REVIEW PAPER

A Review on Nanonisation Techniques for Bioavailability Enhancement of Poorly Water-Soluble Drugs

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ABSTRACT

Of the medicines analysed, 60% possess minimal solubility. One of the main obstacles to the development of these potential therapies is poor solubility. The process of reducing the size of an active beneficial ingredient to submicron size is known as nanonization. Nanoparticles have an average size of 1 to 100 nm. Drug nanocrystals have a mean diameter of less than 1000 nm and are pure solid pharmaceutical particles. Though the word "drug nanocrystal" implies that the discrete particles are in a crystalline condition, they may alternatively be either completely or partially amorphous, depending on their production process. At room temperature as well as body temperature, solid lipid nanoparticles are colloidal carriers with a lipid-forming nucleus that range in size from 50 to 1000 nm. A combination of medications and chemical stabilisers, such as polymers and surfactants, in water is known as a nano suspension. The process of wet and high-pressure uniformity methods is available to prepare a nano suspension. Nano emulsions can be delivered by a variety of paths, including topical, oral, intravenous, sublingual, pulmonary, and ophthalmic. They can be made in a variety of dose forms, including fluids, creams, sprays, gels, vapours, and foams. When taken orally, the tiny droplets of nanoemulsion molecules and their capacity to dissolve highly polarising medications offer a technique to substantially increase the rate of drug dissolution and, consequently, the anticipated systemic bioavailability. By boosting drug disintegration and dissolution caused by a higher surface area following dispersion present in stomach fluids, self-nanoemulsifying delivery systems for drugs are capable of improving the bioavailability of weakly water-soluble medications.

Keywords: *Nanoparticles; Nanostructures; Different routes of administration; Crystallisation..*

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ABBREVIATIONS: BCS: Biopharmaceutical Classification System, SLNs: Solid Lipid Nanoparticles**,** API: Active Pharmaceutical Ingredients, SNEDDS: Self-nanoemulsifying Drug Delivery Systems

INTRODUCTION

The ultimate goal of generating dosage forms is to enhance a substance's or drug's bioavailability and medicinal properties through solubility. The majority of medications used for therapy, however, have a crucial therapeutic activity and fall into class 2 of the Biopharmaceutical Classification Systems (BCS) due to their poor solubility, which prevents absorption. Numerous techniques and strategies have been discovered and are being developed on a daily basis to increase the solubility of insoluble medicines. The published approaches for improving the dissolution of such medications can be separated into two categories: standard methods and new methods[1]. The solubility of medicines that undergo changes chemically and physically is enhanced using traditional procedures. Physical techniques include solid dispersion, cryogenic methods, dispersion in transporters by surfactants, complexing agents, standard micronisation, and change of crystal polymorphic shape. Changes in pH and buffer usage, the utilisation of a soluble pro-drug, salt formation, co-crystallisation, co-solvency, and the addition of hydro-tropes were examples of chemical modification of traditional processes. The use of organic solvents, including dimethyl formamide, ethanol, acetonitrile, etc., to enhance the solubility of poorly soluble treatments that are teratogenic and nephrotoxic, as well as the fact that these substances are expensive, are the primary disadvantages of employing such techniques. Traditional techniques, such as grinding and milling, are not very effective at enhancing solubility. Additionally, additional labour costs are necessary for other methods, including micronisation by standard, spray drying, and extremely concentrated fluid extraction.

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The research had been focused on minimising these issues with traditional forms because of the difficulties with conventional procedures. Innovative approaches have been created to improve the solubility of poorly soluble medications, which are frequently employed in cutting-edge methods[2].

Nanonisation Techniques

The process of limiting the size of an active pharmacological ingredient to a range of 1–100 nm is known as "nanonization," which means that drug administration, biosensors, and other therapeutic applications are all rendered possible by nanotechnology. Production of drug nanoparticles (such as nanocrystals and nanosuspensions) and nanostructured systems for drug delivery (such as liposomes, nanoemulsions, self-nanoemulsifying drug delivery systems, lipid solid nanoparticles, nanostructured lipid carriers, or polymeric micelles) are examples of the different nanonization-based technologies[3]. A few of the nanonization methods covered here are given in Figure 1.

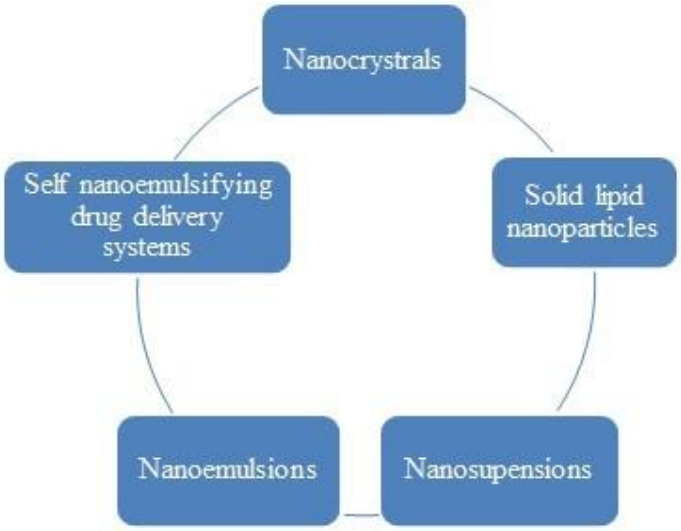


Fig. 1. Nanonisation techniques

Nanocrystals

Pure solid drugs with a mean dimension of less than 1000 nm are known as drug nanocrystals. Although the name "drug nanocrystal" suggests that the discrete particles are in a crystalline condition, they may alternatively be entirely or partially amorphous, determined by the fabrication process[4]. The Nernst-Burnstein equation provides a framework for the dissolution rate. Both saturation solubility and dissolution velocity are increased by the production of nanocrystals. Nearly all medications are present in drug nanocrystals, together with a tiny amount of stabilising substances that stick to the surface. Nanocrystals have excellent drug loading and exact size control. When patients are exposed to solvent mixtures and solvent-soluble agents, nanocrystals are limited since the precise dosage cannot be attained and may result in instability problems.

