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## A review on: Formulation of nanosuspension intended for ophthalmic use

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### Abstract

The intention of this review article is to focus on the formulation related aspects of ophthalmic suspension in form of nanosuspension which is intended for the increase in the solubility and bioavailability of the drugs. In recent times there is remarkable increase in the field of Nano measurement as to increase the solubility and bioavailability of the drugs. The formulation nanosuspension drugs which have the property of Low Solubility and High Permeability i.e those drugs which are under BCS Class II are best. NS drugs can be delivered by parenteral, oral ocular and pulmonary routes. These nanosuspensions can be formulated by various methods such as wet mill, high pressure homogenizer, emulsion-solvent evaporation, melt emulsification method and super critical fluid techniques.

**Keywords:** Nano-suspension; bioavailability; drug delivery; solubility; ocular routes

### Introduction

To develop a drug delivery system targeted to a particular tissue of an eye is one of the major challenges faced by the scientist these days. Most of the diseases related to the eye are treated with the aid of eye drops (ED), which is mainly focused on the anterior eye segment<sup>[1]</sup>. Though ED is easier to administer and have immediate effects, periorbital factors like solution drainage, blinking, induced lacrimation, ect., and anatomical barriers affects the formulation of ED. Hence, ocular drug delivery being a trickiest route for Drug Delivery<sup>[2]</sup>. The use of Novel Drug Delivery System (NDS) strategies like NS, nano-emulsion (NE) etc, helps to sustain the drug at the intended site for a longer time.

### Ocular drug delivery (odd)

As in Fig.-1, an eye has various layers/ barriers, which act as barriers, restricting the drug to reach the intended site of action. The drugs that are carried through Corneal or Non-corneal routes involves several complicated biological processes such as drug of drug penetration (DP) across the ocular barriers and get transferred to posterior and anterior cavity<sup>[3]</sup>. Since most of medications used ED which easily drained away from the ocular surface, they leading to low bioavailability and failure in reaching the posterior segments. When this medication is applied through topical methods, only around 1-7% of the drug reaches the aqueous humor<sup>[4]</sup>.

There are various routes for administering drug to ocular site such as,

- Topical administration
- Systemic (parenteral) administration
- Oral administration
- Periocular and intravitreal administration

The most preferred route preferred among the four is the topical administration method; first pass metabolism can be avoided by ODD. Other advantages of this technique are to target the anterior chamber, it noninvasive and is patient friendly.

### Mechanisms of topical ocular drug absorption

When a drug is administered into the eye cul-de-sac<sup>[5]</sup>, the administered drug must penetrate the eye through the cornea followed by non-corneal routes and the drugs are carried away by the lachrymal fluid. The corneal route plays the important role in the path of absorption. But the rate of absorption in the corneal route is limited due to the presence of corneal epithelium. The second route is through non-corneal routes which involves drug diffusion across the conjunctiva and sclera<sup>[6]</sup>.

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In this route the penetration of the drug to the target site is low due to the local capillary beds. In spite of all the barriers few drugs such as Gentamicin and Timolol Maleate have reached the intraocular section by through penetrating conjunctive and sclera. The absorption of the drugs generally depends on the physicochemical characteristics of the drugs [7].

### Ophthalmic formulation

Ophthalmic Preparation (OP) (eye preparations/medication) are sterile liquid, semi-solid or solid phase which are dissolved in an aqueous phase [8]. The OP may contain one or more Active Pharmaceutical Ingredient(s) (API) which is intended for application in conjunctival sac or the eyelids. The choice of the additives used for OP must be proven through product development studies. The additives must not affect both the stability of final product and the availability of API at the site of action. In case API does not have antimicrobial activity by itself, the OP supplied as multidose containers may include a suitable antimicrobial agent. The antimicrobial activity should stay effective throughout the entire period of use. In case of oily ED, the oily vehicle which has been previously sterilized by heating at 160°C for one hour must be used. Any manufactured ED should be made approximately isotonic with lachrymal secretions by the addition of any suitable substance such as Sodium Chloride. Once the medication is open it shall be used within a month [8].

### Ophthalmic dosage forms

The various types of eye dosage forms are as in fig.2

#### 1. Eye Drops (EDs)

##### a. Ophthalmic solutions (OS)

OS is a sterile solution; free from foreign a particle which is suitable for compounding and packaging for eye medication. OS requires careful preparation, considering the factors such as the toxicity of the drug itself, isotonicity value and added buffering agents preservative.

Example: ketorolac tromethamine OS and levocabastine OS

##### b. Ophthalmic suspensions (OSS)

OSS is a sterile biphasic preparations containing solid particles dispersed (SP) in a liquid vehicle intended for eye medication. It is necessary that should OSS the drug in a micronized form to prevent from irritation and/or scratching of the cornea. OSS should not be dispensed if there is any evidence of caking or aggregation.

Example: neomycin and polymyxin b sulfates and hydrocortisone OSS [12], fluorometholone eye suspension [13].

