2. Introduction

2.1 Introduction to Nanosuspension

The nanotechnology is presently gaining attention from researchers and pharmaceutical world. In the pharmaceutical field, the term "nanoparticle" is usually used to describe submicron sized particles. The drug of interest is dissolved, entrapped or encapsulated within the particles. Nanoparticle technologies have been used as important strategies to deliver drugs, including peptides and proteins, vaccines and more newly nucleotides.[1-4] In pharmaceutical field, nanosuspension, nanoemulsion, self nanoemulsifying drug delivery system, solid lipid nanoparticle (SLN) etc are covered under nanotechnology area.

A nanosuspension consists of drug nanocrystals, stabilizers, typically surfactants or polymeric stabilizers, and a liquid dispersion medium.[5] Drug nanocrystals are pure solid drug particles with a mean particle size less than 1 μm, generally between 200 nm and 500 nm.[6] Although the term nanocrystals implicates a crystalline structure, the particles can be crystalline, partially crystalline or absolutely amorphous. The dispersion medium can be water, mixtures of water and other non-aqueous media or non-aqueous media. Nanosuspension permits delivery of drugs that are poorly soluble in water or unstable in biological fluids.

2.1.1 Method of Preparation of Drug Nanosuspension

Nanosuspensions can be prepared using different techniques, which could be classified generally in two groups based on the principle on which the nanorange is achieved. Top down production, in which the size of drug macrosuspension is reduced up to nanosuspension and second is bottom up technique in which the drug nanoparticles are assembled from a solution of drug by controlling the rate and growth of nuclei formed.

Bottom up technique

a) Nanoprecipitation
b) Supercritical fluid technology
c) Using microemulsions and emulsions as templates.

Top down technique

a) Media milling

b) Dry co-grinding

c) High pressure homogenization

2.1.1.1 Bottom up Technique

a) Nanoprecipitation

In the precipitation method the poorly water-soluble drugs are dissolved in a suitable solvent and the solution is added into a miscible anti-solvent with stirring and/or agitation. Stabilizers are used to avoid the spontaneous aggregation of molecules. Final morphology of nanoparticles are affected by factors such as types of solvents, the volume ratio of antisolvent to solvent, stirring speed, amount of drug etc.[7-10]

Nucleation and crystal (particles) growth of drug particles from a supersaturated solution involves in the precipitation process. The supersaturated solution is a solution in which the concentration of solute exceeds the saturation or equilibrium solute concentration at a given temperature. Thus, a supersaturated solution is not at equilibrium, and crystallization of the solute occurs in order to move about the solution towards equilibrium. After initial particle nucleation, both nucleation and crystal growth attempt to take the supersaturated solution to equilibrium. The time required for crystallization depends on the driving force of supersaturation.

The nucleation velocity decreases with increasing surface energy and increases with increasing temperature and degree of supersaturation. High nucleation rates offer the potential to create a large number of submicron particles in the final dispersion, as long as the growth can be seized by stabilizers. Precipitation method is used in both the chemical and pharmaceutical industries for the production of nanoparticles.[11-12] Solvent evaporation and salting out are the usual precipitation technologies, having common the drawbacks of poor control over particle morphology and particle size and size distribution producing a wide range of particle sizes.[12]

Precipitation process has also been joined with high shear processing. Precipitation of friable materials for subsequent fragmentation under conditions of high shear and/or thermal energy covered under the NANOEDGE technique a registered trademark of Baxter International Inc. and its subsidiaries.[13] It is accomplished by a combination of rapid precipitation and high-pressure homogenization. Rapid adding of a drug solution in

to an antisolvent direct to sudden supersaturation of the mixed solution, and generation of fine crystalline or amorphous solids. Precipitation of an amorphous material may be favored at high supersaturation when the solubility of the amorphous state is exceeded. It has been reported that nanosuspensions are successfully prepared by precipitation techniques.[14-17]

Advantage:

- Simple process
- Ease of scale up
- Low cost equipment

Disadvantage:

- Drug has to soluble at least in one solvent and that this solvent needs to be miscible with a non-solvent.
- Growing of drug crystals needs to be limit by surfactant addition

b) Supercritical Fluid Technology

In supercritical crystallization the supercritical fluid expands into a liquid solvent and the dissolved drug precipitates due to decompression of supercritical fluid. The particles growth in controlled by cosolvents, polymers etc.[18]

The principle is similar to that of conventional liquid antisolvent recrystallization tech. Supercritical antisolvent technologies have been performed using different process arrangements and apparatuses. The main technologies relevant to this group include rapid expansion from a liquefied-gas solution (RESS) and gas anti-solvent precipitation (GAS). The RESS process uses the high solvating power of supercritical fluids. After loading the supercritical fluid with the drug, an extremely fast phase change from the supercritical to the gas like state takes place during the expansion in the supersonic free jet. This phase change leads to high supersaturation and subsequently to particle formation. Since the solvent is a dilute gas after expansion, the RESS process offers a solvent free final product. The improvement of the bioavailability of the RESS-produced griseofulvin has been verified by dissolution experiments according to the Stricker model. The dissolution rate of griseofulvin produced by RESS is about 2-fold higher than the common micronized material.[19]

The GAS process uses high-pressure gas as an anti-solvent (gaseous antisolvent). It is typically operated as a batch process which involves the addition of CO2 to lower the solvent power of a polar liquid solvent in which the solute(s) is dissolved, thus causing the solute to precipitate or re-crystallize. It allows the unidirectional mass transfer of the CO2 diffusion into the organic phase.[20]

Advantage:

- Maximum number of compounds are soluble in SCF
- High drug solubilization

Disadvantage:

- Compound required solubility in SCF
- Not easy process

c) Emulsions and Microemulsions as Templates [21-23]

Emulsions are heterogeneous systems consisting of two immiscible liquids (i.e. organic and aqueous) in which one liquid is dispersed in the form of small droplets throughout the second liquid. Emulsions are generally classified as oil-in-water (o/w) or water-in-oil (w/o) systems, where the first component represents the dispersed phase, and another represent continuous phase. The complex systems (i.e. w/o/w, w/o/w) are feasible and called as multiple emulsion.

Microemulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids such as oil and water stabilized by an interfacial film of surfactant and co-surfactant. The drug can be either loaded into the internal phase or the pre-formed microemulsion can be saturated with the drug by intimate mixing.

Nanosuspension can produced by using emulsions as templates and is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscible solvent. There are two ways for preparation of Nanosuspension by using the emulsification technique. In the first method, an organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure so that the drug particles precipitate immediately to form a nanosuspension stabilized by surfactants. In another method partially water-miscible solvents are dispersed in the

aqueous phase to form an emulsion. Here the drug nanosuspension is obtained by just diluting the emulsion. Dilution of the emulsion with water causes complete diffusion of the disperse phase into the continuous phase, leading to immediate formation of a nanosuspension.