Formulation of Nanocrystals

Nanocrystals are solid particles that have been nanonized and are stabilised by a layer of stabiliser. Vander Barriers forces are created between particles as nanocrystals separate from one another during the drying process. Polymers and surface-active substances like hydroxyl propyl methyl cellulose[5], Tween 80, and sodium lauryl sulphate have all been used as stabilising agents. The preparation, assessment, and commercial use of nanocrystals are described in Tables 1, 2, and 3, respectively.

Table 1: Methods of preparation of nanocrystals

Methods	Process	Advantages	Disadvantages	Examples
Top-down technique[6]	Drug particles are reduced to smaller-sized particles by the use of technologies such as milling and high-pressure homogenization.	Drugs that are insoluble in both aqueous and non-aqueous solvents. High drug loading efficiency.	High energy is required for a long duration for milling. Unwanted drug loss.	Probucol
Wet ball milling/ Pearl milling[7]	The milling chamber is charged with milling media, water, drugs, and stabilisers.	Drugs that are poorly soluble in both aqueous and organic media.	Slow process. Instability.	Brinzolamide
High-pressure homogenization	Cavitation forces, shear forces, and collision.	Narrow size distribution of particles.	Prerequisite of micronised drug	Nimodipine

(HPH)[7]		Ease of scale-up.	particles. Consumes high energy.	
Bottom-up approach[5]	Precipitate the drug particles from a supersaturated solution of the drug.	Simple and less expensive. Minimum energy required. Ease of scale-up.	Extensive optimisation is required in selecting the solvent. Inadequate purification process.	Cesamet
Hydrosol technique[5]	First, the bottom-up process. A classical precipitation process called "via humidaparatum" (VHP)	Form finely dispersed, precipitated drug nanocrystals.	Requires organic solvents for solubility, but they are to be removed.	Hydrosols
Nanomorph[6]	Dissolution –precipitation concept that yields amorphous drug nanoparticles. The drug is dissolved in a water-miscible solvent, which then precipitates in an aqueous polymer solution.	Faster dissolution rate. Higher saturation solubility.	Recrystallisation of the undesired compound and a decrease in bioavailability	Nanopure
Sonoprecipitation[8]	Ultrasound power in the frequency range of 20-100 kHz to induce crystallisation.	Significant reduction in the use of organic solvents.	More suitable for amorphous nanoparticles.	Naproxen

Table 2: Evaluation of nanocrystals[9]

Parameters	Significance	Methods
Particle size distribution	Solubility, dissolution velocity, physical stability, and bioavailability depend on particle size distribution.	Photon correlation spectroscopy. Laser diffraction. Coulter counter.
Shape and morphology	When the formulations are to be converted into a dried powder by using techniques like spray drying or lyophilisation, there are chances for alterations in the particle shape and size because of particle agglomeration.	Transmission electron microscope
Particle surface charge	Measures the velocity of particles when they are placed between two electrodes with specific voltage differences. Highly charged particles experience high repulsion between them, hence they resist aggregation and destabilisation of special properties that are imparted to them by virtue of their nanosize. Zeta potential is measured.	Electrophoresis
Crystalline state	A low-energy stable crystal can have substantially low saturation solubility and dissolution rate compared to its amorphous form.	X-ray powder diffraction. Thermal analytical techniques
Sedimentation	Measured in terms of sedimentation rate	Laser back scattering transmission

Table 3: Commercial products of nanocrystals

Drugs	Trade names	Indications
Diltiazem[10]	Herbesser	Antianginal
Theophylline[11]	Theodur	Bronchodialator
Tizandine HCl[12]	Acorda	Muscle relaxant
Methylphenidate HCl[10]	Ritalin LA	Pscyostimulant
Fenofibrate[10]	Tricor	schizoprenia

Applications of Nanocrystals

The bioavailability of poorly soluble medications taken orally can be significantly increased by the use of drug nanocrystals. Two factors—improved solubility and dissolution rate, and bioadhesion to the gut wall—can account for the increase in bioavailability. When medications are given as nanocrystal formulations, a high concentration gradient is created between the gastrointestinal tract and blood vessels, which greatly enhances absorption and, consequently, bioavailability. When administered by the patient, medication nanocrystals not only offer the benefit of a higher rate of dissolution but also good tissue adhesiveness and extended residence time at the pulmonary route. Wet milling methods were used to create curcumin nanocrystals and curcumin-spray-dried powders for inhalation. The drugs must be dissolved in a proper solvent in order to be prepared as an injectable nanocrystal formulation for parenteral administration. The most popular method of treating eye conditions is topical. Common dosage forms for localised drug administration in the eyes include fluids, suspensions, ointments, and various drug delivery devices

such as inserts, implants, and gelling systems. Reduced dosage, extended residence time, less systemic toxicity, high drug concentrations in the affected area, and suitability for poorly water-soluble medicines are only a few benefits of using nanocrystals. Nanocrystals can increase the penetration of poorly soluble cosmetics and drugs into the skin. This is due to increased saturation solubility, high concentration gradient, better tissue adhesiveness, and prolonged residence time at the application site13.

