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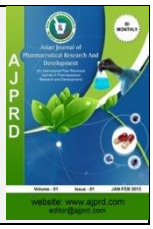

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Review Article

Nanoemulsion as Novel Drug Delivery System: Development, Characterization and Application

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A B S T R A C T

A dispersed nano-system with droplet sizes as small as submicrons is called a nanoemulsion. Nanoemulsions are thermodynamically stable, transparent, isotropic liquid mixtures of oil, water, surfactant, and co-surfactant. Nanoemulsion typically has droplet sizes between 20 and 200 nanometer. The size and composition of the scattered particles in a continuous phase are the primary distinctions between an emulsion and a nanoemulsion. This approach is intended to alleviate some of the issues that low bioavailability and noncompliance, two issues with traditional drug delivery systems, bring up.Today, nano emulsion can be created for a number of administration routes. A nano emulsion formulation can be considered an effective, secure, and patient-compliant pharmaceutical delivery method. Nowadays, nano emulsions have attracted a lot of interest in pharmacotherapy, dosage form design, and research. A surfactant and a cosurfactant can preserves the stability components of nanoemulsion. Brief details on the types, preparation process, stability, assessment, and applications of nanoemulsion are provided in this review.

Keywords: Nanoemulsion, emulsifier, Microfluidization, sonotrode, cosurfactant.

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INTRODUCTION:

In order to generate a single phase, two immiscible liquids are combined with emulsifying agents known as surfactants and co-surfactants in nanoemulsions. These colloidal scattering frameworks are thermodynamically stable. A nanoemulsion is made up of an emulsifier, water, and oil. The term "nanoemulsion" refers to a colloidal particle system with submicron-sized particleswhich serves as a vehicle for medicinal molecules. They have sizes between 10 and 1000 nm. Solid spheres with an amorphous, lipophilic, negatively charged surface make up these carriers. The use of magnetic nanoparticles can improve site specificity. They serve as a medication delivery system that improves the medicinal effectiveness of treatment while minimising harmful effects and severe reactions. Among the principal applications are the treatment of reticulo-endothelial system (RES) infections, liver enzyme replacement therapy, cancer treatment, and immunisation. In a biphasic system known as an emulsion, one phase is widely dispersed as tiny droplets with sizes ranging from 0.1 to 100 lm in the other phase. A solution that is thermodynamically unstable may be stabilised by adding an emulsifying agent (emulgent or emulsifier). The dispersed phase is also referred to as the internal phase or interrupted stage, while the outer phase is also known as the dispersion medium, exterior phase, or continuous phase. The emulsifying substance is also referred to as "interphase" or "intermediate." Miniemulsions, or nanoemulsions, are tiny oil-in-water dispersions stabilised by an interfacial coating of surfactant molecules with droplet sizes between 20 and 600 nm. The tiny size of nanoemulsions makes them transparent.