An example of this technique is the griseofulvin nanosuspension which is prepared by the microemulsion technique using water, butyl lactate, lecithin and the sodium salt of taurodeoxycholate.[24]

Advantage:

- High drug solubilization
- Long shelf life
- Ease of manufacture

Disadvantage:

- Use of hazardous solvent
- Use of high amount of surfactant and stabilizers

2.1.1.2 Top down Methods

a) Media Milling

Liversidge et al had developed the pearl milling method.[25] Wet milling is a particle size reduction technology whereby drug crystals are comminuted using high-shear media mills in the presence of surface stabilizer(s) and grinding media.[26-27] In this technique the drug is milled with milling media in simple glass vials to particular milling chambers for certain hours to some days and nanosuspensions are produced on a principle of high energy and shear forces generated as a result of the impaction of the milling media with the API. The zirconium oxide beads, highly cross-linked polystyrene resin beads, glass beads are used as a media. The erosion from the milling material during the milling process is a problem associated with the media milling technology is. The formation of glass microparticles was reported by Buchmann et al. when using glass as milling material.[28] In order to reduce the amount of impurities caused by an erosion of the milling media, the milling beads were coated with highly cross-linked polystyrene resin.[29] A continuous problem is the adherence of product to the large inner surface area of the milling system. The inner surface area is made up of the surface area of the chamber and

of all milling beads together. Even in recirculation systems, the product adherence causes a product loss. Of course, the undesirable drug loss can be an matter in very costly drugs. The level and variety of stabilizer are important parameters to attain nanoparticle size using this technology. It was found that higher molecular weight polymeric stabilizers were most favorable for effective particle size reduction and shelf stability. The various factors affecting the final product includes number of beads, sizes of beads, milling time, milling speed, characteristics of drug, temperature. Wyeth had launched Rapmune by using this technique as the first product containing sirolimus NanoCrystals. The coated Rapamune tablets are more convenient dosage form as compared to solution and show a 27% increased bioavailability compared to the Rapamune® solution.[30] It is a good for increasing dissolution rate by using nanonization.

Advantage:

- Ease of scale up
- Little batch to batch variation
- High flexibility in handling large quantities of drugs

Disadvantage:

- Generation of residue of milling media
- Require milling process for hours to days
- Prolonged milling may induce the formation of amorphous lead to instability

b) Dry Co-Grinding

Nanosuspensions can be obtained by dry milling techniques. Nanosuspensions are prepared by dry-grinding of poorly soluble drugs with soluble polymers and copolymers.[31-33] Polymers and co-polymers like Polyvinylpyrrolidone (PVP), sodium dodecylsulfate (SDS),polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives are used in dry co-grinding technique for preparation of nanosuspension.[34-36] Itoh et al reported the colloidal particles formation of many poorly water soluble drugs; griseofulvin, glibenclamide and nifedipine obtained by grinding with polyvinylpyrrolidone (PVP) and sodium dodecylsulfate (SDS).[37] Physicochemical properties and dissolution of poorly water soluble drugs were improved

by co-grinding because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug.[38]

Advantage:

- Easy process
- No organic solvent
- Require short grinding time

Disadvantage:

- Generation of residue of milling media

c) High-Pressure Homogenization Techniques

High pressure homogenization is mechanical technology that involves the use of high shear forces to break up particles or droplets into the nanometer range.[39-40] High-pressure homogenization was successfully employed to prepare liposomes, nanosuspensions and solid-lipid nanoparticles.[39] In high pressure homogenization the drug powder is first dispersed into an aqueous surfactant solution and passed through a homogenizer to obtain desired size range. Nanosuspensions are produced on the principle of cavitation forces, high-shear forces and the collision of the particles against each other. These cavitation forces are sufficiently high enough to cause disintegration of the suspended microparticles into nanoparticles. The particle size of the starting material for production of nanoparticulate suspensions is normally less than 100 μm in order to prevent the blockade of homogenization gap.[41] The pressures, number of cycles, concentration of drug are the factors that dictate the final product. The advantages include homogenous particle size distribution, reproducibility, lower production time, continuous production. Different methods developed based on this principle for preparation of nanosuspensions are Dissocubes, Nanopure, Nanoedge, Nanojet technology. Dissocubes developed by R.H. Müller using a piston-gap-type high pressure homogenizer has been used in the commercialization of drug nanoparticles such as Disso Cubes® owned by SkyePharma.[42] Nanopure is suspensions homogenized in water-free media or water mixtures. Nanoedge is combination of precipitation and homogenization techniques resulting in smaller particle size and better stability in a shorter time. Nanojet technology, also called as

opposite stream, uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure.

Advantage:

- General applicability to most drugs
- Useful for formation of very dilute as well as highly concen-trate nanosuspension
- Simple technique
- Aseptic production possible
- Low risk of product contamination

Disadvantage:

- High number of homogenization cycles
- Prerequisite for drug to be in micronized state and suspension formation before homogenization
- Possible contamination of product could occur from metal ions coming off from the wall of the homogenizer

2.1.2 Increasing Dissolution Velocity through Nanosization

The basic challenge faced by the researcher for the formulation of such poorly soluble drugs is the low oral bioavailability and erratic absorption of the drugs from the gastrointestinal tract due to their low saturation solubility and dissolution velocity. The low saturation solubility results in a low concentration gradient between the gut and blood vessel and leads to a limited transport of drug.[43] For poorly soluble drugs as seen in BCS Class II, the dissolution of the drugs in the gastrointestinal fluid media is the rate limiting step for the absorption of the drugs.[44] Hence for efficient absorption of drugs from the gastrointestinal tract for improving their therapeutic efficacy, there is an imminent need for studies in designing novel strategies for their dissolution enhancement. There are number of formulation approaches viz., salt formation, pH adjustment, cosolvency, complexation, etc.[45-48] used for enhancement of dissolution but none of the approach has achieved the merits of being universal. However, there are several disadvantages associated with these approaches. For example, the alteration of chemical structure by forming water-soluble derivatives often requires long processing times at a very expensive cost to derive the new chemical entities (NCEs).[49] The use of solubilizing

excipients is often limited by their toxicity. For example, the nonionic surfactant polyoxyethylated castor oil (Cremophor EL) has been shown to cause nephrotoxicity, hypersensitivity reactions and lowering of the white blood cell count (neutropenia).[50] Micronization of poorly soluble drugs has been applied for many years to improve dissolution velocity of poorly soluble drugs but reducing the drug to micron size does not increase the saturation solubility of the drug, and at such a low saturation solubility, as generally observed in BCS Class II drug, the increment in the dissolution characteristics does not help to a great extent.[51-52] Consequently off late nanonisation has been employed for treating the BCS Class II drugs. When the drug is being reduced to nanosized level there is an obvious increase in its saturation solubility (C_S) and surface area (S) assisted by improvement in the dissolution characteristics which could be attributed to the effective increase in particle surface area according to the Nernst Brunner-Noyes Whitney equation as follow.[53]

$$dm/dt = DS/h\ (C_S\text{-}C) \quad \ldots \quad \ldots \quad \ldots \quad (1)$$

Where dm/dt is the rate of dissolution, S is the surface area, D is the diffusion coefficient, Cs is the apparent solubility of the drug in the dissolution medium, C is the solubility of the drug at time t, and h is the boundary layer thickness. The surface area can primarily be increased by reducing the particle size or increasing the porosity of the particles or a combination of both factors.

