

Nanosuspension: A Potential Nanosystem for Selective Drug Delivery

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Abstract- The drugs are classified according to BCS classification but the classes II or IV have the low solubility. The main goal of pharmaceutical research is to maximise bioavailability of these drugs for desired therapeutic efficacy, however poorly soluble drugs are constantly hindered by their unpredictable absorption patterns. Low water solubility and bioavailability are difficulties that can be solved using nanosuspension technology. All medications that are less soluble in water can benefit from nanosuspension, which belongs to a few nanometre-sized solute particles and greatly affects solubility. Precipitation, milling, high pressure homogenization, the emulsion and microemulsion method, dry co-grinding, and the supercritical fluid method are some of the several methods that have been developed to create nanosuspension. Delivery methods for nanosuspensions include oral, parenteral, pulmonary, and ocular. When included in ocular inserts and mucoadhesive hydrogels, nanosuspensions can also be employed for targeted administration of drugs. In addition to addressing the issues of low solubility and bioavailability, nanosuspensions also change the pharmacokinetics of the medicine, enhancing its safety and effectiveness.

Keywords: Bioavailability, BCS Class II, solubility, nanotechnology, nanosuspensions, bioavailability, Saturation solubility.

INTRODUCTION

The inability of pharmaceutical active components to dissolve in water is a widespread issue in the research and development of new drugs. According to estimates, 40 % of all newly created medicinal molecules are upto 50% of orally administered medication compounds have formulation issues due to high lipophilicity and are poorly soluble or "insoluble" in water. A promising strategy for improving drug solubility in recent years has been the development of nanoparticles. In recent years, nanoparticle engineering process has been seen as a promising approach for the enhancement of drug solubility [1]. Nanosuspensions platform is an efficient and intelligent drug delivery system for water insoluble drugs, as the saturation solubility and the surface area available for dissolution increased [2].

Nanosuspension

It is defined as Drug particles that are nanoscale and stabilised by surfactants are colloiddally dispersed in nanosuspensions. They can also be described as a biphasic system made up of pure drug particles that are scattered in an aqueous medium and have diameters of less than 1 μm . [3]. The solid particles in nanosuspensions typically have a particle-size distribution less than one micron, with an average particle size between 200 and 600 nm [4].

Need for nanosuspension to improve bioavailability :

However, pharmacokinetic investigations of BCS class II medications revealed that they have a low oral bioavailability, which may be caused by the drug's weak water solubility. There are numerous conventional pharmaceutical methods to increase medication dissolving rate, including β -cyclodextrin complex formation, dissolution in aqueous mixtures with an organic solvent, solid dispersions, and drug salt form [5].

Drug selection criteria for nanosuspensions:

For APIs with either of the following qualities, nanosuspension can be selected :

- a) Materials that are insoluble in water but soluble in oil
- B) Both oils and water cannot dissolve (high logP) or API.
- c) Drugs that, independent of the solvent, have a decreased tendency to cause crystals to dissolve
- d) API at a very high dose.

The Advantages of nanosuspension

- 1) Enhanced drug dissolving and saturation solubility;
- 2) enhanced biological performance
- 3) Manufacturing and scaling-up ease
- 4) Physical stability throughout time
- 5) Flexibility
- 6) An improvement in oral absorption

Disadvantages of nanosuspension

- 1) Physical stability, sedimentation, and compaction can be problematic for the nanosuspension drug delivery method.
- 2) It requires careful handling and transportation since it is bulky.
- 3)The wrong dosage.

4) It is impossible to acquire a consistent and precise dosage [6].

Components of nanosuspension include

1. Stabilisers
2. organic solvents
3. cosurfactants
4. buffers, salts, polyols, osmogents, and cryoprotectants.

1. Stabilizers

To stabilize the drug nanosuspensions, stabilizers are usually used; however, the use of common stabilizers is limited by weak stabilization effect and toxicological concerns for long-term treatment. stabilizers are indispensable in the nanosuspension formulations to prevent them from aggregation and agglomeration the commonly use stabilizers include Pluronics, Tweens, d-tocopherol polyethylene glycol 1000 succinate (TPGS), polyethylene glycols (PEGs), polyvinyl alcohols (PVAs), polyvinylpyrrolidone (PVP) and other cellulose polymers [7]. Eudragit, [8]. Soluplus these Commonly used stabilizers provide stabilization by two mechanisms: electrostatic repulsion and steric hindrance [9].

I. Pluronics

Poloxamers, sometimes referred to as Pluronics®, are block copolymers comprising poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) that exhibit amphiphilic characteristics and advantageous association and adsorption capabilities as a result. There are several uses for poloxamers, including have remarkable physiological qualities, like reduced toxicity, and also necessitate the solubilization or stabilisation of chemicals. Poloxamers are therefore useful as excipients for medications. Poloxamers are a family of water-soluble nonionic A-B-A and B-A-B triblock copolymers, where A is poly(ethylene oxide) (PEO) and B is poly(propylene oxide)(PPO). They are also sold under the brand name Pluronics® (BASF) (PPO). Tetronic® block copolymers, also provided by BASF, have four PPO-PEO chains that branch out from a central chain with an amine end [10].