#### 2. Eye lotions (EL)

EL are used for cleansing the eye surface or for impregnating during eye dressings and also to relieve any eye irritation.

#### 3. Eye ointments (EO) [9]

EO must be sterile. Like suspensions or other eye medication, EO can be more difficult to manufacture in sterile form. They can be terminally sterilized, or, alternatively they must be these EO must be manufactured from sterile ingredient in an class A (aseptic area). The ointment base selected for an EO must be non-irritating to the eye and must permit the diffusion of the API throughout the secretions of the eye. EO has longer ocular contact time when compared to OS. Through Studies it was found that the ocular contact time is 2 to 4 times greater.

One disadvantage to EO is the blurred vision that occurs as the ointment base melts and is spread across the eye lens.

Example: ciprofloxacin [14] and oxytetracycline hydrochloride with polymyxin b sulfates n [15] eye ointments.

#### 4. Ophthalmic emulsions (OE)

OE are generally dispersion of oily droplets in an aqueous phase. There should be no evidence of breaking or coalescence

Example: tromethamine, cetalkonium chloride [15] and ciclosporin [16] eye emulsions.

#### 5. Ocuserets [9, 11]

Ophthalmic inserts and ocular systems are solid dosage forms of suitable size and shape that are placed in the conjunctival fornix, in the lachrymal punctum. Ocuserets are classified as erodible (soluble) and non-erodible (insoluble). These devices allow accurate dose delivery, can avoid the use of preservatives, and can notably increase ocular bioavailability. Drug release from soluble inserts involves two steps

Step 1—fast release of a portion of the drug as the tear fluid penetrates into the system;

Step 2—slow release as a gel layer is formed on the surface of the insert.

Example: hydroxypropyl cellulose ophthalmic insert [17].

#### Novel ophthalmic dosage forms [9]

##### Colloidal Dosage (CD)

CD forms have been broadly studied and employed in the field of ODD. These dosage forms include liposomes, nanoparticles, micro-emulsions, nano-emulsion, etc. Advantages of CD forms include controlled release and sustained release of the drug to the targeted site, thereby reducing the frequency of administration and the ability to overcome Blood Ocular Barriers (BOB). Further, this Colloidal Carriers (CC) can also overcome/ bypass various stability-related problems of drug molecules. Encapsulation of drugs in these carriers can also significantly improve permeation of drug across the membrane and prevent degradation which is caused by the ocular enzymes. Such biodegradable CC can be developed as an alternative to the implants prepared from non-biodegradable polymers, which needs to be removed surgically after a specific time period.

Although very promising, commercial development of this CC remains limited because of the difficulties in manufacturing, due to the problems faced in stability during sterilization, which are not offset by substantial improvements in pharmacokinetic and pharmacological performance.

##### Micro emulsions (ME)

ME are dispersion of water and oil i.e (W/O or O/W) facilitated by a combination of surfactant and co-surfactant in a manner to reduce interfacial tension. These systems are usually characterized by higher thermodynamic stability, small droplet size (approximately 100 nm) and clear appearance. Their transparent appearance is due to the high level of dispersion of the internal phase, the size of it ranges from 100–1000 angstroms Apart from solubility; ME systems have also been exploited to improve permeation across the cornea. Such formulations often provide extended drug release thereby reducing frequency of the drug administration. Although ME have excellent advantages, limitations in the selection of surfactant/co-surfactant system and potential toxicity associated with higher concentrations of

surfactant/co-surfactant often restricts its use.

### Nano Suspensions (NS)

NS can be defined as sub-micron colloidal systems that consist of poor water soluble drug, suspended in an appropriate dispersion medium stabilized by surfactants. Usually NS consist of colloidal carriers like polymeric resins which are inert in nature. They help in enhancement of drug solubility and bioavailability. They are not irritant as ME. The charge on the surface of NP facilitates their adhesion to the cornea.

### Nano particles (NP)

NP can be defined as particles with a diameter of > than 1  $\mu\text{m}$ , comprising of various biodegradable or non biodegradable polymers, lipids, phospholipids or metals. They can be classified as nanospheres (NS) or nanocapsules (NC) depending upon whether the drug has been uniformly dispersed or coated within polymeric material. The uptake and distribution of NP depend on its size.

### Liposomes

Liposomes are lipid vesicles having aqueous core and have been widely exploited in ODD for various drug substances. Depending on the character of the lipid composition selected, liposomes can provide extended release (ER) of the drug, rapid erosion, and non-biodegradability. In case of cellulose derivative like hypromellose, gelation is a result of interaction of hydrophobic components at higher temperature. Another approach is having the polymer dissolved in a suitable carrier. The polymer and carrier are both biodegradable and biocompatible. Once injected into the subcutaneous space, water in surrounding tissues causes the precipitation of polymer which immediately entraps the drug and releases it in a controlled manner.