Classically saturation solubility in a given solvent is defined as a compound-specific constant depending only on the temperature however the saturation solubility is also a function of the crystalline structure (i.e. lattice energy) and particle size. In general, solubility is best for the polymorphic modification that is characterized by highest energy and lowest melting point. In addition to the dissolution rate enhancement described above, the reason why saturation solubility is also a function of particle size and an increase in the saturation solubility of the nanosized drug is also expected[54] as described by the Freundlich– Ostwald equation:

$$S = S_\infty \ \exp\left(\frac{2\gamma M}{r\rho RT}\right) \quad \ldots \quad \ldots \quad \ldots \quad (2)$$

where S=saturation solubility of the nanosized drug, S_∞=saturation solubility of an infinitely large crystal, . γ is the crystal-medium interfacial tension, M is the compound

molecular weight, r is the particle radius, . ρ is the density, R is a gas constant and T is the temperature. The increase in surface wetting by the surfactants in the nanosuspension formulations also results in a further enhancement of the dissolution rates compared to micronized suspensions.

2.1.3 Evaluation Parameters of Nanosuspensions

The following are the essential evaluation parameters for nanocrystal suspensions.

2.1.3.1 Shape, Size and Size Distribution

Structural characteristic like size, size distribution, shape, surface morphology, etc are the parameter that plays important role in determining various attributes of a nanosystem. Transmission electron microscope (TEM) and/or a scanning electron microscope (SEM) are the technique which are used for determination of shape of nanosuspension.[55] Size and size distribution are the mainly important parameter in the evaluation of the suspensions as it is having the direct effects on saturation solubility and dissolution velocity, physical stability of drugs. Photon Correlation Spectroscopy (PCS) is used for determination of the mean particle size and the width of particle size distribution i.e. polydispersity index (PI).[56] PI governs the physical stability of nanosuspension and should be as low as possible for long-term stability (Should be close to zero). A PI value of 0.1–0.25 indicates a fairly narrow size distribution whereas a PI value greater than 0.5 indicates a very broad distribution. However, due to a narrow measuring range of PCS, approximately from 3 nm to 3 μm, laser diffractometry (LD) is needed to study the content of particles in the micrometer range of approximately 0.05–80 μm up to a maximum of 2000 μm, depending on the type of equipment used.

2.1.3.2 Particle Charge (Zeta Potential)

The particle charge is one of importance parameter in the study of the stability of the nanosuspensions. Zeta potential is used for determination the charge at particle surface. Particle charge is measured by electrophoresis and expressed as electrophoretic mobility [(μm/S) /(V/cm)] or converted to the zeta potential (mV). Generally the zeta potential of more than ±40mV will be considered to be required for the stabilisation of the dispersions. Minimum ±30mV zeta potential is required for electrostatically stable

suspension and in case of combined steric and electrostatic stabilization it should be a minimum of ±20mV of zeta potential is required.[57]

2.1.3.3 Crystalline Status

The evaluation of crystalline state is essential in case of drug having different polymorphic forms. When nanosuspensions are prepared drug particles may get converted to amorphous form hence it is necessary to measure the extent of amorphous drug generated during the manufacturing of nanosuspensions. The drug nanosuspension can evaluated for crystallinity usion Differential scanning calorimetry (DSC) and X-ray diffraction.[58]

2.1.3.4 Dissolution Velocity and Saturation Solubility

The enhancements of saturation solubility as well as dissolution velocity are the main advantage associated with the nanosuspensions. Measurement of the saturation solubility and dissolution velocity are very significant parameter which help to measure the benefits compared to the conventional or microparticle formulation. Dissolution velocity is measured by the method given in pharmacopoeia. Saturation solubility is measured by shaking the drug in different solvent at different temperature up to equilibrium. Kelvin equation and the Ostwald-Freundlich equations can explain increase in saturation solubility.[59]

2.1.3.5 Stability of Nanosuspensions

Stability of the suspensions is dependent on the particle size. As the particle size reduces to the nanosize the surface energy of the particles will be increased and they tend to agglomerate. Therefore stabilizers are used which will reduce the chances of Ostwald ripening and improving the stability of the suspension by providing a steric or ionic barrier.

2.1.3.6 In *vivo* Evaluation

The in *vivo* evaluation of the nanosuspensions is specific to drug and route of administration. Usually the formulation was given by required route of administration

and the plasma drug levels were estimated using HPLC-UV visible Spectrophotometry. Other such parameters like surface hydrophilicity/hydrophobicity (determines interaction with cells prior to phagocytosis), adhesion properties, interaction with body proteins etc are also evaluated in vivo.

2.1.3.4 In *vitro* Drug Release

The drug dissolution testing is routinely used to get critical in *vitro* drug release information. The dissolution of most commonly dosage form performed using USP dissolution apparatus I/II and drug release is estimated using HPLC-UV visible Spectrophotometry.

2.1.4 Application

The saturable solubility, dissolution velosity and bioavailability of the drug are increased by formulating the drug as nanosuspensions. From the formulation view point, nanosuspensions having almost all the needs of an ideal drug delivery system for the parenteral route. The nanosuspensions are having application in different routes of administrations like oral, parenteral, topical, ophthalmic, mucoadhesive, pulmonary and targeted drug delivery. The administration of nanosuspensions is a drug delivery approach, not only to improve bioavailability, but also to reduce the sum of those drugs used, to localize the release of potent compounds and, therefore, to decrease side effects.

2.1.4.1 Application for Oral Delivery

The oral route is the primary choice for drug delivery because of its abundant advantages, such as safety, Patient convenience, etc. At present, most nanosuspension products on the market are for oral delivery.[55] The increased dissolution velocity and saturation solubility lead to fast and complete drug dissolution, an important prerequisite for drug absorption. The formulation of drug nanocrystals can impressively improve the bioavailability of perorally administered poorly soluble drugs. So, nanosuspension mostly associated with delivery of poorly water-soluble drugs regarding low oral bioavailability, high intersubject variability and poor or suboptimal therapeutic response. It was reported that these formulation enhance the bilavailability of different class of drufs, like

antihypertensives,[60-61] anti-cancer drugs,[62-63] anticoagulants,[64] antibiotics,[65] and hormones.[66-68]

Liversidge and Cundy have studied an increase in bioavailability for the drug Danazol from 5.1 ± 1.9% for the conventional suspension to 82.3 ± 10.1% for the nanosuspension.[67] In case of rapid onset of a poorly soluble drug, the formulation of drug nanocrystals can be beneficial, for example, in case of analgesics. The analgesic naproxen, formulated as a nanosuspension, has shown a reduced tmax but simultaneously approximately threefold increased AUC in comparison to a normal suspension (Naprosyn®).[69] Besides the faster onset of action, the naproxen nanosuspension has also shown a reduced gastric irritancy.[70-71]

Another most important advantage of drug nanocrystals is their adhesiveness and the increased residence time, which can absolutely enhance the bioavailability. The mucoadhesiveness can be raised by the use of mucoadhesive polymers during the preparation of nanosuspension.[72-73] Sometimes the utilized mucoadhesive polymers can prevent the drug from degradation since it degreded. Muller et al the use of mucoadhesive nanosuspensions as layering dispersions for preparation of multiparticulate drug delivery systems was investigated. A ketoprofen nanosuspension has been successfully incorporated into pellts to release drug over a period of 24 hrs.[74] O.kayser prepared bupravaquone mucoadhesive nanosuspensions, a potential drug delivery system for poorly soluble drugs has been investigated to overcome bioavailability problems caused by the pathophysiological diarrhoeic situation in patients suffering from cryptosporidiosis.