Pluronic® Notation	MW	PO Units	EO Units	cmc at 25 °C (% w/v)	cmc at 30 °C (% w/v)	cmc at 35 °C (% w/v)
L64	2900	30	26	n/a	1.5	0.4
P65	3400	17	36	n/a	4	1
P84	4200	43	38	2.6	0.6	0.15
P85	4600	40	52	4	0.9	0.2
F88	11,400	39	206	n/a	n/a	1.7
P103	4950	60	34	0.07	0.01	0.002
P104	5900	61	54	0.3	0.04	0.008
P105	6500	56	74	0.3	0.025	0.005
F108	14,600	50	264	4.5	0.8	0.15
P123	5750	69	38	0.03	0.005	0.001
F127	12,600	65	200	0.7	0.1	0.025

Table a) The Pluronic® PEO-PPO-PEO block copolymer's physicochemical characteristics make it a popular choice for medication. Critical micellization concentration is denoted by the letters L liquid, P paste, and F flake.

Pluronic of different grade is used in different formulations. Ciprofloxacin mucoadhesive nanosuspension was developed to increase the drug's solubility, bioavailability, and effectiveness in treating typhoid fever here pluronic f 68 grade has used by the researcher

By adjusting various factors while employing various polymers, such as soya lecithin, pluronic F68, polyvinyl alcohol, and polyvinylpyrrolidone K30, four distinct formulations were created. Photon correlation spectroscopy was used to assess particle size and polydispersity index. It was discovered that the range of average particle sizes for various formulations was 503–1844 nm. All formulations' potentials were determined to be about 20 Mv, which indicates adequate physical stability. At 25 °c, a physical stability investigation of the produced ciprofloxacin nanosuspension was completed. Using a light microscope RXLr-3T, the morphological changes, Ostwald ripening, and settling behaviour were observed at specified intervals of 24 hours, one week, and two weeks (Radical, India [11])

II. Eudragit

A copolymer of acrylic and methacrylic acid esters called Eudragit RS 100 contains 5% functional groups of quaternary ammonium. Eudragit RS 100's permeability is pH independent since it includes the ammonium groups as salts. There are different grades of eudragit polymer on the basis of physical and chemical characteristics used in pharmacy field they are as follows

Sr. No.	Eudragit grade	Chemical composition	Available as/ polymer dry content	Solubility	Applications
Cationic (Aminoalkyl methacrylate copolymers)					
1	Eudragit E 100	Poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1	Granules/98%	Soluble in gastric fluid to pH 5	Film coating
2	Eudragit E 12.5	Poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1	Organic solution/12.5%	Soluble in gastric fluid to pH 5	Film coating
Anionic (Methacrylic copolymers)					
1	Eudragit L 100	Poly(methacrylic acid, methyl methacrylate) 1:1	Powder/95%	Soluble in intestinal fluid from pH 6	Enteric coating
2	Eudragit L 12.5	Poly(methacrylic acid, methyl methacrylate) 1:1	Organic solution/12.5% (without plasticizer)	Soluble in intestinal fluid from pH 6	Enteric coating
3	Eudragit L 12.5 P	Poly(methacrylic acid, methyl methacrylate) 1:1	Organic solution/12.5% (with 1.25% dibutyl phthalate as plasticizer)	Soluble in intestinal fluid from pH 6	Enteric coating
4	Eudragit L 100-55	Poly(methacrylic acid, ethyl acrylate) 1:1	Powder/95%	Soluble in intestinal fluid from pH 5.5	Enteric coating
5	Eudragit L 30 D-55 (formerly Eudragit L 30 D)	Poly(methacrylic acid, ethyl acrylate) 1:1	Aqueous dispersion/30%	Soluble in intestinal fluid from pH 5.5	Enteric coating
6	Eudragit S 100	Poly(methacrylic acid, methyl methacrylate) 1:2	Powder/95%	Soluble in intestinal fluid from pH 7	Enteric coating
7	Eudragit S 12.5	Poly(methacrylic acid, methyl methacrylate) 1:2	Organic solution/12.5% (without plasticizer)	Soluble in intestinal fluid from pH 7	Enteric coating
8	Eudragit S 12.5 P	Poly(methacrylic acid, methyl methacrylate) 1:2	Organic solution/12.5% (with 1.25% dibutyl phthalate as plasticizer)	Soluble in intestinal fluid from pH 7	Enteric coating
9	Eudragit FS 30 D	Methyl acrylate, methyl methacrylate and methacrylic acid	Aqueous dispersion/30%	Soluble above pH 6.8	Enteric coating
Neutral (Ammonioalkyl methacrylate copolymers)					
1	Eudragit RL 100 (Type A)	Poly(ethyl acrylate, methyl methacrylate, trimethyl aminoethyl methacrylate chloride) 1:2:0.2	Granules/97%	High permeability	Sustained release
2	Eudragit RL PO	Poly(ethyl acrylate, methyl methacrylate, trimethyl aminoethyl methacrylate chloride) 1:2:0.2	Powder/97%	High permeability	Sustained release
3	Eudragit RL 30 D	Poly(ethyl acrylate, methyl methacrylate, trimethyl aminoethyl methacrylate chloride) 1:2:0.2	Aqueous dispersion/30%	High permeability	Sustained release
4	Eudragit RS 100 (Type B)	Poly(ethyl acrylate, methyl methacrylate, trimethyl aminoethyl methacrylate chloride) 1:2:0.1	Granules/97%	Low permeability	Sustained release
5	Eudragit RS PO	Poly(ethyl acrylate, methyl methacrylate, trimethyl aminoethyl methacrylate chloride) 1:2:0.1	Powder/97%	Low permeability	Sustained release
6	Eudragit RS 30 D	Poly(ethyl acrylate, methyl methacrylate, trimethyl aminoethyl methacrylate chloride) 1:2:0.1	Aqueous dispersion/30%	Low permeability	Sustained release
Neutral (Methacrylate copolymer)					
1	Eudragit NE 30 D (formerly Eudragit E 30 D)	Poly(ethyl acrylate, methyl methacrylate) 2:1 with nonoxynol (1.5%)	Aqueous dispersion/30%	Swellable, permeable	Sustained release