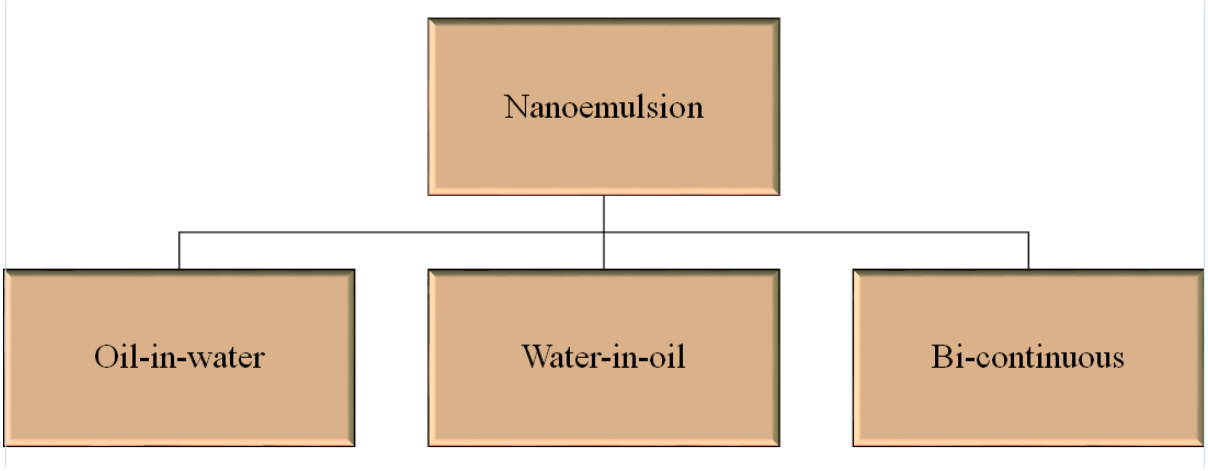

Figure 1: Types of Nanoemulsion

ADVANTAGES[4]:

- They can easily be the administration to mucous membranes and skin because they are non-toxic and non-irritating.
- The nanoemulsions' small size allows them to penetrate the "rough" skin surface, which improves the penetration of active ingredients.
- If the formulation includes biocompatible surfactants, it can be taken orally.
- It is the first stage in the manufacture of nanocapsules and nanospheres employing interfacial poly-condensation and nanoprecipitation.
- Nanoemulsions have a high surface area and low free energy, making them an effective transport mechanism.
- It could be used for vesicles and liposomes, and lamellar liquid crystalline phases can be created around the nanoemulsion droplets.
- It enables toxicity studies of oil-soluble medications and greater uptake of oil-soluble nutrients in cell cultures to increase the proliferation of cultured cells.
- The issues with natural creaming, flocculation, coalescence, and sedimentation are not displayed.
- It is possible to create it in a variety of ways, including foams, creams, liquids, and sprays.
- It is acceptable for both veterinary and human therapeutic reasons, because it does not harm both healthy animal and human cells.

DISADVANTAGES[5]:

- Although pH and temperature have an effect on the solidity of surfactants and cosurfactants, extensive grouping of these substances is necessary for adjustment, and uncertainty can be brought about by impact of Oswald's maturation, which is expensive because of the size of the droplets reduces.
- Due to the tiny reduction of the droplets, which necessitates a special set of instruments and procedural techniques, the creation of nanoemulsionsis a costly process.
- The setup of the homogenizer, a necessary tool for the formulation of nanoemulsions, is a costly process. Additionally, ultrasonication and microfluidization (producing processes), They need significant financial support.
- Nanoemulsion formulation storage is a significant problem. The delivery of nanoemulsions is said to be expensive in the cosmetics business.
- The cosmetics sector is particularly affected by the high cost of production due to the use of emulsifiers in high concentrations during commercial manufacture.

Method of Preparation of Nanoemulsions:

The best technique to create nanoemulsions, which have a very limited range of particle sizes, is with high-pressure equipment. Microfluidization and high-pressure homogenization are the most common processes for making nanoemulsions at laboratory and industrial scales. The creation of nanoemulsions can also be accomplished using ultrasonification and in-situ emulsification.

Microfluidization: A tool called a micro-fluidizer is utilized in mixing process called as micro-fluidization. The object is pushed through the interaction chamber using a positively dispersed pump (500 to 20,000 psi) in this device. This is made up of tiny channels, or "microchannels." The substance travels via narrow passageways and impinges on a surface, producing particles that are in the submicron range. Aqueous and viscous phases are mixed, then treated in an internal homogenizer to create a coarse emulsion. In a micro-fluidizer, a coarse emulsion either treated to create a permanent nanoemulsion. The coarse emulsion is sent through the microfluidizer with interaction chamber repeatedly until the desired particle size is reached. A uniform nanoemulsion is created when the large particles from the core emulsion are removed using a filter submerged in nitrogen.

High Pressure Homogenization[4]:Thesemethod utilizing a high-pressure homogenizer or piston homogenizer, consequently it produces nanoemulsions with very tiny particle sizes (up to 1 nm) By applying extreme pressure to a small inlet aperture, two liquids (viscous phase and aqueous phase) are forced through it to become dispersed (500 to 5000 psi), putting the product under harsh pressure.