### Niosomes

Niosomes are bilayer structural vesicle which are capable of encapsulating both lipophilic and hydrophilic compounds and are made up of nonionic surfactant and. They are not dependent on the pH hence, can release the drug independent of pH thereby enhancing ocular bioavailability. These are microscopic lamellar structures formed on a mixture of nonionic surfactant of the alkyl or diacyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. They are structurally similar to liposomes. Though, the bilayers in the case of niosomes are made up of nonionic surface-active agents rather than phospholipids as in the case of liposomes. Niosomes may be uni- lamellar/multi- lamellar depending on the method used to for preparation. They are capable of entrapping hydrophilic and hydrophobic solutes. They have high stability and may overcome many disadvantages faced in liposomes such as high cost and the variable purity of phospholipids.

### Dendrimers

Dendrimers are compounds made up of a series of branches around a central core to form a macromolecular. Their nano size helps in easy preparation, functionalization, and possibility to attach multiple surface groups render them suitable alternative vehicles for ODD. This system of polymers represents unique architecture and can entrap lipophilic and hydrophilic drugs into their structure. Selection of functional group on the surface (amine, carboxylate and

hydroxyl), size and molecular weight of the dendrimer are important parameters to be considered in designing a delivery system.

### Hydrogels

Hydrogels are three-dimensional (3D), hydrophilic, polymeric networks capable of taking in large amounts of water or biological fluids. Dwelling time can be significantly enhanced with hydrogel formulation. The gelation can be obtained by changing temperature and pH. Poloxamers is the most widely used polymer, contains the hydrophobic part in the centre surrounded by a hydrophilic part. Though they are widely employed to enhance the residence time, they suffer from a major drawback of having weak mechanical strength.

### Microneedle (Ultrasound-, and iontophoresis-Based ODD)

These delivery systems are noninvasive methods designed to deliver the drugs into the intraocular regions, mainly it's used for the treatment of posterior segment diseases. Drug-coated micro needles have been developed with an length of 500–750  $\mu\text{m}$ . The drug can be coated on the solid metal. Following administration, coated molecules dissolve rapidly, and subsequently, micro needles are removed from the tissue. This delivery system generates a much higher conc. compared to a free-drug solution. Similarly, ultrasound-mediated ODD has also received attention in recent years. Delivery of beta-blockers such as Timolol Maleate and Atenolol was applied with ultrasound application (20kHz for 1 h) across cornea in the treatment of glaucoma. Corneal permeability of these compounds has been significantly enhanced with ultrasound. These days Ocular iontophoresis has received a lot of notice, particularly to deliver drugs across cornea and sclera. Some API such as Ciprofloxacin hydrochloride, Gentamicin, Dexamethasone were successfully delivered using this technique.

### Advantages of NS<sup>[10]</sup>

The advantages for NS drugs, which makes it a suitable for many kind of OP are the following,

- NS Enhance the solubility and bioavailability of drugs
- NS Suitable for hydrophilic drugs
- NS Higher drug loading can be achieved
- NS Dose reduction is possible
- NS Enhance the physical and chemical stability of drugs
- NS Provides a passive drug targeting

Different type of NS preparation<sup>[25]</sup>

NS are formulated by two method the 'Top down technology' and Bottom up technology' as shown in fig. 3.

1. Bottom up technology is an assembling method to form NP like precipitation, micro emulsions melt emulsification method.
2. Top down technology involves the disintegration of larger particles into VNP, examples of which are high-pressure homogenization and milling methods.

The principles of these methods are described below:

#### 1. Precipitation Method(PM)<sup>[26]</sup>

For the preparation of sub-micron particles of poorly soluble drug PM is used. In this method the drug is dissolved in the solvent and then solution is mixed with solvent to which drug is insoluble in the presence of an surfactant. Rapid addition of solution to such solvent (generally water) leads to rapid supersaturation of drug in the solution thus ultrafine amorphous or crystalline drug are formed (fig.4).

## 2. Homogenized at high pressure <sup>[27]</sup>

In this technique the initially the drug are dispersed in a stabilizer solution to form a per-suspension. This per-suspension is then homogenized at low pressure followed by high pressure for 10 to 25 cycles until and unless the NP of the preferred size are formed (fig.5).

## 3. Homogenization in aqueous media (Dissocubes)

In this technique the formulated suspension is forced through a narrow valve under high pressure by pressure plunger pump. When the suspension is permitted through the orifice the static pressure will be reduced below the boiling pressure of water which results in the boiling of water and formation of gas bubbles. When it leaves the orifice pressure will be normal and bubbles will implode. So surrounding particles will rush into the surface which causes the size reduction.

## 4. Homogenisation in non-aqueous media (Nanopure)

The suspension is homogenized in water mixture or water free media. Temperature will be 0oC or even at freezing point. So it is known as deep freeze homogenisation. It is the finest method for the thermolabile substances.

## 5. Nanoedge

The basic principles of Nanoedge are the same as that of homogenization and precipitation. A mixture of these techniques results in smaller particle size and better stability in a shorter time. In this technique, precipitated suspension is further homogenized, leading to reduction in particle size thereby avoiding crystal growth.