2	Eudragit NE 40 D	Poly(ethyl acrylate, methyl methacrylate) 2:1 with nonoxynol (1.5%)	Aqueous dispersion/40%	Swellable, permeable	Sustained release
3	Eudragit NM 30 D	Poly(ethyl acrylate, methyl methacrylate) 2:1 with PEG stearyl ether (0.7%)	Aqueous dispersion/30%	Swellable, permeable	Sustained release

Table b) Different eudragit grades their chemical composition and properties with applications

Sr no.	Eudragit grade	Density (g/cm ³)	Glass transition temperature (°C)	Minimum film forming temperature (°C)	Water vapor transmission rate (WVTR) (g/m ² .day)
1	Eudragit E	0.811 -- 0.821	~ 4	-	~ 350 (organic)
2	Eudragit L 100, S 100	0.831 -- 0.852	-	> 85	~ 150 (redispersed)
3	Eudragit L 30 D-55	1.062 -- 1.072	~ 110	~ 25	~ 100 (10% TEC)
4	Eudragit L 100-55	0.821 -- 0.841	~ 110	-	-
5	Eudragit RL PO	0.816 -- 0.836	~ 70	~ 40	~ 450 (RL 100-organic)
6	Eudragit RS PO	0.816 -- 0.836	~ 65	~ 45	~ 250(RS 100-organic)
7	Eudragit NE 30 D	1.037 -- 1.047	~ 9	~ 5	~ 300
8	Eudragit FS 30 D	1.058 -- 1.068	~ 48	~ 27	~ 100 (3% TEC)

Table c) Physical properties of different grades of eudragit [12]

The study was to assess the potential of a Eudragit based nanosuspension of the class II medication glimepiride (glimepiride), which is appropriate for oral administration, to increase its solubility and overall therapeutic effectiveness. The production of nanosuspension was improved using the nanoprecipitation process since it is straightforward and less complex. According to the aforementioned study, Eudragit polymer was successful in delaying the release of GLM, a representative weakly water soluble anti-diabetic medication, and it delivered a sustained and extended impact over a 24-hour period. The foregoing data suggest that patient compliance can be improved by lowering therapeutic dosage, dosing interval, and systemic adverse effects, although more research in clinical trials [4].

III.Soluplus

A new amphiphilic polymer called Soluplus® may be used to solubilize polymers. It is a grafted copolymer of polyvinyl acetate, polyvinyl acetate, and polyethylene glycol. It is hydrophilic and nonionic [13]. Soluplus® is a polymeric solubilizer with an amphiphilic chemical structure, having large number of hydroxyl groups which make it a good solubilizer for poorly soluble drugs in aqueous media [14]. High flowability and regulated extrudability characteristics of Soluplus® make it appropriate for use as stabilisers in pharmaceuticals [15].

Hua Yang et al. practicality of employing Soluplus in creating a fenofibrate (FBT) (FBT) was carried out using wet medium milling method for nanosuspension. Stabilizers HPMC and Soluplus were utilised to Prepare the FBT/Soluplus nanosuspension (F2) and the FBT/HPMC nanosuspension (F1), respectively. The Evaluations of nanosuspensions' particle size, solubility, and initial stability were performed as well as pharmacokinetic activity. Nanosuspensions successfully reduced particle size by a significant amount (from 17.55µm to 642 nm (F1) and 344 nm (F2)). Due to a lesser Ostwald, Soluplus was able to stabilise the nanosuspension more successfully. ripening effect brought on by a slower dispersion of the micelles that Soluplus generated by capturing dissolved substances FBT than FBT exposed to clean water directly [16].