2.1.4.2 Parenteral Drug Delivery

Parenteral administration of drugs by injection is the ordinary route of administration to achieve rapid therapeutic drug levels for the treatment of acute treatment.[75] The current approaches for parenteral delivery include salt formation, solubilization using co-solvents, micellar solutions, complexation with cyclodextrin and recently liposomes. However, there are limitations on the use of these approaches because of the limitations on their solubilization capacity, large injection volumes or toxic side effects and parenteral acceptability. Nanosuspensions would be able to solve the problems mentioned

above. In addition, nanosuspensions have been found to increase the efficacy of parenterally administered drugs. Because of their small size below 1 μm, nanoparticles favour the passage of the drug particles into the small capillaries in the body without any blockade.[75-76] They can be injected either intravenously, intramuscularly or subcutaneously or direct injection into solid tissues or organs. Intraperitonal administration can be used for local treatment or to obtain a depot with prolonged release into the blood. Nanoparticles has higher intracellular uptake, which makes nanoparticles potential candidates for delivering drug to infected macrophages for effective microbial killing.[77-78] Infections like tuberculosis, listeriosis, leishmaniasis, and toxoplasmosis are caused by parasites residing the macrophages of the MPS, thus being relatively easily accessible by I.V. injected particles. The I.V. injected particles are heavily and quickly taken up by the MPS cells in case they absorb uptake promoting proteins like apolipoproteins. Another therapeutic targets include local inflammations, e.g. in joints. For instance, arthritic joint inflammations are caused by secretion products of activated macrophages. An interesting approach is therefore the administration of a corticoid nanosuspension directly into the joints. Administration of nanosuspsensions into body cavities is also of great interest, e.g. to increase the tolerability of the drug, to achieve a local treatment or to have a depot with slow release (e.g. into the blood). A stable intravenously injectable formulation of omeprazole has been prepared by Moschwitzer & co workers to prevent the degradation of orally administered omeprazole.[79] Moschwitzer & co workers stated that even after 1 month of production, no discoloration or recognizable drug loss was observed.

2.1.4.3 Pulmonary Drug Delivery

The pulmonary route has been used since decades to administer drug to the lung for the local or systemic treatment of diseases.[80] Pulmonary administration of drugs can give more rapidly onset of action and higher systemic bioavailability than other noninvasive routes because of the large surface area with highly vascularized regions and relatively low drug-metabolizing enzyme activity in the lung.[81] The pulmonary route is not subject to first pass metabolism, so it is especially useful for many drugs which undergo extensive metabolism in liver. The first commercial pulmonary formulation of rapid-

acting insulin (Exubera®) is now approved by the FDA. It is manufactured by Pfizer using Nektar Therapeutics proprietary inhalation technology. Inhaled insulin enters the blood circulation more rapidly than by subcutaneous injection while increasing patient compliance.[82] Aqueous suspensions of the drug can be easily nebulised and given by pulmonary route as the particle size is very less for lung as well as respiratory track delivery. Disposition in the lungs can be controlled via the size distribution of the generated aerosol droplets. Compared with microcrystals, the drug is more evenly distributed in the droplets when using a nanosuspension. The number of crystals are higher, consequently, the possibility that one or more drug crystals are present in each droplet is higher. Besides this, drug nanocrystals show an increased mucoadhesiveness, leading to a prolonged residence time at the mucosal surface of the lung.[83] Different types of nebulisers are available for the administration of liquid formulations. Some of the drugs successfully tried with pulmonary route are budesonide, ketotifen, ibuprofen, indomethacin, nifedipine, itraconazole, interleukin-2, p53 gene, leuprolide, doxorubicin etc.[84] Claudia Jacobs et al studied budenoside nanosuspension by highpressure homogenization and obtained mean particle size of about 500-600nm, showed a long-term stability; no aggregates and particle growth occurred over the examined period of 1 year.[85]

2.1.4.4 Brain Drug Delivery

The administration of drugs to the central nervous system (CNS) is a major challenge because most of the drugs have great difficulty crossing the blood–brain barrier (BBB). The blood brain barrier is a complex structure composed of endothelial cells connected by highly restrictive tight junctions.[86] This unique structure protects the brain against peripheral neurotransmitters, cytotoxins and microorganisms. However, it also restricts the passage of potential drugs for the treatment of neurological or psychiatric disorders, and of other brain pathologies (such as infections and tumors).Some parasites do also reside in the brain (CNS). The brain-localized parasite mostly leads to relapsing infections if not cured. Therefore, it would be of importance to target drug nanoparticles via surface modification to the brain. A successful targeting of the peptide, dalargin, to

the brain using Tween 80® surface modified polyisobutylcyanoacrylates nanoparticles has been reported.[87]

2.1.4.5 Targeted Drug Delivery

Most drugs currently used in pharmaceutical industry are delivered in a non-specific manner throughout the whole body, rather than directly to the site of action where they are needed. This may result in unintentional side effects or toxicity in other tissues. Drugs used in cancer therapy represent an excellent example of the same. Utilization of nanosuspension represents a potential opportunity in the field of drug targeting. Nanosuspension can be used for targeted deliver as their surface properties & changing of the stabilizer can easily alter in vivo behaviour. The engineering of stealth nanosuspensions by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems. The surface of nanoparticle alternatively can be coated which phagocytes will recognize as "self" to improve biological uptake.[88] Aphidicolin nanosuspension was reported to improve the drug targeting effect against Leishmania-infected macrophages that aphidicolin was highly active at a concentration in the microgram range.[89] Targeting of Cryptosporidium parvum, the organism responsible for cryptosporidiosis was achieved by using surface modified mucoadhesive nanosuspensions of bupravaquone.[90]

2.1.4.6 Topical Drug Delivery

Topical drug delivery of nanosuspensions is mainly of interest if conventional formulation approaches can not give good results. Drug nanosuspension can be incorporated into creams and water-free ointments. The nanocrystalline form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin.[91] The use of drug nanocrystals leads to an increased concentration gradient between the dosage form and the skin. This effect can further be enhanced by the use of positively charged polymers as stabilizers for the drug nanocrystals.