## 6. Nanojet-technology

The other name for nanojet technology is known as opposite stream technology. In this technique a stream of suspension in 2 or more divided parts were passed with high pressure were colloid with each other, due to high shear forces which is formed during the process leads to results in reduction of particle size.

## 7. Media milling <sup>[28]</sup>

Drugs are subjected to media milling. Effect of impaction between milling media and drugs gives essential energy for disintegration of the micro - particulates system into NP. In this process, the chamber of milling is charged with the milling media involving drug, stabilizer, and water or suitable buffer, which is rotated at a very high shear rate to generate suspension. Thus the finished product is the residues left behind (fig.6).

## 8. Dry-Co-grinding

Recently many NS are prepared by dry Co-grinding milling technique. This method is very economic and very easy. And can be conducted without organic solvents. Physicochemical properties and dissolution of poorly water soluble drugs can be improved by Co-grinding.

## 9. Emulsification-solvent evaporation technique

This method involves in preparing solution of drug by emulsification in or another liquid that is a non-solvent for the drug. On evaporating the solvent the drug get precipitation. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.

## 10. Melt emulsification method

In this method the drug is dispersed in aqueous/water solution of stabilizer and is heated above the melting point of the drug and homogenized to form emulsion. During this process, the sample holder was enwrapped with a heating tape fitted with temperature controller and the temperature of emulsion shall be maintained above the melting point of the drug. Emulsion is then cooled down either slowly to room temperature or on an ice bath.

## 11. Solvent evaporation

In the method, the solutions of polymer are prepared in volatile solvents and emulsions. The emulsion is then converted into a NP suspension on evaporation of the solvent for the polymer, which is allowed to diffuse through the continuous phase of the emulsion. These methods require high-speed homogenization or ultra-sonication, followed by evaporation of the solvent, either by continuous magnetic stirring at room temperature.

## 12. Supercritical fluid method

Various methods like RESS- Rapid Expansion of Supercritical Solution process, SAP-Supercritical Anti solvent Process, and PCA- Precipitation with Compressed Anti solvent process are used to produce NP. In RESS technique, drug solution is expanded through a nozzle into supercritical fluid, thus results in precipitation of the drug as fine particles by loss of solvent power of the supercritical fluid. This supercritical anti solvent process, drug solution is injected into the supercritical fluid and the solvent gets extracted as well as the drug solution is formed as supersaturated.

## Evaluation on eye suspension <sup>[29]</sup>

### 1. Description

A qualitative narration of the drug product shall be provided. The description part shall include the acceptance criteria of the final drugs acceptable-appearance which shall also include clarity and color, of the dosage form.

### 2. Identification (IDT)

IDT shall establish the identity (ID) of the drug or drugs present and should separate the compounds of closely related structures that are likely to be present. IDT should be specific for the drug substance(s) [e.g., IR- infrared spectroscopy, NIR-Near-infrared or Raman spectro-photometric methods] shall be used for identification of the drug product. Chromatographic procedures are the most widely used IDT for drug substance(s).

### 3. Assay

Assay is performed to determine the strength (content) of the drug product.

### 4. Impurities

Impurities such as synthetic byproducts/ inorganic/ organic impurities may be present in the drugs and excipient's which are used in the manufacture of the drug products. These impurities are can be deducted by the help of drug substance and excipients monographs.

### 5. pH

Normal pH of eye tears about 7.4. The eye can tolerate products over a range of pH values from about 3.0 to about 8.6, depending on the buffering capacity of the formulation.

The pH value of the formulation should be the one where the drug product is the most stable.

## 6. Osmolarity

OP may be tolerated over a fairly wide range of tonicity (0.5%–5% sodium chloride, equivalent to about 171–1711 mOsm/kg). Hypotonic solutions are better tolerated than hypertonic solutions. Precautions shall be taken to ensure that the osmolarity of the product are maintained throughout its shelf life. Any possible contributions or interferences from the packaging system shall be taken into consideration.

## 7. Particulate and foreign matter

All OP shall be checked for package integrity and, to the extent possible, for the presence of foreign/particulate matters (visible particles). These unwanted particles arise from two sources: extrinsic (i.e., foreign matter); and intrinsic (i.e., product-related matter). Extrinsic matter is not associated with the product or process. Intrinsic particles are added during assembly of the product or result from a change over time. A 3<sup>rd</sup> category, inherent matter, describes the physical state or particles that are anticipated matters of the product.

## 8. Sterility

OP must meet the requirements of sterility test. The immediate container i.e., Primary Packing Material for OP shall be sterile at the time starting from filling and closing. It is mandatory that the immediate containers for OP shall be sealed and tamper proof so that sterility is ensured at the time of first use.

## 9. Antimicrobial preservatives

Antimicrobial agents must be added to formulations that are packaged in containers which allow withdrawal or administration of multiple doses, the preservative need not be added unless one of the following conditions prevails:

- If the OP contains a radio-nuclide with a physical half-life of <24 hr; and
- If the OP, without additional agents, is sufficiently microbicidal to meet the requirements of antimicrobial.