2.organic solvents

Using organic solvents might be necessary while preparation of nanosuspension the likelihood organic solvents used in the pharmaceutical industry arena, their potential for toxicity hence it must be removed from the formulation taken into account while creating nanosuspensions following tabulated data shows the safe and unsafe sol vents in formulation of nanosuspension

Type of solvent	name	Remark
Water miscible solvents	Ethanol, Isopropanol, methanol[17], chloroform [17]	Pharmaceutically accepted less hazardous
Partially water-miscible solvents	Ethylacetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, benzyl alcohol	Preferred in the formulation over the conventional hazardous solvents such as dichloromethane

[18]

3. surfactants

Utilization of additional components that is surfactant is dependent upon either the method of administration or Candidate's physicochemical characteristics a medication. the addition of organic phase to inorganic phase taken place in nanosuspension process so the surfactants plays the major role in miscibility of those two phases [17].

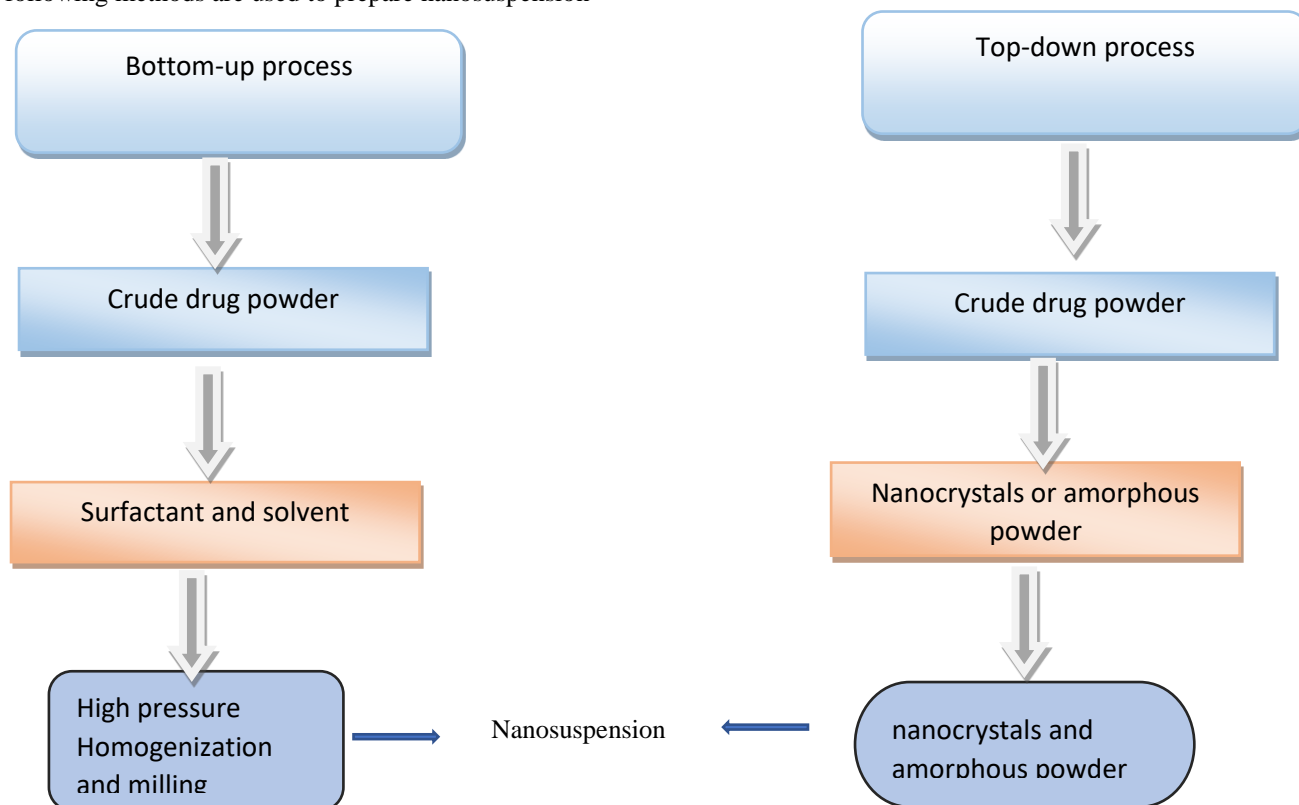
Example of surfactants used in nanosuspension

Tween® 80, PVP K-30 ,SDS [1] sodium cholate (SC), sodium lauryl sulphate (SLS), poly ethylene glycol 4000 (PEG) [19].

4. buffers as per required dissolution media for the drug and candidate are used like pH 6.8 buffer ,pH 7.4 buffer other additives of cytoprotectants , osmogens ,polyols and salts are also added as per need.