Solid Lipid Nanoparticles (SLNs)

SLNs are colloidal carriers with a lipid-forming core at room temperature and body temperature, ranging in size from 50 to 1000 nm. This is one of the most widely used methods for increasing the oral bioavailability of medications that are poorly soluble in water. These are made up of physiologically acceptable lipid components that are solid at room temperature. These serve as a substitute for conventional colloidal carriers such as emulsions, liposomes, and polymeric micro- and nanoparticles. The system is made up of nanoscale spherical solid lipid particles scattered in aqueous surfactant solutions or water. SLN is composed of a monolayer of phospholipids covering a solid hydrophobic core. Phospholipids' hydrophobic chains are integrated into the fat matrix and may transport hydrophilic or lipophilic medications or diagnostic tools. Physiologic lipids make up SLNs, which differentiate them by their nanosize, high drug loading, surface area, minimal toxicity, and manufacturing stability. For effective drug administration through the blood-brain barrier, the SLNs are effectively surface-integrated with ligands. Its disadvantages are unexpected dynamics of polymeric transitions and unpredictable gelation tendency14.

Formulation of SLNs

Water, emulsifiers, co-emulsifiers, and solid lipids are the typical excipients utilised in SLNs. Emulsifiers are employed to stabilise the lipid dispersion and avoid agglomeration, whereas lipids are used to extend the shelf life. Zeta potential may generally be altered by using lipid mixes in various combinations, and choosing an emulsifier also results in a decrease. in partitions and surface tension during homogenisation. Triglycerides, waxes, fatty acids, stearic acid, cyclodextrin, copolymers such as poloxomer 188 and polysorbate 20, and alcohols like ethanol15 are among the materials. Tables 4, 5, and 6 list the SLN preparation, assessment, and commercial goods, respectively.

Table 4: Methods of preparation of SLNs

Methods	Process	Advantages	Disadvantages	Examples
Double emulsion[16]	Solvent emulsification-evaporation method. Used for the production of lipid nanoparticles loaded with hydrophilic drugs.	No need for specialised equipment and energy for production.	High concentration of surfactants and cosurfactants.	Cisplatin
Solvent injection[16]	Lipids and drugs are dissolved in a water-miscible organic solvent (ethanol, acetone, isopropanol), and this solution is injected through a syringe needle in water under stirring.	No need for high-pressure homogenization.	Use of solvent and surfactant.	Elvitegravir
HPH[9]	Pushes a liquid with high pressure (100-2000 bar) through a narrow gap. The fluid accelerates from a very short distance to a very high velocity.	Scalability. Short production time.	High energy-intensive process.	Quercetin Curcumin
Cold HPH[9]	Dissolve active ingredients in the lipids. Cooling and re-crystallization of the active lipid mixture using liquid nitrogen or dry ice. Milling of the active lipid mixture using a ball-mill. Disperse lipid microparticles in cold aqueous surfactant solution. High-pressure homogenization at or below room temperature.	Hydrophilic drugs	Higher polydispersity.	Hydrocortisone acetate
Membrane[17]contractor technique	The liquid phase was pressed at room temperature above the	Simple method, process	Low nanoparticle	Paclitaxel

	melting point of the liquid through the membrane pores, allowing the formation of small droplets. SLNs were formed by the cooling of the preparation at room temperature.	parameters	concentration.	
Ultrasonic dispersion[17]	The lipid and the drug were put into suitable organic solutions. After decompression, rotation, and evaporation of the organic solutions, a lipid film was formed, and then the aqueous solution, which includes the emulsions, was added. Using the ultrasound with the probe to diffuse at last, the SLNs with a small and uniform particle size are formed.	No need for specialised equipment	Metallic particle contamination	Ciprofloxacin

Table 5. Evaluation of SLNs

Parameters	Significance	Methods
Size, Zeta potential, Polydispersity index[18]	All samples were diluted with deionised water before analysis to ensure a fixed 90^0 light incidence angle.	Zetasizer Nano-ZS
Drug entrapment efficiency[18]	SLN samples were centrifuged at 500 rpm for 10 minutes using a fixed 230-angle rotor after being filtered via centrifugal filter devices. A UV spectrophotometer was used to measure the sample's concentration in the supernatant.	UV spectroscopy
In vitro drug release[18]	A hermetically sealed dialysis sac that is dialysed against an appropriate dissolving medium at room temperature. The samples are taken out of the dissolution medium at appropriate intervals, centrifuged, and subjected to an appropriate analytical technique to determine the drug concentration.	Dialysis tubing apparatus
In vitro drug release - reverse dialysis[18]	Several small dialysis sacs containing 1ml of dissolution medium are placed in the SLN dispersion. The SLNs are then displaced into the medium.	Dialysis apparatus
Diffusion[19]	The Franz diffusion cell's donor chamber, which has a cell membrane installed, is filled with the SLN dispersion. After that, the dispersion is examined against appropriate intervals and its drug concentration is determined using appropriate techniques such as spectroscopic and HPLC.	Franz diffusion cell

Table 6: Commercial products of SLNS[20]

Drugs	Trade names	Indications
Nimesulide	AbinimP	Primary dysmenorrhoea
Insulin	Novolin R	Diabetic
Clozapine	Fazaclo	Schizoprenia
Repaglinide	Rapalin	Diabetic