## 10. Uniformity of dosage units

Uniformity of dosage units is applicable to dosage forms which are packaged in single-unit containers. It includes both the mass and the content of the drug substance(s) in the dosage form. This can be performed by either content uniformity or weight variation.

## 11. Container contents

Container contents of OP shall be determined

## 12. Leachables and extractables

The OP packaging system especially the primary packing material shall not interact physically or chemically with the product in any manner to alter the strength, quality, or purity of the OP. The evaluation of possible leachables and/or extractables shall be taken into the account the risk assessment of the product, its indication, and its packaging system. Furthermore, it should be noted that a risk assessment of extractable/leachable impact on topical or intraocular route of administration is a challenging undertaking. Toxicological or safety assessments of primary or secondary packaging component extractable and leachable are not typically available for ophthalmic routes of administration. A risk

assessment may include evaluation of toxicology and safety from other routes of administration and an assessment of the Total Daily Intake of the extractable/leachable being evaluated. The preponderance of such assessments leads to an estimate of extractable/leachable risk via ODD to the patient.

## 13. Container–Closure integrity

The packaging system of OP shall be closed or sealed in such a manner as to prevent any kind of contamination or loss of contents and shall provide supporting information of being tamper proof.

## Specific Tests <sup>[29]</sup>

### 1. Viscosity

By increasing the viscosity, the residence time in the eye also increases. On the other hand, the drug diffusion out of the formulation into the eye may be reduced due to high product viscosity.

### 2. Anti-Oxidant content

When anti-oxidants are present in the drug product, tests of their content shall be conducted; acceptance criteria for antioxidant content should be mentioned. They should be based on the levels of antioxidant necessary to maintain the product's shelf life at all stages throughout its proposed usage.

### 3. Re-suspendability / Re-dispersibility

Consideration must be given to establishing good physical stability of a suspension. If the particles gets settle and eventually forms cake at the bottom of the container, they must re-dispersed readily at the time of use to achieve dosage uniformity.

### 4. Particle size and particle size distribution

The potential for any changes in the particle size of OS and OE needs to be evaluated through stability testing.

### 5. Drop size

For OP are dispensed as drops, drop sizes may typically range from 20 to 70  $\mu$ L. Drop size can be controlled by weight or by volume, and mostly it is typically evaluated during product development.

### 6. Added substances

Suitable substances may be added to OP to increase shelf life, unless approved in the individual monograph and also provided that they are harmless in the amounts administered and do not interfere with the therapeutic activity or with responses to the specified assays and tests. Typically, this study shall be conducted during product development. The use of ingredients solely to impart a color, odor, or flavor is prohibited.

## Characterization of NS

NS are characterized in alike ways as those used for conventional suspensions such as appearance, colour, odor, assay, related impurities, etc. Apart from the above mentioned parameters, the NS should be evaluated for their particle size distribution, zeta potential, crystalline status, dissolution studies and *in vivo* studies.

### 1. Size

Particle size and polydispersity Index (PI) is the most important characteristics of NS. Particles size of NS critically determines the following characteristics of NS

- Drug saturation solubility,
- Physical stability,
- Dissolution rate,
- Bioavailability. According to Noyes-Whitney equation

**2. Particle size distribution**

The physiochemical behavior of the formulation, such as saturation solubility, dissolution velocity, physical stability, etc is determined using Particle size distribution. The particle size distribution can be determined by [30].

- Photon correlation spectroscopy (PCS)- The PCS method can measure particles in the size range of 3 nm to 3 μm
- Laser diffraction (LD) - This method has a measuring range of 0.05-80 μm.
- Coulter Counter Multisizer. (CCM)- This gives the absolute number of particles, in contrast to the LD method, which gives only a relative size distribution.

**3. Zeta potential**

The long term stability study information and Surface charge property information can be know by Zeta potential.

- A minimum zeta potential of ±30 mV is required for a stable suspension stabilized only by electrostatic repulsion,
- whereas, a zeta potential of ±20 mV would be sufficient for combined electrostatic and steric stabilizer

**4. Crystal morphology**

To characterize the changes in polymorphic due to the impact of high-pressure homogenization in the crystalline structure of the drug, techniques like.

- Scanning electron microscopy (SEM),
- X-ray diffraction analysis (XRD) in combination with differential scanning calorimetry or
- Differential thermal analysis (DSC) can be utilized.

NS can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms because of high pressure homogenization [31].