Techniques of nanosuspension Preparation

The following methods are used to prepare nanosuspension



- Homogenization in non-aqueous media (Nanopure)
- Combined precipitation & homogenization (Nanoedge)
- Nanojet technology
- Emulsification-solvent evaporation techniques
- Hydrosol method
- Supercritical fluid method
- Precipitation technique
- Dry-co-grinding [20]

1]Media milling

The method is first developed by liversidge et.al [20]

Pearl mills or high-shear media mills are used to make nanosuspensions. The mill is made up of a recirculation chamber, a milling chamber, and a milling shaft. medicine is then put into a mill containing tiny grinding balls or pearls in aqueous solution. These balls fly through the grinding jar interior at a high shear rate while operating at a regulated temperature, striking the sample on the opposite grinding jar wall. A significant amount of particle size reduction results from the combined forces of friction and impact. The milling media or balls are constructed of zirconium oxide, aluminium oxide, or strongly cross-linked polystyrene resin with great abrasion resistance and are sintered in ceramic. One piece of machinery that can be utilised to obtain a grind size below 0.1 μm is a planetary ball mill. Wet milling was used to create a nanosuspension of zinc-insulin with a mean particle size of 150 nm. Heat generated during the procedure and the presence of relatively large fractions of particles (5mm) cause the thermolabile medicines to degrade [20]

Advantages

1. Both very diluted and highly concentrated nanosuspensions
1 mg to 400 mg of medication per millilitre is handled during preparation.
2. The ultimate nanosized product's dissemination.

Disadvantages

1. The media milling method takes a lot of time.
2. Some particle fractions fall within the micrometre category.
3. Due to mill size and weight, scaling up is difficult. [21]

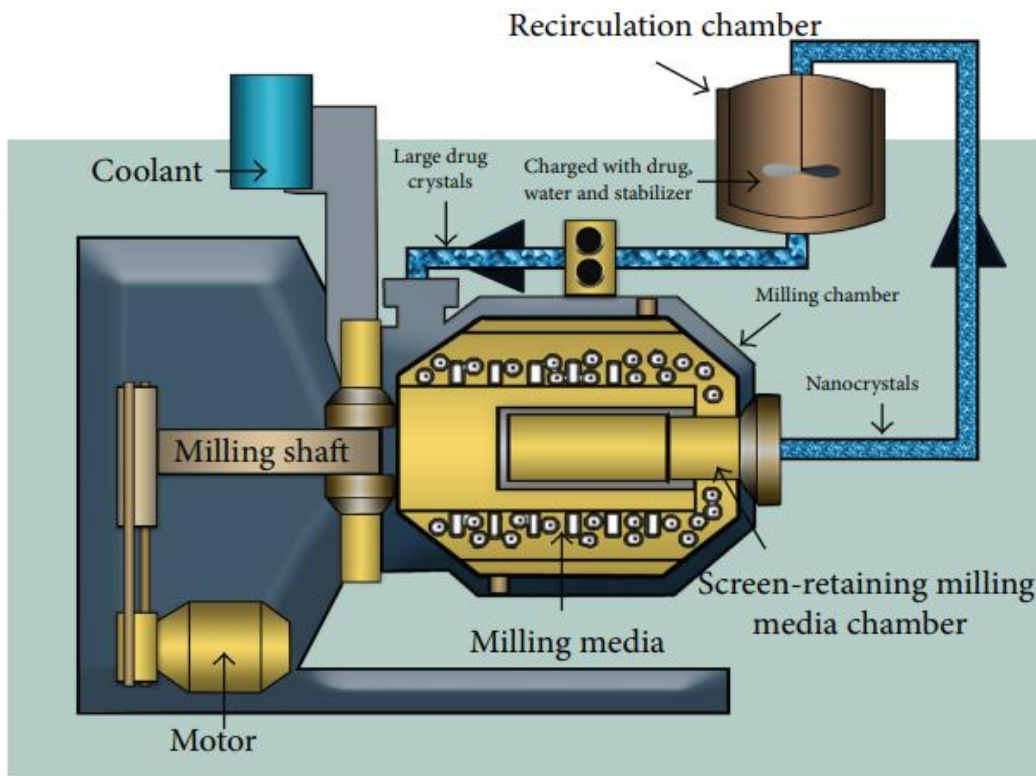


Fig: schematic representation of media milling technique [22]

1) Homogenization in non-aqueous media

The method was created by R. H. Muller, and DDS Gmbh obtained the first patent. Later, Skype received the patent. The APV Micron Lab 40 homogenizer is often employed (APV Deutschland Gmbh, Lubeck, Germany). Homogenizers with a piston-gap are still another form. Additionally, Avestin manufactures it (Avestin Inc., Ottawa, Canada). Stansted is yet another (Stansted Fluid Power Ltd. Stansted, UK) The fundamental idea is high pressure, which is between 100 and 1500 bars.