Applications of SLNS

In order to boost the immune response, adjuvants are utilised in vaccinations. Effective adjuvants are necessary since, in a more secure environment, new vaccines are less effective in immunisation. It has been demonstrated that the results of these examinations increase the effectiveness of chemotherapeutic medications while also lowering their negative effects. The key characteristics of SLNs that make them an appropriate carrier for delivering chemotherapeutic medicines include increased drug stability, enhanced pharmacokinetics, and decreased in-vitro toxicity. SLNs as targeted anticancer drug transporters to solid tumours (SLNs in lymph node metastatic tumours and breast cancer). SLNs may contain or adsorb proteins and antigens meant for therapeutic purposes. The formulation in SLNs confers improved protein stability, avoids proteolytic degradation, and sustained release of the incorporated molecules. SLNs are very attractive colloidal carrier systems for skin

applications due to their various desirable effects on skin, besides the characteristics of a colloidal carrier system. Essential oil extracted from Artemisia arborescens L., when incorporated into SLN, was able to reduce the rapid evaporation compared with emulsion, and the system has been used in agriculture as a suitable carrier of ecologically safe pesticides**.** SLNs have been used as an active carrier agent for molecular sunscreens and UV blockers, as well as in sunscreen manufacturing. The in vivo investigation showed that adding 4% SLN to a traditional cream will boost skin hydration by 31% after four weeks[17].

Nanosuspensions

Nanosuspensions are aqueous dispersions of active pharmaceutical ingredients (API) and stabilisers like polymers and surfactants in water. There are two ways to make nanosuspension: wet milling and high-pressure homogenisation. The increased surface area of nanosuspensions improves their bioavailability. Surfactant concentrations are lowest in nanosuspensions. sparingly soluble chemical nanosuspensions to achieve 100% bioavailability. It is able to be given intravenously. Nanosuspensions are capable of being easily scaled up and transformed into more useful dose forms (tablets, pellets, and capsules). Stabilisers and medications are among the constituents of nanosuspensions. nanocrystals, and a liquid dispersion medium, which indicates that nanocrystals are one of the compositions of nanosuspension. In this case, the dispersed medium may be crystalline or amorphous, and the medium for dispersion can be either water or non-aqueous media. Because of their higher bio-adhesiveness and reduced toxicity, nanosuspensions have improved solubility and therapeutic efficacy. Particle size reduction increases absorption capacity and dissolution rate. Components that are soluble in oil but insoluble in water can be combined to create nanosuspensions. Medication nanosuspensions can facilitate large-scale manufacture, make manufacturing simple, and target the medication passively. The amorphous proportion of particles can be increased via nanosuspension technology, which could result in modifications to the solubility and crystalline structure of the particles. Tablets, pellets, hydrogel, and suppositories can all include nanosuspensions. The disadvantage of nanosuspension is that the nanocrystal to microparticle size distribution leads to improper suspension. Nanosuspension particle size aggregation also occurs[21].

Formulation of Nanosuspensions

The formulation of nanosuspensions involves mainly stabilizers which wet the drug first to prevent agglomeration of particles. Stabilisers such as lecithin and poloxamers are used. The cosurfactant addition influences phase behaviour. Organic solvents are acceptable, such as methanol and ethanol. The temperature must be adjusted as per the route of administration through different processes[22]. The classification of methods of preparation and a detailed review of methods are given in Figure 2 and Table 7. The quality control and commercial products of nanosuspensions are given in Tables 8 and 9, respectively.

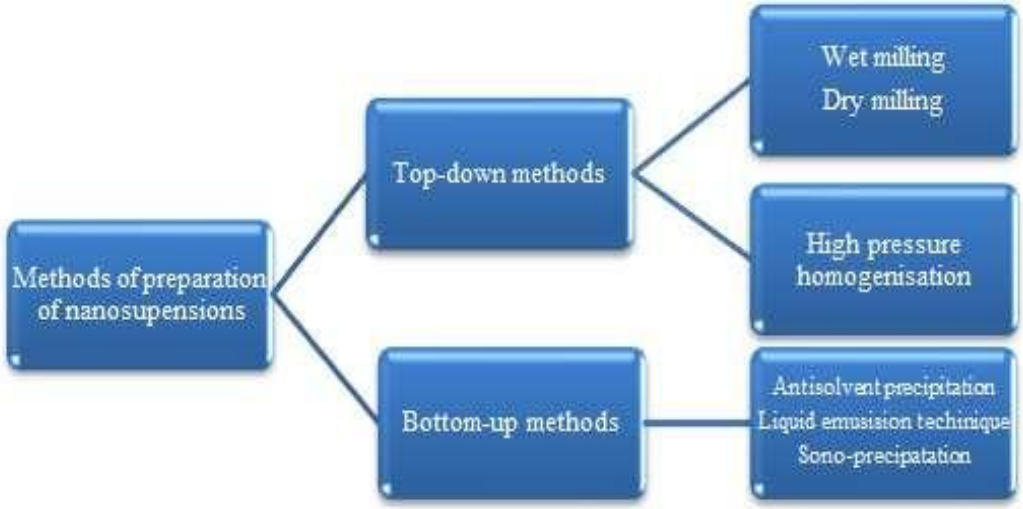


Fig. 2: Methods of preparation of nanosuspensions

Table 7: Methods of preparation of nanosuspensions

Methods	Process	Advantages	Disadvantages	Examples
High-pressure homogenization[23]	Driving the suspension under high pressure.	Ease of acceptability of the process to dilute or concentrate the suspension.	Repeated cycles are required. Possibility of contamination. Requires high energy.	Paliperidone palmitate, Docetaxel
Wet milling[23]	Size reduction by both impact and	Uniform-sized particles	Extended milling time leads to instability.	Rilpivirine, Miconazole

	attrition.			
Sono-precipatation[24]	Ultrasound at a frequency of 20 – 100khz	Prevents the aggregation of nanosized particles.	Complicated	Nitrendipine
Mechanical micronization[24]	Mechanical force	Widely used for nanosystems	A large fraction of micro-particles exists in the final product.	Indomethacin
Supercritical fluid process[25]		Nontoxic. Inflammable. High speed.	Very expensive. No polar substances are extracted	Benzodiazepines
Antisolvent precipitation[26]	CO_2 is used as an antisolvent.	Reduces the solubility of a solute and induces rapid crystallisation.	Can influence the mechanism of particle formation.	Beclomethasone dipropionate
Cryogenic spray process[25]	The droplets gradually solidify passing through cold hydrocarbon vapour.	Maintain homogeneity	Expensive	Ibuprofen
Solvent evaporation in aqueous solution[25]	Rapid phase separation	Available in a variety of single and double emulsions. Less cost.	Thermolabile drug substances may decompose due to high temperatures.	Paclitaxel