**5. Dissolution velocity and saturation solubility [32]**

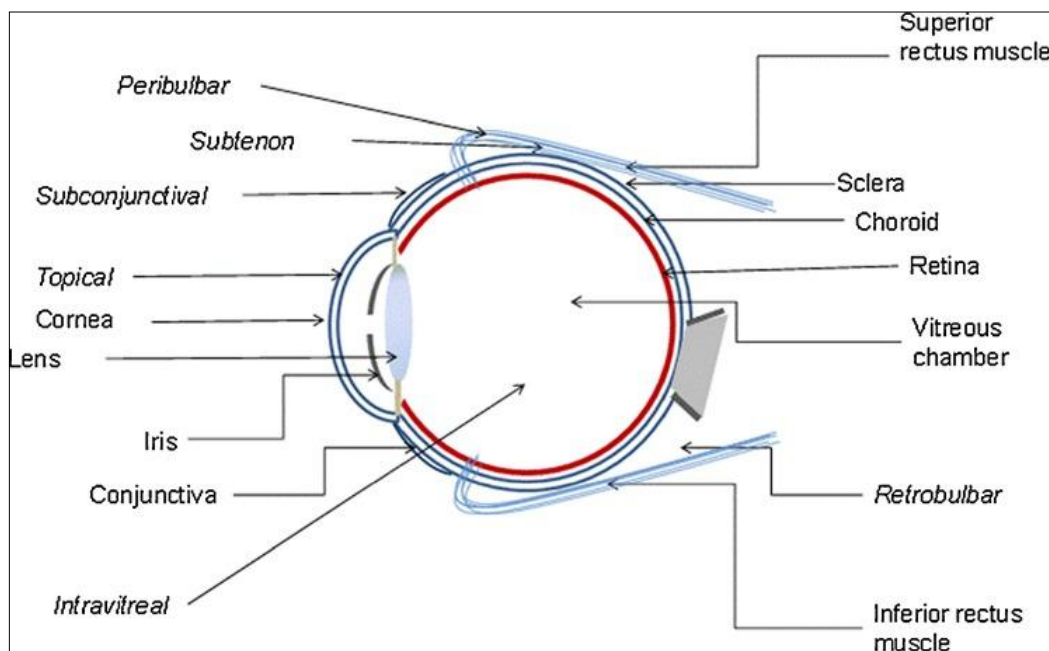
NS have an significant advantage over other techniques, as NS increases the dissolution velocity as well as the saturation solubility. These two parameters need to be determined in various physiological solutions. The above two assessment i.e. the saturation solubility and dissolution velocity helps in determining the In-vitro behavior of the formulation. Reduction in size leads to an increase in the dissolution pressure and an increase in solubility Muller explained that the energy introduced during the particle size reduction process leads to an increase in the surface tension and a related increase in the dissolution pressure.

**6. Physical stability of NS [32]**

The small particle size of NS, which inbuilt to their success, which is also responsible for their physical instability. NS consist of hydrophobic particles dispersed in a hydrophilic medium (usually water). The enormous surface area coupled with the nano-sized particles results in high interfacial tension and increased free energy, NS are basically are thermodynamically unstable systems to decrease their free energy nano-particles tend to reduce interaction with water via flocculation, aggregation or crystal growth. However, these processes affect the central characteristics of NS (i.e., small size and high surface area) and consequently the benefits of the NS formulations, as discussed above, are lost. Stabilizers are added to reduce the free energy of the system by decreasing interfacial tension and to prevent NP aggregation by electrostatic or steric stabilization. Stabilizers can be

- Surfactants,
- Polymers or
- A mixture of both.

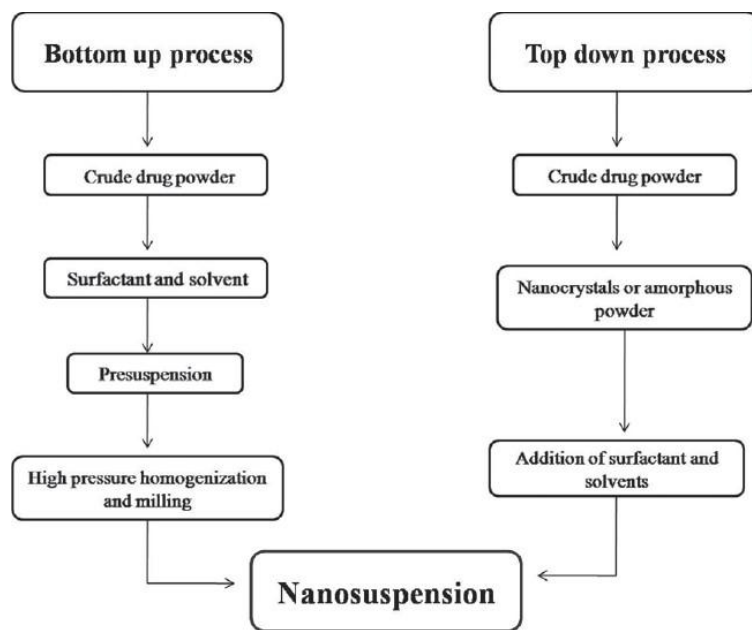
Examples of some of the commonly used surfactants include tween 80, sodium lauryl sulfate and poloxamer 188. polyvinylpyrrolidone (PVP), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), and polyvinyl alcohol (PVA) are examples of polymeric stabilizers [31]. (Table 2).