We can readily change micron-sized particles into nanosized particles by applying this pressure. And because we can reduce the particle size using a jet mill to a maximum of < 25 nanometres, it first requires the micron range particle that is < 25 micrometre, therefore we must obtain the sample from the jet mill

Additionally, we may perform batch and continuous operations with this equipment. The capacity ranges from 40 mL to 1,000 litres. Here, we must first transform the particles into a suspension state (after jet milling) [22]

Advantages

Application to most drugs

- (ii) Preparation of diluted and highly concentrated nanosuspensions

- (iii) Ease of use
- (iv) Preparation of sterile products
- (v) drugs classified as BCS Classes II and IV drugs

Disadvantages

- (i) Prerequisite micronized drug particles
- (ii) High number of homogenization cycles
- (iii) Potential product contamination from metal ions emitted from the homogenizer wall
- (iv) Need for presuspension
- (v) High number of homogenization cycles
- (vi) Scale-up is simple, and there is minimal batch-to-batch variance [22]

2) Combined Precipitation and homogenization

As the term implies, both homogenization and precipitation are done simultaneously. The process of combined precipitation, also known as nanoedge, involves mixing a medication with an organic solvent before adding a miscible antimicrobial to the mixture a precipitation solvent Drug precipitates and water-solvent mixtures have limited solubility. High shear processing has been combined with precipitation. Nanoedge operates on the same principles as homogenization and precipitation.

This method produces particles in the nano range and provides improved stability in a short amount of time. The drug is dissolved in an organic solvent, and the resulting solution is combined with a miscible anti-solvent to precipitate the drug. The solubility is in the water-solvent combination low and the medication precipitates High shear processing has been combined with precipitation. Precipitation and homogenization have the same fundamental concepts as Nanoedge. Combining these methods yields smaller particle sizes and improved stability in a shorter amount of time [23] [24].

3) Nanojet technology

Most often, nanojet technology is employed, which involves applying high pressure of force to move a suspension that is divided into at least two parts and which collide with one another. Due to the strong shear pressures generated throughout the procedure, the particle size is reduced.

Advantages

- 1) This method does not need any special equipment
- 2) By using this method we can have easy control on particle size during entire formulation Preparation

Disadvantages

- 1) this method is not in that much use because purification of drug is costly
- 2) this method is not that much helpful for the poorly water soluble compounds
- 3) this method requires the stabilizer and surfactant in large amount [25].
- 4) Due to the method's use of potentially dangerous chemicals, there are safety issues [23].

4) Emulsification-solvent evaporation techniques

In addition to being employed as a medication delivery system, emulsions can also serve as templates for the creation of nanosuspension. For medications that are soluble, using emulsions as templates is appropriate. either a solvent that is somewhat water-miscible or a volatile organic solvent. such solvents are used for the emulsion's dispersed phase. To create an emulsion, an organic solvent or combination of solvents containing the medicine are stirred into an aqueous phase that also contains appropriate surfactants. The created emulsion undergoes further homogenization under high pressure. The emulsion was diluted with water and homogenised using a homogenizer after homogenization cycles in order to disperse the organic solvent and turn the droplets into solid particles. Since one particle develops in each emulsion droplet, it is feasible to regulate the size of the nanosuspension's particles by regulating the emulsion's size. by increasing the intake of organic phase and, eventually, the drug loading in the emulsion, the surfactant composition can be improved. Originally, organic solvents including methanol, ethanol, ethyl acetate, and chloroform were utilised. However, their application in standard manufacturing processes has been restricted due to environmental risks and worries about residual solvents endangering people. This approach was used to create nanosuspensions of ibuprofen [53], diclofenac [54], and acyclovir [55].

[56]

They can be used as models to create nanosuspension in addition to being used as a medication delivery system. For medicines that are soluble in either a volatile organic fluid or a partly water-miscible solvent, emulsions can be used as templates. These solvents can be used as the emulsion's distributed component [20]. In this method, a drug solution is prepared, then it is emulsified in a different substance that isn't a carrier for the drug. The liquid evaporates, causing the substance to precipitate.

Using a high-speed stirrer, one can regulate crystal development and particle agglomeration by applying high shear pressures [21]. Globule size and stabiliser content are important variables to take into account when using the emulsification technique [26].

5) Hydrosol method

This is comparable to the technique of emulsification and liquid evaporation. The fact that the drug liquid is miscible with the drug is the only distinction between the two procedures. anti-solvent. Higher shear force guarantees that the precipitates stay smaller by preventing crystal development and Ostwald ripening [27].

6) Supercritical fluid method

Particle size reduction using supercritical fluid (SCF) techniques is another revolutionary nanosizing and solubilization technology whose use has grown in recent years. Supercritical fluids can take on the characteristics of both a liquid and a gas because their temperature and pressure are higher than their critical temperatures (T_c) and critical pressures (T_p). Since SCFs are extremely compressible at near-critical temperatures, even small changes in pressure can significantly influence the fluid's density and mass-transport properties, which are key factors in determining its solvent power. The drug particles may be recrystallized at significantly smaller particle sizes after being solubilized within the SCF (often carbon dioxide).

7) Precipitation technique

Precipitation has been used to create submicron particles in the past ten years, notably for the less soluble materials, drugs [28]. The drug is first dissolved in a solvent, and after that, while surfactants are present, this solution is combined with a miscible antisolvent. When a drug solution is added quickly to an antisolvent, the drug becomes suddenly super-saturated and forms ultrafine crystalline or amorphous drug solids [29].