Table 8: Evaluation of Nanosuspensions

Parameters	Significance	Methods
Particle size distribution[4]	Uniform particle size distribution	Photon correlation spectroscopy Laser diffraction.
Surface morphology[4]	Crystals of nanoparticle size are observed	SEM, TEM, and AFM.
Surface morphology[4]	Observing the nanosized particles	Optical microscope
Differential scanning calorimetry[27]	Polymorphic transitions	DSC
Stability [27]	Determine the shelf life of the product.	Stability chamber

Table 9: Commercial products of nanosuspensions[7]

Drugs	Trade names	Indications
Paliperidone palmitate	Invega sustenna	Schizophrenia
Griseofulvin	Giris-PEG	Antifungal
Tizanidine HCl	Zanaflex	Muscle relaxant

Applications of Nanosuspensions

The dissolution rate, which is enhanced by decreasing particle size and improving oral bioavailability, is another crucial factor limiting absorption following administration, inadequate solubility, and low permeability. Although solubilising agents are used in the formulation of poorly soluble injections, the excessive use of complexing agents, solubilising agents, and toxic cosolvents has adverse consequences. Hydrophobic medications may be replaced by nanosuspensions. The anatomical and physicochemical limitations of the eye reduce the medicine's ocular bioavailability in traditional ophthalmic drug delivery. Nanosuspensions prolong the residence duration for poorly soluble medications at the intended site and raise their concentrations[28].

Nanoemulsions

Oil in water and water in oil dispersions of two immiscible liquids stabilised with a suitable surfactant are known as nanoemulsions. Typically, the droplet diameter is less than 500 nm. They seem clear or hazy due to their small droplet size, which contrasts with the creamy white colour of coarse emulsion. Though it should not be confused with microemulsion, nanoemulsion is occasionally employed interchangeably with a submicron or tiny emulsion. Nanoemulsions can be applied topically, orally, intravenously, intranasally, pulmonary, or ocularly, and in a variety of dose forms, including liquids, creams, sprays, gels, aerosols, and foams. The ability of small particles in nanoemulsions to dissolve extremely hydrophobic medications when taken orally offers a technique to significantly boost the rate of drug dissolution and, consequently, the anticipated systemic bioavailability. Partitioning the drug from oil into a surfactant layer and then into the aqueous phase is the process of drug release from a standard nanoemulsion. When the solubilised drug moiety diffuses out of the oil, it comes into contact with nearby water and experiences nanoprecipitation. The bitter or metallic aftertaste of medications that induce nausea and related non-compliance can be efficiently screened using nanoemulsion. Additionally, compared to other colloidal dispersions, nanoemulsions usually require less

surfactant. Because costly equipment is frequently used, the cost-effectiveness of nanoemulsion production is another issue that must be addressed beforehand[29].

Formulation of Nanoemulsions

Although they may occasionally be larger, nanoemulsions typically include 5–20% oil/lipid droplets in the case of o/w emulsions. Reesterified fractions from soybean oil, coconut oil, and rice bran oil are among the lipids or oils that are typically employed in nanoemulsions based on the drug's solubility. Surfactants are amphiphilic compounds that prevent droplet aggregation and lower interfacial tension to stabilise nanoemulsions. They often offer electrosteric stabilisation and quickly adsorb at the oil-water interface. Preservatives used in nanoemulsions should have a wide range of antimicrobial activity and satisfy requirements such as low toxicity, stability to be consumed and stored, physical and chemical compatibility, affordability, ease of availability, and acceptable odor [30]. The methods of preparation, evaluation, and commercial products of nanoemulsions are presented in Tables 10, 11, and 12, respectively.

Table 10. Methods of preparation of nanoemulsions

Methods	Process	Advantages	Disadvantages	Examples
Persuasion method/phase inversion method[31]	It can be broadly categorised as 1. Phase transition from the near-optimisation state via a change in a single variable. 2. Phase transition from the near-optimal state via a change in multiple variables, meaning altering more than one variable of formulation. 3. Catastrophic inversion. 4. Phase transition stabilised by liquid crystal formation.	Good physicochemical stability.	Heat input is necessary.	Aclycovir
Brute force method[31]	Utilisation of brute force for breaking the oil droplets into the nanorange.	Breaking the oil droplets into the nano range.	Influence of processing variables.	Ibuprofen
High-pressure homogenization[31]	High shear force.	Most efficient method.	Requires larger homogeniser cycles.	Prednicarbate
Microfludisation[32]	Microfluidiser that utilizes high-pressure positive displacement pump that pushes the product out through the interaction chamber containing stainless steel microchannels in the infringement area, resulting into formation of very small particles of sub-micron range.	Highly stable process. Zero contamination of feed material, as reduction is affected by the source material.	Time-consuming process	Pitavastatin
Ultrasonication[32]	A premixed emulsion is exposed to agitation at an ultrasonic frequency of 20 kHz reducing the droplets to a nanodroplet size. The resultant emulsion is then passed through a high shear region to form droplets with a uniform size distribution.	Droplet size decreases with an increase in sonication time and input power. Less energy required	Contamination is initiated by the probe.	Quercetin
Spontaneous emulsification[33]	Preparation of nanoemulsion in three stages. Formation of an organic solution, and then injecting this organic phase into the aqueous phase under stirring. The organic solvent was then removed in the third stage by evaporation.	Used to prepare very small droplets.	Require a high ratio of water-miscible components to oil in the organic phase before mixing.	Cinnamaldehyde
Solvent	The drug solution is prepared and		Requires a high-	Lidocaine

evaporation technique /hydro-gel method[34]	emulsified into another liquid and then the solvent is evaporated, which leads to drug precipitation.		speed stirrer.	