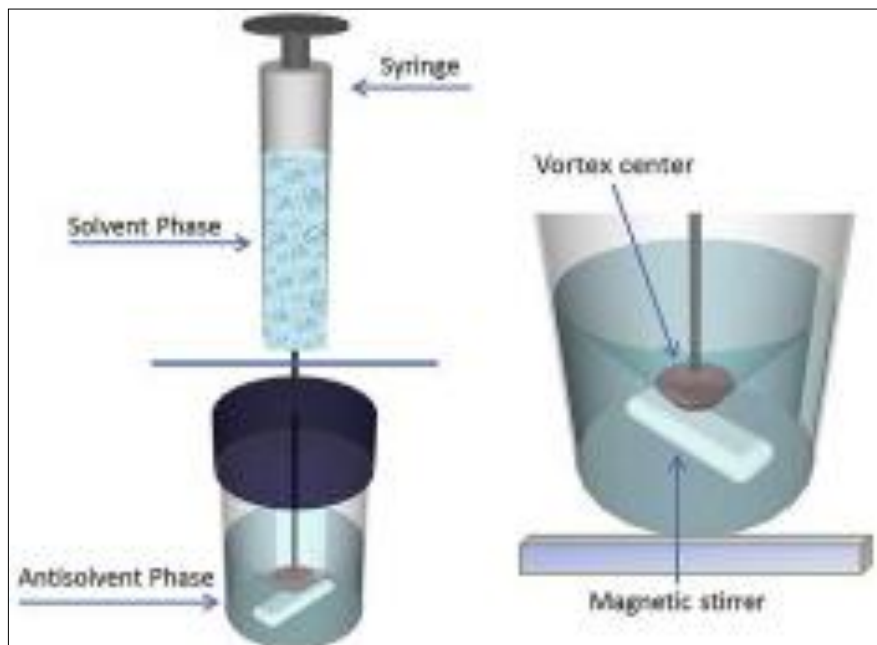
**Fig 1:** Structure of Eye



**Fig 2:** From left to right (a) Ophthalmic solution, (b) Ophthalmic solution, (c & d) Ocusersts, (e) Eye Lotion, (f) Eye Emulsion, (g) Eye Ointment