Advantages

- 1) Precipitation is very simple process
- 2) it has a ease of scale up and economical production

Disadvantages

- 1) The inclusion of surfactants is necessary to control crystal growth. The drug needs to be soluble at in at least one solvent [30].

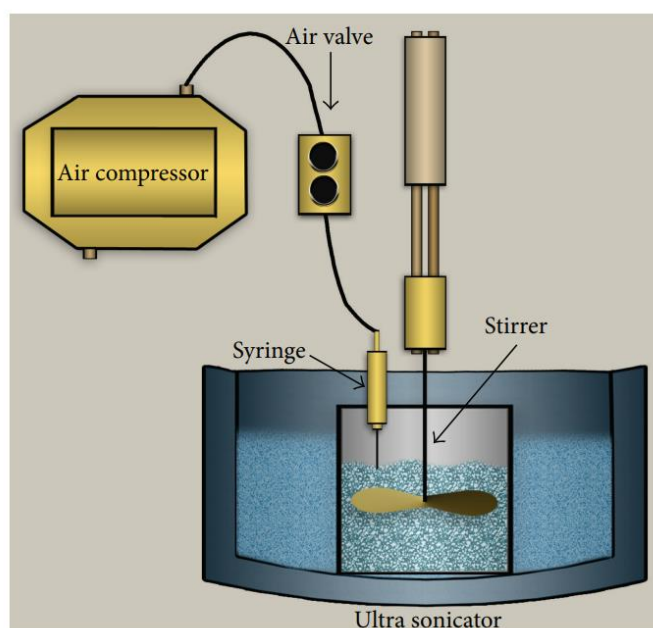


Fig: schematic representation of the precipitation method

8) Dry cogrinding

Dry co-grinding is a milling method wherein poorly soluble pharmaceuticals are dry-ground with soluble polymers and other materials. After dispersion in a liquid medium, copolymers are used to create a stable nanosuspension. Various polymers and copolymers, including polyvinyl pyrrolidone, hydroxypropyl methylcellulose (HPMC), polyethylene glycol, sodium dodecyl sulphate, and derivatives of cyclodextrin, were used to create a stable nanosuspension utilising the dry co-grinding method [31],[32]. The improvement of surface polarity and transformation of the majority of the drug's crystallised state into an amorphous form are the most notable effects of this method. An increase in the saturation solubility and, consequently, the rate of dissolution of weakly soluble drug nanosuspensions might be achieved by carefully controlling the stability of the amorphous phase [31],[32].

Recent Advances in nanosuspension

Nanosuspension proves the increase in bioavailability of poorly water soluble drug by Dissolution study. by using lyophilization of nanosuspension the powdered nanosuspension is prepared which is futhur use for making pellets and tablets shows the same increased dissolution rate [33]. Numerous nanosuspensions have been successfully created with various medication candidates by utilising a range of techniques. The primary goal of designing and developing these nanosuspensions is to increase the solubility and bioavailability of the Active Pharmaceutical Ingredient because many medications have low water solubility. some recent developments in nanosuspension technology, which are briefly summarised in Table.

Drug	Type of Studies	Particulars	Refs.
Valsartan	<i>In vitro</i> studies	The prepared valsartan nanosuspension indicated high drug solubility in hypromellose. The FTIR data reflected no interaction between the drug and polymer.	[34]
Aceclofenac	<i>In vitro</i> studies	Prepared nanosuspension of aceclofenac showed quick release behaviour. The formulation demonstrated better solubility and fast dissolution rate in comparison of marketed preparations for effective treatment of pain.	[35]
Diacerein	<i>In vitro</i> studies	Diacerein nanosuspension reflected high dissolution rate and solubility and around 400 times increased saturation solubility of the bulk drug in comparison to free drug in order to effectively treat osteoarthritis.	[36]
Metformin	<i>In vitro</i> studies	The formulation utilized a high ratio of stabilizer & polymer that induced nanosuspension with fine particle size, better release rate, and encapsulation efficiency. The mean particle size was estimated at 399 nm.	[37]
Ezetimibe	<i>In vitro</i> studies	In this research, the optimized formulation exhibits the 99% of drug release in 25 minutes for efficaciously treatment of hyperlipidemia.	[38]
Celecoxib	<i>In vivo</i> and <i>in vitro</i> studies	Fabricated nanosuspension of celecoxib possessed enhanced solubility and <i>in vitro</i> dissolution rate. The <i>in vivo</i> pharmacokinetic data also revealed enhanced oral bioavailability of celecoxib in rats.	[39]
Zerumbone	<i>In vitro</i> studies	<i>In vitro</i> data of zerumbone nanosuspension, which was prepared with hypromellose (HPMC), demonstrated increased solubility as well as the rate of drug dissolution.	[40]
Bifonazole Nitrate	<i>In vitro</i> studies	The topical formulation of nanosuspension reflected enhanced saturation solubility with controlled release rate. The developed formulation also reduces the side effects of Bifonazole like burning and itching.	[41]
Tinidazole	<i>In vivo</i> and <i>in vitro</i> studies	The prepared tinidazole nanosuspension showed better stability, palatability with increased dissolution rate and oral bioavailability.	[42]

Patents in nanosuspension:

Regarding nanosuspension technology, several patents have been awarded. Following Table provides a summary of these patents.