Table 11: Evaluation of nanoemulsions

Parameters	Significance	Methods
Encapsulation efficiency[35]	The formulation is dispersed in an organic solvent by ultrasonication and the drug is extracted into a suitable buffer. Drug content is estimated by analysing the extract spectrophotometrically.	Encapsulation efficiency analyser
Particle size and polydispersity[35]	Stability	Photon correlation spectroscopy using Malvern zeta-sizer
Zeta potential[34]	Stability	Zetasizer
Fourier-transform infrared spectroscopy (FTIR)[32]	Drug excipient interaction.	FTIR spectroscopy

Table 12: Commercial products of nanoemulsions

Drugs	Trade names	Indications
Propofol[36]	Diprivan	Anesthetic
Dexamethasone[36]	Limethason	Steroid
Palmitate[36]	Liple	Vasodilator
Curcumin[36]	Wild Curcuma	Modulation of pro-inflammatory biomarkers in plasma
Diclofenac[32]	Cambia	Osteoarthritis
Cyclosporine[32]	Gengraf	Dry eye syndromes

Applications of Nanoemulsions

There are several uses for parental nanoemulsions. They are employed in the delivery of medications with reduced bioavailability. For the oral administration of lipophilic medications such as antibiotics, hormones, steroids, cytotoxics, diuretics, antifungals, etc., nanoemulsions are perfect. Because of their capacity to coat medications, nanoemulsions offer a platform for shielding them from hydrolytic enzymes, extreme pH levels, and other environmental factors. Topical medication absorption has been investigated using nanoemulsions. They offer a mix of concentration gradient and penetration increase by serving as a little drug reservoir. Oil-in-water nanoemulsions have been used in ocular administration to administer medications that are poorly absorbed, poorly retained, water-incompatible, or environmentally sensitive. The transparency, viscosity, and refractive index of nanoemulsions are taken into particular account when creating them for use in ocular applications. It is usually necessary to titrate any nanoemulsion meant for ocular delivery against various doses in order to assess its acceptability. To provide complete parental nourishment, nanoemulsions have been created. For critically ill patients who are unable to eat fats orally, the oil content of parental nanoemulsions serves as a substitute energy source to fulfil daily needs for fat-soluble vitamins A, D, E, and K.

Self-nanoemulsifying drug delivery systems (SNEDDS)

Formulation of SNEDDS

Oil phase: The oil phase has great importance in the formulation of SNEDDS as the physicochemical properties of oil significantly govern the spontaneity of the nanoemulsification process, droplet size of the nanoemulsion, and drug solubility. Usually, the oil, which has maximum solubilising potential for the selected drug candidate, is selected as an oily phase for the formulation of SNEDDS.

Surfactants: The choice of surfactant is also critical for the formulation of SNEDDS. The properties of the surfactant, such as HLB, viscosity, and affinity for the oil phase, have a great influence on the nanoemulsification process, self-nanoemulsification region, and the droplet size of the nanoemulsion.

Co-emulsifiers and co-surfactants: They can be incorporated in SNEDDS for different purposes, including increasing the drug loading to SNEDDS, modulating the self-nanoemulsification time of the SNEDDS; and modulating the droplet size of nanoemulsion.

Aqueous phase: The droplet size and stability of nanoemulsion are influenced by the nature of the aqueous phase, where SNEDDS would be introduced. Hence, the pH and ionic content of the aqueous phase should be given due importance while designing SNEDDS[37,38].

The methods of preparation, evaluation, and commercial products are given in Tables 13, 14, and 15, respectively.

Table 13: Methods of preparation of SNEDDS

Methods	Process	Advantages	Disadvantages	Examples
Self-emulsifying nanoparticle[39]	Molten lipid mass containing lipid, surfactant, and drug was injected dropwise into a non-solvent system. This is filtered and dried to get nanoparticles.	Improves low aqueous solubility, enzymatic degradation, and stability.	Physicochemical instability issues	Cinnarizine
Sonication emulsion diffusion evaporation[39]	5-Flurouracil and anti-sense EGFR plasmids were coloaded into biodegradable PLGA/O-CMC nanoparticles. The mixture of PLGA (poly-lactide-coglycolide) and O-CMC (O-carboxymethyl-chitosan) had an SE effect with no additional surfactant required.	Fewer side effects. Good bioavailability enhancement.	Time-consuming. High energy requirements.	5-fluorouracil
Multiple emulsion solvent evaporation[40]	Chitosan and glyceryl monooleate for the delivery of paclitaxel. Chitosan with bio-adhesive properties increased cellular association and was prepared by multiple emulsion solvent evaporation methods.	More particles adhere and nanosized particles are formed	Expensive process. May cause toxic effects.	Procainamide hydrochloride