2.1.4.7 Ophthalmic Drug Delivery

Nanosuspensions may also beneficial in ocular drug delivery for drugs that shows poor solubility in lachrymal fluids. Nanoparticles possess a prolonged retention time in the eye, most likely due to their adhesive properties, which is desirable for most ocular diseases for effective treatment. Generally ophthalmic preparation has dropable dosage form, so it must required the formulation contain high amount of drug as well as retain higher time in eye. Polymeric nanosuspension of Ibuprofen was reported for ophthalmic drug delivery.[92] In vitro dissolution tests indicated a controlled release profile of Ibuprofen from nanoparticles and in vivo study showed, an inhibition of the miotic response to the surgical trauma was achieved, compared to a control aqueous eye-drop formulation, on the rabbit eye after induction of an ocular trauma (paracentesis). Drug levels in the aqueous humour were also high after use of the nanosuspensions. In addition, Ibuprofen nanosuspensions did not show toxicity on ocular tissues. It was also reported that nanosuspensions of glucocorticoid drugs; hydrocortisone, prednisolone and dexamethasone enhance rate, drug absorption and increase the extent of drug action.[93]

2.2 Introduction to Drugs[94-100]

2.2.1 Introduction to Nifedipine

2.2.1.1 Category

A potent vasodilator agent with calcium antagonistic action. It is a useful anti-anginal agent that also lowers blood pressure.

2.2.1.2 Class

BCS Class II (Low solubility – High Absorption)

2.2.1.3 Chemical IUPAC Name and Formula

dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate ($C_{17}H_{18}N_2O_6$)

2.2.1.4 Chemical structure

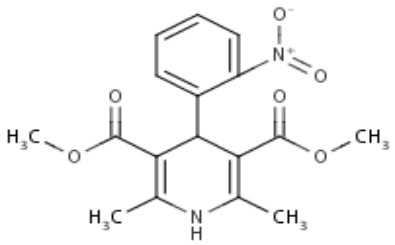

Figure 2.1 Nifedipine

2.2.1.5 Molecular weight

346.335 gm/mol

2.2.1.6 Solubility

1.77e-02 mg/mL (Sparingly Soluble in water)

2.2.1.7 Melting point

172 - 174 °C

2.2.1.8 Partition co-efficient (log P)

2.49

2.2.1.9 Indication

For the management of vasospastic angina, chronic stable angina and hypertension.

2.2.1.10 Pharmacology

Nifedipine, the prototype of the dihydropyridine class of calcium-channel antagonists, is similar to other dihydropyridines including amlodipine, felodipine, isradipine, and nicardipine. Nifedipine is used to treat Prinzmetal's angina, hypertension, and other vascular disorders such as Raynaud's phenomenon. By blocking the calcium channels, Nifedipine inhibits the spasm of the coronary artery and dilates the systemic arteries, results in a increase of myocardial oxygen supply and a decrease in systemic blood pressure.

2.2.1.11 Mechanism of action

Nifedipine inhibits the influx of extracellular calcium through myocardial and vascular membrane pores by physically plugging the channel. The decrease in intracellular calcium inhibits the contractile processes of smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.

2.2.1.12 Absorption

Rapidly and fully absorbed following oral administration.

2.2.1.13 Toxicity

Symptoms of overdose include dizziness, drowsiness, and nausea, severe drop in blood pressure, slurred speech, and weakness. LD_{50}=494 mg/kg (orally in mice); LD_{50}=1022 mg/kg (orally in rats)

2.2.1.14 Protein binding

92-98%

2.2.1.15 Biotransformation

Gastro retentive, Hepatic.

2.2.1.16 Half-life

2 - 4 hours

2.2.1.17 Food interactions

- Avoid alcohol.
- Avoid taking with grapefruit juice.
- Avoid natural licorice.
- Take with low fat meal.

2.2.2 Introduction to Nimodipine

2.2.2.1 Category

A potent vasodilator agent with calcium antagonistic action. can be used for the prevention and treatment of ischemic neurological deficits.

2.2.2.2 Class

BCS Class II (Low solubility – High Absorption)

2.2.2.3 Chemical IUPAC Name and Formula

3-(2-methoxyethyl) 5-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate ($C_{21}H_{26}N_2O_7$)

2.2.2.4 Chemical structure

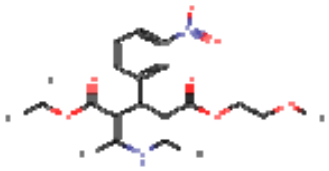

Figure 2.2 Nimodipine

2.2.2.5 Molecular weight

418.44 gm/mol

2.2.2.6 Solubility

1.20e-02 mg/mL (Sparingly Soluble in water)

2.2.2.7 Melting point

125 °C

2.2.2.8 Partition co-efficient (log P)

2.7

2.2.2.9 Indication

Therapeutic use is the prevention and treatment of delayed ischemic neurological disorders, which often occur in patients with subarachnoid hemorrhages.

2.2.2.10 Pharmacology

Nimodipine, the prototype of the dihydropyridine class of calcium-channel antagonists, is similar to other dihydropyridines including amlodipine, felodipine, isradipine, and nicardipine. Nimodipine is used to treat hypertension, and other vascular disorders such as multi-infarct dementia and ischemic neurological disorders.

2.2.2.11 Mechanism of action

Although the precise mechanism of action is not known, nimodipine blocks intracellular influx of calcium through voltage-dependent and receptor-operated slow calcium channels across the membranes of myocardial, vascular smooth muscle, and neuronal cells. Nimodipine binds specifically to L-type voltage-gated calcium channels. The inhibition of calcium ion transfer results in the inhibition of vascular smooth muscle contraction. Evidence suggests that the dilation of small cerebral resistance vessels, with a resultant increase in collateral circulation, and/or a direct effect involving the prevention of calcium overload in neurons may be responsible for nimodipine's clinical effect in patients with subarachnoid hemorrhage.

2.2.2.12 Absorption

Bioavailability is 3-30% following oral administration due to extensive first-pass metabolism.

2.2.2.13 Toxicity

Symptoms of overdosage would be expected to be related to cardiovascular effects such as excessive peripheral vasodilation with marked systemic hypotension.

2.2.2.14 Protein binding

95%

2.2.2.15 Biotransformation

Hepatic

2.2.2.16 Half-life

1.7-9 hours

2.2.2.17 Food interactions:

- Grapefruit down regulates post-translational expression of CYP3A4, the major metabolizing enzyme of nimodipine. Grapefruit, in all forms (e.g. whole fruit, juice and rind), can significantly increase serum levels of nimodipine and may cause toxicity. Avoid grapefruit products while on this medication.
- Take at the same time each day, with or without food, but always in the same manner.