A topical nanosuspension was created using the method described in the patent WO2016135753. The water-soluble active component or its salt is present in this nanosuspension, with a system with a non-aqueous solvent and a wetting agent. A topical nanosuspension was created from this nonaqueous nanosuspension [43].

The therapeutically active moiety in the pharmaceutical nanosuspension is described in the patent WO2016081593. This moiety may be an active nutraceutical component with a low solubility. According to the patents, at least for creating the nanosuspension, one alginate moiety, either sodium alginate or potassium alginate, was used [36]. Another US patent, 20160317534, illustrates the nanosuspension of a lyophilized (freeze-dried) pharmaceutical. It was discovered that the stability of this freeze-dried medication nanosuspension was adequate for long-term preservation [45].

A procedure for creating a nanosuspension of an antibacterial moiety is described in US patent 20160206577. The new formulation offers improved stability and less toxicity, according to this patent [38].

The stable nanosuspension, namely hexaflumuron, a chitin synthesis inhibitor, is mentioned in US Patent 20150238446 and is utilised as an injectable to treat sea lice [47].

A developed technique for ophthalmic nanosuspension is described in Chinese patent 105708844. Tobramycin and dexamethasone were employed as the active ingredients in this procedure. It was discovered that the developed method of making such nanosuspension was repeatable, efficient, stable, and easy to utilise [48].

The creation of the nanosuspension process employing the potential medication simvastatin is covered by another Chinese patent, 105315249. According to the researchers, the strategy improved the effectiveness of the medication delivery system [49].

Another Chinese patent, number 105534947, details a manufacturing process appropriate for creating celecoxib nanosuspension capsules, which were afterwards turned into solidified powder by the process of freeze-drying [50].

In accordance with Chinese Patent No. 104814926, lurasidone nanosuspension was created by combining the processes of high-pressure homogenization and nano-precipitation. This technique was discovered to be effective for increasing the drug's bioavailability and stability [51].

A poorly soluble medication was used in the creation of a nanosuspension, according to US patent 9023886. The researchers created nanosuspension in this patent using the microfluidization process. The produced nanosuspension was shown to be more bioavailable and appropriate for application [52].

Patent/ Application Number	Publication/ Application Date & Year	Publication/ Application Date & Year	Refs.
WO2016135753A1	Sept. 1, 2016	This patented work involves the development of a methodology for topically utilized nanosuspension through the process of milling.	[43]
WO2016081593A1	May 26, 2016	The patented invention describes the nanosuspension fabricated with a therapeutically active moiety. Such moiety is an active nutraceutical having poor solubility profile.	[44]
US20160317534A1	Nov. 3, 2016	This patent gives information about a nanosuspension prepared with the lyophilized drug. Such nanosuspension possessed sufficient stability during long-term storage.	[45]
US20160206577	Jul. 21, 2016	This patented study reflects the method of fabrication of nanosuspension of an antibacterial moiety that improves the stability and reduced toxicity of the drug.	[46]
US20150238446A1	Aug. 27, 2015	The researchers reported the development of stable hexaflumuron nanosuspension that can be injected into fishes for controlling sea lice.	[47]
CN105708844A	June 29, 2016	This patented work describes the development method of ophthalmic nanosuspension of tobramycin & dexamethasone. The process was found to be reproducible, effective, stable and convenient	[48]
CN105315249A	Feb. 2, 2016	This patent is related to the development method of simvastatin nanosuspension to enhance the efficiency of drug delivery systems.	[49]
CN105534947A	Feb. 16, 2016	The patented work involves a method of developing a celecoxib nanosuspension capsule which can be converted into solidified powder through freeze drying. [[50]
CN104814926	Aug. 5, 2015	This invention stated that the nanosuspension of lurasidone was fabricated through the combination of nano-precipitation and high-pressure homogenization method.	[51]
US9023886B2	May 5, 2015	The patented invention demonstrates the formation of nanosuspension of poor water-soluble drug through microfluidization technique.	[52]

Conclusion

Hydrophobic drugs are mainly poorly soluble in water which results in poor bioavailability of drug in systemic circulation in our body. nanosuspension is the novel and promising technology to increase the aqueous solubility of drugs. the technique has benefits as it is simple to formulate nanosuspension, cost effective ,increases the dissolution velocity of drugs, improved bioadhesivity. nanosuspension can be administered by easy way from oral route and futhur applications in pulmonary and ocular delivery are under process of development.However, their topical, nasal, and buccal administration methods have not yet been completed.

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