Table 14: Evaluation of SNEDDS

Parameters	Significance	Methods
Physical stability[39]	Poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance but visual appearance as well.	Heating and cooling cycle. Centrifugation. Freeze-thaw cycle.
Dispersability[10]	Visually assessed.	Standard USP dissolution apparatus.
Turbidity[10]	Turbidity should not be increased.	Turbidometer
Viscosity[10]	If a system has low viscosity then it is an o/w type of the system and if high viscosity then it is a w/o type of the system.	Brookfield viscometer
Droplet size[10]	Size affects the stability.	Photon correlation spectroscopy
Electro-conductivity[41]	Determines the type of emulsion.	Electro conductometer
Invitro diffusion[41]	Drug content in the solvent extract was analysed by a suitable analytical method against the standard solvent solution of the drug.	Diffusion apparatus
Bioavailability[41]	The in-vitro study is performed to quantify the drug after administration of the formulation. Pharmacokinetic parameters of the maximum plasma concentration and corresponding time for the drug following oral administration are calculated.	Pharmacokinetic study

Table 15: Commercial products of SNEDDS

Drugs	Trade names	Indications
Teprenone[42]	Selbex	Acute gastritis
Amprenavir[42]	Angerase	HIV antiviral
Cyclosporin A[43]	Sandimmun	Immunosuppressant
Calcitriol[43]	Rocaltrol	Calcium regulator
Valproic acid[44]	Convulex	Antiepileptic
Morphine sulfate[44]	MXL	Analgesic
Menatetrenone[37]	Glakay	Osteoporosis

Case Study for each Nanoformulation

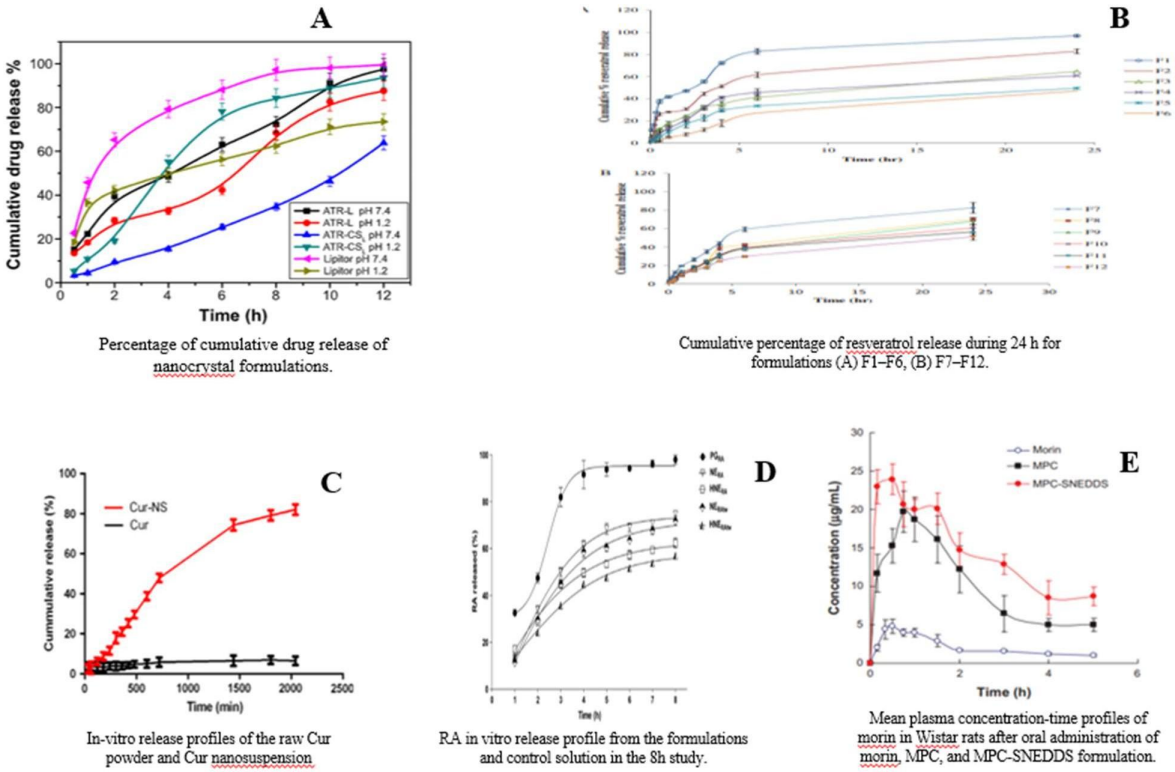
Kurakula M. et al. evaluated the usage of cationic charged chitosan as a stabiliser by creating nanocrystals using the probe sonication method. The effects of cationic charge densities of chitosan (low CSL, medium CSM, and high CSH molecular weights) and Labrasol® on solubility augmentation and altering the release were investigated using atorvastatin (ATR) as a poorly soluble model medication. Unlike CSM and CSH, CSL's low cationic charge acted as an electrostatic and steric stabiliser, greatly reducing the size to 394 nm with a charge of 21.5 meV. The solubility of ATR-CSL increased to 60 times that of ATR-L and pure ATR. The physicochemical properties of nanocrystals were explained. Scanning electron microscopy revealed high surface area structures that resembled scaffolds. X-ray powder diffractometry and differential scanning calorimetry were used to examine crystalline to slightly amorphous state changes after the cationic charge size was reduced. Fourier transform infrared spectra did not reveal any significant drug-excipient interactions. When compared to ATR-L and Lipitor®, the better dissolution profile of ATR-CSL demonstrates that sustained release was achieved (Figure 3A). In comparison to Lipitor® and pH 6, ATR-CSL showed an increase of 2.5 times in efficacy at pH 5, suggesting that pH affected anti-hyperlipidemic performance. Stability tests showed that ATR-L differed significantly in size and charge from ATR-CSL, indicating the importance of the stabilizer[45].

