distribution. The Coulter Counter is a more efficient and suitable method for the determination of particle size, which gives the absolute number of particles per volume for the different size classes. [66]

4.7 Saturation Solubility and Dissolution Velocity- Saturation solubility and Dissolution velocity depend on factors such as temperature and type/nature of the dissolution medium, pH, Physical and chemical nature of the drug compound. These may affect the bioavailability of the drug and can also help in determining the in-vitro behaviour of formulation. Saturation solubility & Dissolution velocity should be studied under different temperatures and physiological media according to the methods reported in the different pharmacopeia.[67,54]

Pharmaceutical Applications of Nanosuspension.

Nanotechnology has been proven as a better formulation technique and having a lot of applications in the therapeutics, which are explained below.

1. In the oral drug delivery.

Oral drug delivery route is the easiest and more convenient route for the drug administration but, Poor solubility, incomplete dissolution, and insufficient efficacy are the major problems of oral drug delivery. Rapamune® (Wyeth) is the first nano-crystalline marketed product. This formulation is based on the macro-cyclic immunosuppressive drug Sirolimus (Rapamycin) available in oral suspension and tablets. Rapamycin is the oral liquid lipid-based formulation, which requires refrigeration and protection from the sunlight upon the storage. The rapamune nanocrystalline based tablet which has 27% more bioavailability as compared to the lipid-based solution (Vasquez. et al. 2000). Emend® (Merck) is the antiemetic formulation containing Aprepitant as an API which was developed using Elan'sNanoCrystal® technology. This formulation is prepared by coating to the Aprepitant nanosuspension capsule containing sugar beads and its administration revealed similar bioavailability during fasting and fed state as compared to the conventional micronized formulation. [68]

Parenteral Administration of Nano suspension.

Parenteral route of drug administration possesses the greater advantages, having more applicability with higher bioavailability; still, the particle size creates the problem for absorption from parenteral routes i.e. subcutaneous, intramuscular, and intradermal route. Particle size should be less than 600 Dalton for the passive absorption of drugs through the biological membrane. Nanosize leads to easily cross the biological barriers and gives faster absorption, bioavailability, and therapeutic effect. [69, 70] Nowadays, nanocrystals are playing an important role in the tumour and antiretroviral targeting drug delivery system by which facilitates the accumulation at the target site by passive diffusion. [71]

2. As a Pulmonary Drug Delivery:-

In pulmonary drug delivery, particle size plays an important role in drug absorption and bioavailability through the nasal cavity. The nanoparticle of drugs allows the rapid diffusion and dissolution at the site of action. Particle size should be optimized for pulmonary drug delivery. Aqueous suspensions of the drug can be easily nebulized into the pulmonary route as the particle size in the range of aerodynamic (1 to 5 mm) by using a mechanical or ultrasonic nebulizer. [72] Various drugs are available in the market in the form of nebulizer such as Budesonide, Ketotifen, Ibuprofen, Indomethacin, Nifedipine, Itraconazole,

Interleukin-2, p53 gene, Leuprolide, Doxorubicin, etc. Nanosuspension offers quick onset of action initially, and then a controlled release pattern possesses highly beneficial which is required in most of the pulmonary diseases. [73]

3. Ophthalmic Drug Delivery.

An ocular route is commonly used for the treatment of various eye diseases such as infection, inflammation, dry eye syndrome, glaucoma, and retinopathy. Eye structure is very complex, also delicate, and sensitive, which makes a challenging task for the scientists to develop the formulation of an ocular route. Bioavailability through the ocular route is very low usually < 5 % due to lacrimal secretions.[74] Nowadays Nano-carrier (Liposomes and polymeric micelles) based drug delivery has emerged into the market for the treatment of ocular diseases. The nano-crystal approach in the ocular drug delivery for the poorly water-soluble drugs gained more popularity due to their capability of overcoming the many biological barriers of the eye. [75Nano-suspension increases ocular bioavailability by increasing precorneal residence time and enhance the solubility of drugs. Glucocorticoids are widely used in treating anterior segment inflammatory diseases. As compared to conventional eye drops, Nanosuspension possesses higher antibacterial activity against S. aureus and P. Aeruginosa. [76]

4. Topical Drug Delivery.

Vidlarova et al.[77] suggesting that then a no crystals formulation increases the concentration gradient, saturation solubility and low density of nano-crystals cover the sufficiently large area of skin with direct contact and easily crosses the skin barrier layers. Nanosuspension formulation accumulates into the skin and minimizes drug diffusion through the skin into the systemic circulation for local therapeutic effect. Nanosuspension can also improve the diffusion of drugs through the skin and also enhance the photo-stability of Tretinoin as compared with the nanoemulsion and methanolic solution of the drug [78] (Pireddu et al. 2016). Currently, drugs like antioxidants, caffeine, and diclofenac acid formulated for dermal application. [79]

5. Nanoparticles as a mucoadhesive drug delivery system.

Mucoadhesion means the simply improves absorption of the drug by residing it on the biological membrane. In the mucoadhesive drug delivery system, polymers are used to

promote adherence to drug particles on the biological membrane by swelling. The mucosal area having high blood perfusion so, residence/contact time increases leads to an increase in bioavailability. Concentrated nanosuspension acts as a reservoir for the drug particles and absorption takes place very rapidly through the mucosa. [80] Drugs such as Buparvaquone, Carbamazepine, Ondansetron HCl, Acyclovir, Clonazepam, Risperidone, etc. Lipid-based nasal mucoadhesive nano-carriers, oil-based nasal mucoadhesive nano-carriers, polymer-based nasal mucoadhesive nano-carriers, and protein-based nasal mucoadhesive nano-carriers are developed for the mucoadhesive route. [81]

6. Targeted Drug Delivery

In the targeted drug delivery, the drug should be reached at a particular target with maximum therapeutic concentration to achieve the desired pharmacological effect. At the targeted site possess various factors, which led to affecting the entry of drug at the site of absorption but, the drug nanoparticle which crosses the biological barriers easily and reaches to the target site. Nano suspension is appropriate for targeting particular organs, due to their surface property. [82]

CONCLUSION:

To develop the formulation of poorly soluble drugs to yield optimal bioavailability is the biggest problem being faced by pharmaceutical scientists. Continuously growing availability of sophisticated instruments and formulating techniques to formulate such drugs into the nanosize range are offering tremendous benefits. Nano suspension is a feasible, inexpensive, scalable approach for improving the bioavailability of all kinds of drugs. Several methods are available to develop the appropriate nano-formulation of the drug which can be administered by various routes such as oral, parenteral, ocular, and mucoadhesive routes. These nano-formulations need appropriate evaluations performed for optimal benefits like better patient.

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