2.2.3 Introduction to Nitrendipine

2.2.3.1 Category

A calcium channel blocker with marked vasodilator action. It is an effective antihypertensive agent and differs from other calcium channel blockers in that it does not reduce glomerular filtration rate and is mildly natriuretic, rather than sodium retentive. A potent vasodilator agent with calcium antagonistic action can be used treatment of systemic hypertension.

2.2.3.2 Class

BCS Class II (Low solubility – High Absorption)

2.2.3.3 Chemical IUPAC Name and Formula

3-ethyl 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate ($C_{18}H_{20}N_2O_6$)

2.2.3.4 Chemical structure

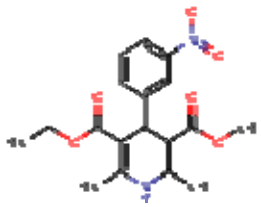

Figure 2.3 Nitrendipine

2.2.3.5 Molecular weight

360.36 gm/mol

2.2.3.6 Solubility

Insoluble

2.2.3.7 Melting point

156 - 160 °C

2.2.3.8 Partition co-efficient (log P)

2.4

2.2.3.9 Indication

Therapeutic use is the prevention and treatment of delayed ischemic neurological disorders, which often occur in patients with subarachnoid hemorrhages.

2.2.3.10 Pharmacology

Nitrendipine, the prototype of the dihydropyridine class of calcium-channel antagonists, is similar to other dihydropyridines including amlodipine, felodipine, isradipine, and nicardipine. Nitrendipine is used to treat angina pectoris and systemic hypertension.

2.2.3.11 Mechanism of action

By deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum, Nitrendipine inhibits the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.

2.2.3.12 Absorption

Well absorbed from the GI tract (oral).

2.2.3.13 Toxicity

Symptoms of overdose include Flushing, headache, BP reduction with circulatory collapse, changes in heart rate (tachycardia, bradycardia).

2.2.3.14 Protein binding

> 99%

2.2.3.15 Biotransformation

Extensive first-pass effect

2.2.3.16 Half-life

10 - 22 hours

2.2.3.17 Food interactions

Concentration may be increased with grapefruit juice.

2.3 Introduction to Polymer & Excipients [101]

2.3.1 Introduction to Hypromellose

2.3.1.1. Non proprietary name

BP	:	Hypromellose
JP	:	Hydroxyl propyl methyl cellulose
PhEur	:	Hypromellosum
USP NF	:	Hypromellose

2.3.1.2. Description

Odorless, tasteless, white to creamy white fibrous and granule powder.

2.3.1.3. Chemical name

cellulose, 2- hydroxypropyl methyl ether

2.3.1.4. Structural formula

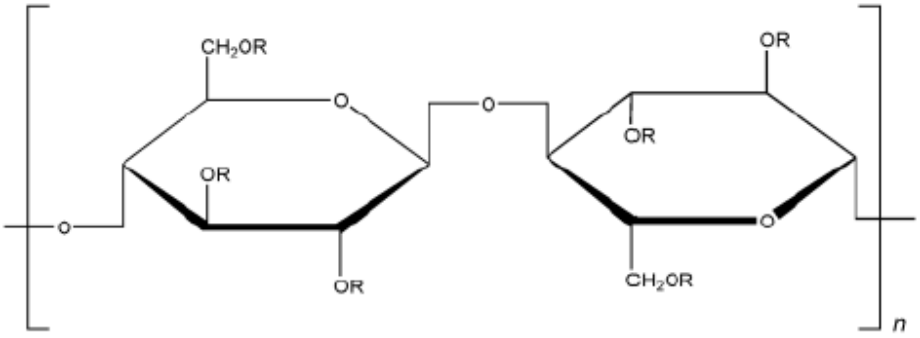

Figure 2.4 Hypromellose

2.3.1.5. Molecular weight

10, 000 to 15, 00, 000

2.3.1.6. Functional categories

Coating agent, film former, rate controlling polymer for sustained release, stabilizer, suspending agent, tablet binder, viscosity-increasing agents.

2.3.1.7. Application in pharmaceutical formulations

Used in topical and oral formulation.

Primarily used as

- Binder (2-5%),
- In film coating (2- 20%),
- In extend release matrix (10-80%).
- As thickening agent (0.45-1%) in eye drops.

2.3.1.8. Typical properties

pH	:	5.5 - 8 (1% aqueous solution at 25 °C)
Bulk density	:	0.341 gm/ml
Tapped density	:	0.557 gm/ml
Moisture content	:	5-10%
Melting point	:	190-2000C
Solubility	:	Soluble in cold water, forming a viscous colloidal solution. Practically insoluble in chloroform, ethanol, and ether. But soluble in mixture of ethanol and dichloromethane, and mixture of water and alcohol.

2.3.1.9. Stability and storage condition

It is stable, although it is hygroscopic after drying. But it should be Store in well closed container in cool and dry place. Solution are stable at pH 3-11.increase the temp reduce the viscosity. it undergoes sol-gel transformation on heating and cooling. The gel point is 50-90.

2.3.1.10. Incompatibilities

Incompatible with oxidizing agent.

2.3.2 Introduction to Hydroxypropyl cellulose

2.3.2.1. Non proprietary name

BP	:	Hydroxypropylcellulose
JP	:	Hydroxypropylcellulose
PhEur	:	Hydroxypropylcellulosum
USP NF	:	Hydroxypropyl cellulose

2.3.2.2. Description

Odorless, tasteless, white fibrous and granule powder.

2.3.2.3. Chemical name

Cellulose, 2-hydroxypropyl ether

2.3.2.4. Structural formula

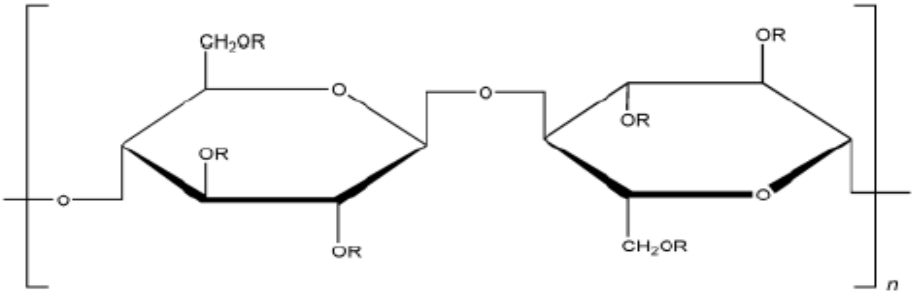

Figure 2.5 Hydroxypropyl cellulose

2.3.2.5. Molecular weight

Variable

2.3.2.6. Functional categories

Coating agent, film former, rate controlling polymer for sustained release, stabilizer, suspending agent, tablet binder, viscosity-increasing agents.

2.3.2.7. Application in pharmaceutical formulations

Used in topical and oral formulation.

Primarily used as

- Binder (2-5%),
- In film coating (2- 20%),
- In extend release matrix (10-80%).
- As thickening agent (0.45-1%) in eye drops.