Jose S et al. prepared solid lipid nanoparticles (SLN) of resveratrol. In comparison to free resveratrol (3.45 0.3961 mg/g), SLN could considerably ($P < 0.001$) raise the brain concentration of resveratrol (17.28 0.6344 mg/g) in the in vivo biodistribution investigation conducted on Wistar rats. The values of the cumulative percentage of drug released during 24 h vary from 46.96 (F6, drug–lipid – 1:15) to 97.03 (F1, drug–lipid – 1:5) as represented in Figure 3B. The Results showed that our SLNs infused with resveratrol are effective therapeutic platforms for treating brain tissue neoplastic diseases. This study effectively synthesised SLN encapsulating resveratrol for brain targeting using the emulsion solvent evaporation method, using Compritol as the lipid core and a mixture of Tween 80 and PVA as the shell material. The drug-lipid ratio and the composition of the surfactant in the formulation have an impact on the drug's encapsulation into the lipid core. The formulation's fat content negatively impacts the drug's size and in vitro release. The cytotoxicity data[46] showed that the resveratrol-loaded SLN was equally effective to the free drug. Li X et al., enhanced curcumin's poor water solubility and short biological half-life. Cur nanosuspension (Cur-NS) was produced using PVPK30 and SDS as stabilisers. The physical-chemical characterisation of Cur-NS was methodically described in this work. Cur-NS's in-vitro cytotoxicity, pharmacokinetic, and dissolution studies were also assessed. Cur-NS morphologies were shown using a scanning electron microscope to be spherical or ellipsoidal. The development of Cur as nanoparticles with an amorphous phase in Cur-NS was confirmed by X-ray diffraction. There seems to be no degradation of Cur in the Cur-NS, according to Fourier transform infrared spectroscopy. Additionally, the in-vitro investigation demonstrated that the Cur-NS's cumulative release was 82.16 2.62% in 34 hours (Figure 3C) and that it was far less harmful to HepG2 cells than raw Cur[47].

One potential approach for developing innovative anti-ageing skin care products is the use of rosmarinic acid (RA), a naturally occurring source of antioxidant activity. Paula Marafon P et al. synthesised hydrogels using RA-loaded nanoemulsions and evaluated the effects of adding the nonionic cosurfactant Tween 80 to topical formulations. In vitro release, skin retention/permeation, and physicochemical characterisation of hydrogels containing RA-loaded nanoemulsions (with or without Tween 80) were evaluated in this study. The in vitro RA release profile investigations from formulations and the control dispersion are displayed in Figure 3D. Every formulation had a comparable RA release profile, releasing considerably less RA ($P < 0.05$) than the control. The safety characteristics of RA-loaded nanoemulsions were also examined in keratinocytes (HaCaT cells). Every formulation was found to have sufficient physicochemical characteristics for topical use. Additionally, the outcomes showed that Tween 80 reduced the droplet size and polydispersity index of hydrogels and nanoemulsions. For the hydrogels, a longer RA release was seen. On the other hand, a favourable impact of Tween 80 on RA retention/permeation throughout the entire skin was observed when comparing the hydrogels. In HaCaT cells, the safety profiles of the RA-loaded nanoemulsion showed good tolerance (3.125–100 lM)[48].

Morin's weak water solubility limits its oral use and results in a low oral bioavailability. Using a unique self-nanoemulsifying drug delivery system (SNEDDS) based on the phospholipid complex method, Zhang J et al. enhanced the oral bioavailability of morin. X-ray diffraction and infrared spectroscopy were used to produce and analyse the morin-phospholipid complex (MPC) using a solvent evaporation approach. Solubility tests verified that morin's lipid solubility significantly increased after the production of MPC. Particle size and emulsifying rate were used as evaluation indices in the orthogonal design screening of the blank SNEDDS. To examine how drug loading affected the optimised blank SNEDDS's capacity to self-emulsify, ternary phase diagrams were made. The in vivo pharmacokinetic properties of the morin-phospholipid complex self-nanoemulsifying drug delivery system (MPC-SNEDDS) were investigated after 200 mg/kg of morin was administered orally to Wistar rats. With a mean particle size of about 140 nm, the ideal formulation consisted of Labrafil ® M 1944 CS, Cremophor ® RH40, and Transcutol ® P (3:5:3, w/w). When the MPC-SNEDDS was administered orally, its C max (28.60 µg/mL) was substantially higher than when the morin suspension (5.53 µg/mL) or the MPC suspension (23.74 µg/mL) was used. For MPC and MPC-SNEDDS, t_{max} was extended from 0.48 to 0.77 hours and from 1

hour, respectively. Furthermore, the morin suspension's relative oral bioavailability was notably lower than that of the MPC suspension and 6.23 times higher than that of the morin synthesised in the MPC-SNEDDS[49].



Percentage of cumulative drug release of nanocrystal formulations.

Cumulative percentage of resveratrol release during 24 h for formulations (A) F1–F6, (B) F7–F12.

In-vitro release profiles of the raw Cur powder and Cur nanosuspension

RA in vitro release profile from the formulations and control solution in the 8h study.

Mean plasma concentration-time profiles of morin in Wistar rats after oral administration of morin, MPC, and MPC-SNEDDS formulation.

Fig. 3: Case study for each nanoformulation

CONCLUSION

Low aqueous solubility is a consequence of the spike in drug development of prospective medications with the highest targeting. There are several ways to increase the solubility and rate of dissolution of these medications. One possible strategy to improve the solubility of medications is to reduce particle size to the nanoscale. Nanocrystals, solid lipid nanoparticles, nanosuspensions, nanoemulsions, and self-nanoemeulsifying drug delivery systems can all accomplish nanonization.

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