**Fig 3:** Preparation of nanosuspension



**Fig 4:** Precipitation method

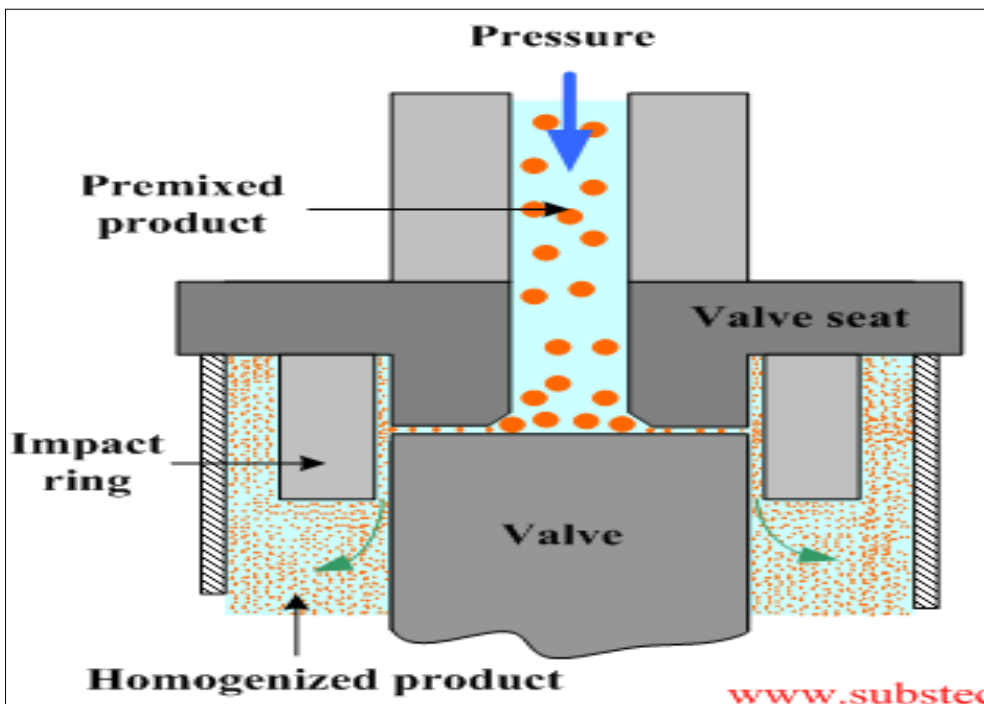


Fig 5: Homogenized at high pressure

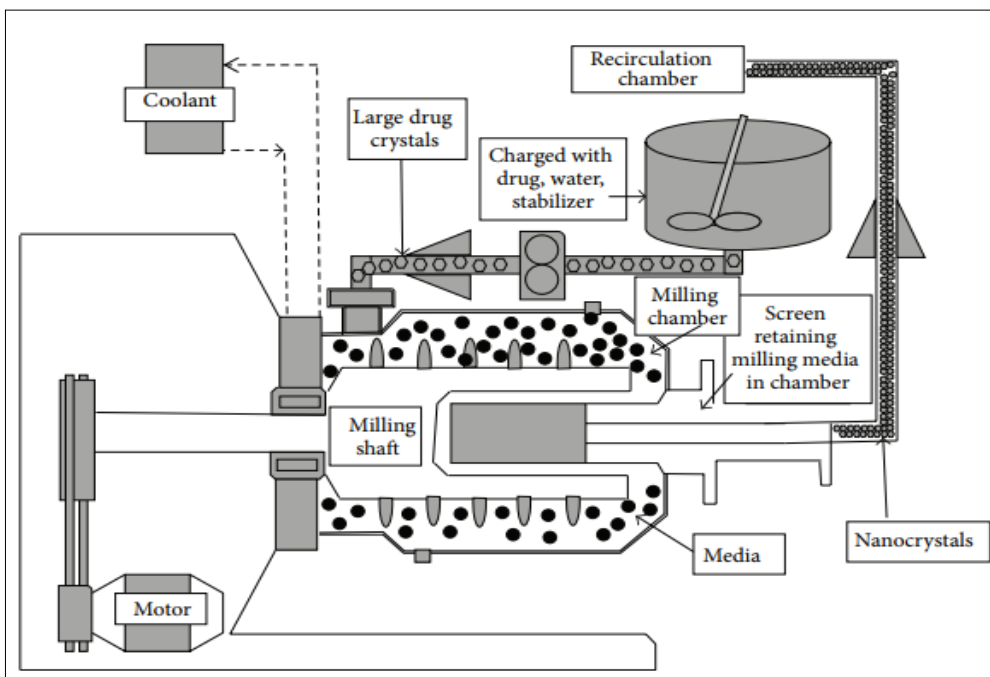


Fig 6: Media milling

Table 1: Nano suspension technology employed in eye preparation

Title	Authors name	Drug used	Technology used
Eudragit RS100® nanosuspensions for the ophthalmic controlled delivery of ibuprofen	Pignatello, <i>et al.</i> , <sup>[18]</sup>	Ibuprofen	Freeze-drying
Flurbiprofen-loaded acrylate polymer nanosuspensions for ophthalmic application	Pignatello, <i>et al.</i> , <sup>[19]</sup>	Flurbiprofen	Freeze-drying
Glucocorticoid drugs	Kassema, <i>et al.</i> , <sup>[23]</sup>	Hydrocortisone, prednisolone or dexamethasone	High pressure homogenization
Diclofenac-loaded biopolymeric nanosuspensions for ophthalmic application	Sagar, <i>et al.</i> , <sup>[20]</sup>	Diclofenac	Freeze-drying
Brinzolamide nanosuspension used	Sòngxiāngróng and	Brinzolamide	A method for preparing brinzolamide or



for eyes	Wèiyúquán <sup>[21]</sup>		Brinzolamide nanosuspension salts, comprising the steps of: (1) mixing the drug and the solvent, and an amount of a stabilizer; (2) homogenization machine, a high pressure homogenizer, a ball mill and the like, or a physical ultrasound probe prepared as nanosuspension; (3) adding an osmotic pressure adjusting agents, ph adjusting agents; (4) direct addition of a preservative or sterile filtration; (5) or Add additional pharmaceutically acceptable ophthalmic composition such as a metal ion complexing agent; (6) Filling the nanosuspension obtain Brinzolamide or lyoprotectant added to the lyophilized formulation prepared.
Preparation and evaluation of vitamin A nanosuspension as a novel ocular drug delivery	Abbas Akhgari <i>et al.</i> , <sup>[22]</sup>	Vitamin A	High pressure homogenization
Formulation and process development of Azithromycin ophthalmic nanosuspension	Rashesh K <i>et al.</i> <sup>[24]</sup> ,	Azithromycin	High pressure homogenization

**Table 2:** List of solvents and polymers used

Solvents	Polymers
Ethyl acetate	Ethyl Cellulose
Methylene Chloride	Cellulose Acetate Butyrate
Chloroform	Poly methyl methacrylate
Ethanol	Eudragit RS 100, Eudragit RL 100, Hydroxy propyl methyl cellulose E-5 (HPMC E-5), Poloxamer 407

## Conclusion

From the above literature survey which has been conducted it can be concluded that, NS solved the problem of poor solubility of the drugs. Media Milling, Freeze-drying and high pressure homogenizer production methods, are being widely used for large scale production of NS. NS really plays a very important role for betterment of human as the production method is simple compare to other type of NDDS formulation, NS required less additives/ excipients and also increases dissolution velocity and saturation solubility. By emphasizing this technology, our society will be surely be benefited. Thus NS technology is able enough to bring enormous immediate benefits and will revolutionize the research and practice of medicine in the field of pharmacy.

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