2.3.2.8. Typical properties

pH	:	5.5 - 8 (1% aqueous solution at 25 °C)
Bulk density	:	0.33 gm/ml
Tapped density	:	0.567 gm/ml
Moisture content	:	5-10%
Melting point	:	190-200^{0}C
Solubility	:	Not soluble in water, Swells in water.

2.3.2.9. Stability and storage condition

It is stable, although it is hygroscopic after drying. But it should be Store in well closed container in cool and dry place. Solution is stable at pH 3-11. It undergoes sol-gel transformation on heating and cooling. The gel point is 50-90.

2.3.2.10. Incompatibilities

Incompatible with oxidizing agent.

2.3.3 Introduction to Polyethylene glycol 6000

Poly ethylene glycols (PEGs) are family of water-soluble linear polymers formed by the additional reaction of ethylene oxide (EO) with mono ethylene glycols (MEG) or diethylene glycol.There are many grades of PEGs that represents them by theirs average molecular weight. Polyethylene glycols are available in average molecular weight ranging from 200 to 8000; this wide range of products provides flexibility in choosing properties to meet the requirements of many different applications. PEGs have low volatility and are thermally stable for limited period of time below 300°C and without O_2. Polyglycols are not volatile, which is a considerable advantage in view of their applications as plasticizers and humectants. When they are heated to temperatures exceeding 150°C, the resulting weight losses are not due to evaporation, but rather to release of volatile decomposition products. Thermal decomposition of polyglycols results neither in hard encrustations nor to deposit of viscous sludge. The decomposition products of polyglycols vary according to air exposure. In addition to water, carbon dioxide and aldehydes, simple alcohols, acids and glycol esters also form. When handling polyglycols at temperatures above 100°C, we recommend the addition of suitable oxidation stabilizers. The type and amount of stabilizer required depend on what is expected from the PEG. Substances have proved useful as antioxidants are polymeric tri methyl dihydroquinoline, diphenylamine derivative, phenothiazine, phenyl-alpha naphthylamine, 4, 4' methylene-bis-2, 6-di-tert-butylphenol, Butylated hydroxyanisole, methoxyphenol (hydroxyanisole).

2.3.3.1 Nonproprietary Names

BP: Macrogols

JP: Macrogol 400

PhEur: Macrogola

USPNF: Polyethylene glycol

2.3.3.2. Description

Depending on their average molecular weights, the poly ethylene glycols may be liquid or solid at standard condition.

PEG grades: 200,300,400,600 in liquid form,

PEG 1000, 1500 soft solid (white) and

PEG 2000, 3000,4000,6000,8000 hard solid (white)

2.3.3.3. Chemical name

α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl)

2.3.3.4. Structural formula

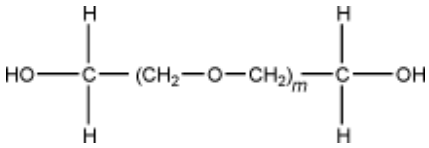

Figure 2.6 Poly ethylene glycol

2.3.3.5. Molecular weight

$HOCH_2(CH_2OCH_2)_mCH_2OH$ where *m* represents the average number of oxyethylene groups. Alternatively, the general formula $H(OCH_2CH_2)_nOH$ may be used to represent polyethylene glycol, where *n* is a number *m* in the previous formula + 1.

2.3.3.6. Functional categories

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

2.3.3.7. Application in pharmaceutical formulations

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems (Price, 2003). In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules. However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5% w/w. When used for thermoplastic granulations, a mixture of the powdered constituents with 10–15% w/w PEG 6000 is heated to 70–75°C. The mass becomes paste like and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as

lozenges when prolonged disintegration is required. Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol. Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps.

In film coatings, solid grades of polyethylene glycol can be used alone for the film-coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers. Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate, and stickiness may develop if the material becomes too warm during compression. An antiadherent effect is also exerted, again subject to the avoidance of overheating.

Polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents. It has also been used in insulin-loaded microparticles for the oral delivery of insulin; it has been used in inhalation preparations to improve aerosolization; polyethylene glycol nanoparticles have been used to improve the oral bioavailability of cyclosporine; it has been used in self-assembled polymeric nanoparticles as a drug carrier; and copolymer networks of polyethylene glycol grafted with poly(methacrylic acid) have been used as bioadhesive controlled drug delivery formulations.

2.3.3.8. Typical properties

Pharmaceutical specification of PEG 6000

pH	:	4.5 – 7.5 (5% aqueous solution)
Density	:	1.080 g/cm^3
Hydroxyl value	:	16-22
Freezing point	:	56-61^{0}C
Melting point	:	55-63^{0}C
Viscosity (dynamic)	:	200–270 mPa s (cP)

Solubility : All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

2.3.3.9. Stability and storage condition

Under dry conditions and at room temperature in sealed containers.

2.3.3.10. Incompatibilities

Glycols are not compatible with Penicillin, Bicitracine, Iodine, Potassium Iodide, Sorbitol, Tannic Acid, Bismuth salts. Glycols are also not suitable with Polyethylene, Bakelite & celluloid.

2.3.4 Introduction to Polyvinyl alcohol

23.4.1. Non proprietary name

PhEur : Poly(vinylis acetas)

USP NF : Polyvinyl alcohol

2.3.4.2. Description

Odorless, white to cream-colored granular powder..

2.3.4.3. Chemical name

Ethenol, homopolymer

2.3.4.4. Structural formula

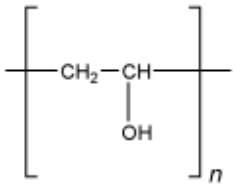

Figure 2.7 Polyvinyl alcohol

2.3.4.5. Molecular weight

20, 000 to 2, 00, 000

2.3.4.6. Functional categories

Coating agent; lubricant; stabilizing agent; viscosity-increasing agent.

2.3.4.7. Application in pharmaceutical formulations

Polyvinyl alcohol is used primarily in topical pharmaceutical and ophthalmic formulations.

Primarily used in

- Emulsions (0.5%),
- Ophthalmic formulations (0.25-3%).
- Topical lotions (2.5%).

It is used as a stabilizing agent for emulsions (0.25–3.0% w/v). Polyvinyl alcohol is also used as a viscosity-increasing agent for viscous formulations such as ophthalmic products. It is used in artificial tears and contact lens solutions for lubrication purposes, in sustained-release formulations for oral administration, and in transdermal patches. Polyvinyl alcohol may be made into microspheres when mixed with a glutaraldehyde solution.

2.3.4.8. Typical properties

Specific gravity	:	1.19–1.31 for solid at 25°C
Refractive index	:	1.49–1.53
Specific heat	:	1.67 J/g (0.4 cal/g)
Melting point	:	228°C for fully hydrolyzed grades
Solubility	:	soluble in water; slightly soluble in ethanol (95%); insoluble in organic solvents.

2.3.4.9. Stability and storage condition

Polyvinyl alcohol is stable when stored in a tightly sealed container in a cool, dry place. Aqueous solutions are stable in corrosion-resistant sealed containers. Preservatives may be added to the solution if extended storage is required. Polyvinyl alcohol undergoes slow degradation at 100°C and rapid degradation at 200°C; it is stable on exposure to light.

2.3.4.10. Incompatibilities

Polyvinyl alcohol undergoes reactions typical of a compound with secondary hydroxy groups, such as esterification. It decomposes in strong acids, and softens or dissolves in weak acids and alkalis. It is incompatible at high concentration with inorganic salts, especially sulfates and phosphates; precipitation of polyvinyl alcohol 5% w/v can be caused by phosphates. Gelling of polyvinyl alcohol solution may occur if borax is present.

2.3.5 Introduction to PVP-K 30

PVP exists as powder or aqueous solution. It can dissolve in water and variety of organic solvent. It is generally used in cosmetics, surfactants, pharmaceutical industry and other related industrial fields.

2.3.5.1. Non proprietary name

BP	:	Povidone
JP	:	Povidone
PhEur	:	Povidonum
USP NF	:	Povidone

2.3.5.2. Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder

2.3.5.3. Chemical name

1-Ethenyl-2-pyrrolidinone homopolymer

2.3.5.4. Structural formula

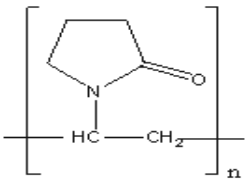

Figure 2.8 PVP-K 30

2.3.5.5. Molecular weight

35,000-51,000

1.3.5.6. Functional categories

Disintegrant; dissolution aid; suspending agent; tablet binder.

2.3.5.7. Application in pharmaceutical formulations

PVP K series can be used as film forming agent, viscosity-enhancement agent, lubricator and adhesive. They are the key component of hair sprays, mousse, gels and lotions & solution. They are also convenience assistant in skin care product, hair-drying reagent, shampoo, eye makeup, lipstick, deodorant, sunscreen and dentifrice.

(a) Pharmaceutical

PVP K 30 is new and excellent pharmaceutical excipients. It is mainly used as binder for tablet, dissolving assistant for injection, flow assistant for capsule, dispersant for liquid medicine and pigment, stabilizer for enzyme and heat sensitive drug, co precipitant for poorly soluble drugs, lubricator and antitoxical assistant of eye drug. PVP has been used as excipients in more than one hundred drugs.

(b) Other utility

Disperser and emulsifier, Paint & coating, Film, Tabletting, Glass fiber, Plastics & resin, Detergent, Ink, Textile dying & printing, Adhesive, TV tube.

2.3.5.8. Typical properties

pH	:	3 - 7 (5% aqueous solution at 25 °C)
Bulk density	:	0.29-0.39 gm/cm^3
Tapped density	:	0.39-0.54 gm/ cm^3
Melting point	:	Soften at 150°C
Solubility	:	Soluble in water (>100 mg/ml), methanol, ethanol, alcohol, chloroform and glycerol, acetic acid, insoluble in dimethyl ether, ethyl acetate, acetone, toluene, xylene, mineral oil, carbon tetrachloride.

2.3.5.9. Stability and storage condition

It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties. Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

2.3.5.10. Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds. The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

2.3.6 Introduction to Polysorbate 80

2.3.6.1. Nonproprietary Names

BP : Polysorbate 20, Polysorbate 40, Polysorbate 60,Polysorbate 80

PhEur : Polysorbatum 20, Polysorbatum 40, Polysorbatum 60, Polysorbatum 80

JP : Polysorbate 80

USPNF : Polysorbate 20, Polysorbate 40, Polysorbate 60, and Polysorbate 80

2.3.6.2. Synonyms

Polyoxyethylene (20) sorbitan monooleate, (x)-sorbitan mono-9-octadecenoate poly(oxy-1,2-ethanediyl), Alkest TW 80, Tween 80, POE (20) sorbitan monooleate

2.3.6.3. Structural Formula

Figure 2.9 Polysorbate 80

2.3.6.4. Chemical name

Polyoxyethylene (20) sorbitan monooleate

2.3.6.5. Empirical formula

$C_{64}H_{124}O_{26}$

2.3.6.6. Functional Category

Nonionic surfactant and emulsifier

2.3.6.7. Applications in Pharmaceutical Formulation or Technology

Polysorbate 80 is an excipient that is used to stabilize aqueous formulations of medications for parenteral administration, and used as an emulsifier

2.3.6.8. Typical properties

pH	:	5.5 - 8 (1% aqueous solution at 25 °C)
Density	:	1.06-1.09 gm/ml
Viscosity @250C	:	300-500 centistokes
Melting point	:	190-2000C
Solubility	:	Very soluble in water

2.3.6.9. Stability and Storage condition

It should be stored in container in a cool, dry place

2.3.6.10. Incompatibilities

Polysorbate 80 is compatible with most organic and inorganic.

2.3.7 Introduction to Sodium lauryl sulfate

2.3.7.1. Nonproprietary Names

BP	:	Sodium lauryl sulfate
JP	:	Sodium lauryl sulfate
PhEur	:	Natrii laurilsulfas
USPNF	:	Sodium lauryl sulfate

2.3.7.2. Synonyms

Sodium monododecyl sulfate; Sodium lauryl sulfate; Sodium monolauryl sulfate; Sodium dodecanesulfate; dodecyl alcohol, hydrogen sulfate, sodium salt; n-dodecyl sulfate sodium; Sulfuric acid monododecyl ester sodium salt;

2.3.7.3. Structural Formula

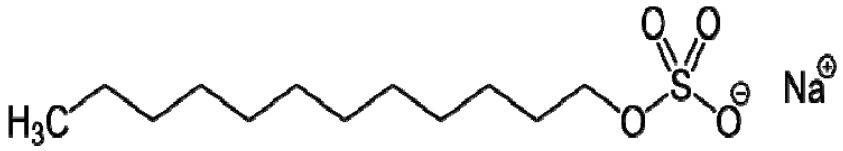

Figure 2.10 Sodium lauryl sulfate

2.3.7.4. Chemical name

Sodium lauryl sulfate

2.3.7.5. Empirical formula

$NaC_{12}H_{25}SO_4$

2.3.7.6. Functional Category

Surfactant

2.3.7.7. Applications in Pharmaceutical Formulation or Technology

SDS is mainly used in detergents for laundry and many cleaning applications. SDS is a highly effective surfactant and is used in any task requiring the removal of oily stains and residues. For example, it is found in higher concentrations with industrial products

including engine degreasers, floor cleaners, and car wash soaps. It is found in toothpastes, shampoos, shaving foams, and bubble bath formulations in part for its thickening effect and its ability to create a lather.

2.3.7.8. Typical properties

Density	:	1.01 gm/ml
Melting point	:	2060C

2.3.7.9. Stability and Storage condition

It should be stored in container in a cool, dry place

2.3.7.10. Incompatibilities

SLS is compatible with most organic and inorganic pharmaceutical ingredients.

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