Hydraulic shear and turbulence lead to exceedingly fine fragments of the emulsion. A monomolecular coating of phospholipids surrounds the liquid, lipophilic core of the produced particles, keeping them distinct from the neighbouring aqueous phase. Although this method is quite effective, its only drawbacks are the significant energy consumption and temperature increase. This processing produces an emulsion.

- Effect of Homogenization Pressure: The process parameters, which range from 100 to 150 bars, have been optimised. The particle size obtained, for example, using RMRP 22, decreases as the size increases.

- Number of cycles of homogenization: The resulting particle size decreases as the homogenization cycles increase. 3, 4, or 10 cycles can used to complete the cycles. The poly disparity index of medicine analyses the no. of cycles following each cycle.

Advantages:

- Scale-up is simple, and there is little batch-to-batch variance.
- Used well with thermolabile compounds.
- Narrow range of sizes for the drug's nanoparticles.
- Ability to be flexible while handling medicine quality.

Ultrasonication[14]: Several academic studies that aim to use ultrasonic sound frequency to reduce droplet size report on the creation of nanoemulsions. Utilising a system pressure-dependent constant amplitude sonotrodehigher than ambient pressure is an alternative strategy. It is understood that raising exterior pressure also decreases cavitations in an ultrasonic field. Because of this, bubbles appear. Therefore, increased exterior pressure also raises the cavitation bubbles' collapse pressure. This indicates that when cavitation occurs, the bubbles' violent and greater collapse when there is atmospheric pressure. These changes in the intensity of navigation can be connected to cavitation, which is the most significant cause of power loss in a low-frequency ultrasonic system. Variations in power density are directly proportional to changes in power supply. In order to maintain the ideal temperature, the system also employs a water jacket.

Drug used in Nanoemulsion preparation:

Phase Inversion Method [15]: This technique uses chemical energy from phase transitions caused by the emulsification pathway to achieve fine dispersion. A phase transition occurs when the composition of the emulsion changes while the temperature remains constant, or vice versa. When the phase inversion temperature was originally investigated, it was found that a rise in temperature causes the polyoxyethelene surfactants to undergo chemical changes due to the degradation of the polymer chain.

Solvent Evaporation Method: This method entails making a medication solution, then emulsifying it in a different liquid that isn't the drug's solvent. The drug precipitates as a result of the solvent evaporating. A high-speed blender may generate strong shear forces, which can be utilised to control crystal formation and particle size reduction.

Hydrogel Method: It is same as solvent evaporation technique. The fact that the solvent for drugs and drug anti-solvent are miscible is the only distinction among the two methods. Higher shear forces hinder Ostwald ripening and crystallisation.

FACTORS CONSIDERED DURING PREPARATION OF NANOEMULSIONS:

- To achieve the ultralow surface tension required to produce nanoemulsion, a carefully designed surfactant is required.
- The surfactant concentration must be strong enough to stabilise the microdroplets in order to produce a nanoemulsion.
- The surfactant must be pliable or sufficiently liquid to encourage the creation of nanoemulsions.

Table 1: Drugs Used in Nanoemulsion

Drug	BCS class	Method of Preparation	Application	Reference
Coenzyme Q10 Vitamin C and E	Class II	High Pressure Homogenisation	NanoMaxMibelle Biochemistry	16
Eugenol	Class II	High Speed Sharing Technique	Anti-inflammatory activity	17
Resveratrol	Class II	Phase Inversion Composition Technique	Protection against UV radiation Antioxidant activity	18
Ibuprofen	Class II	D-Phase Emulsification Technique	Anti-inflammatory Analgesic activity Increased drug solubility Increased permeability	19
Betulin	Class II	Interfacial Polymerisation	Increase solubility and bioavailability Anti-inflammatory activity Ant carcinogenic activity	20
5-Fluorouracil	Class III	Oil Phase Titration Method	Chemo preventive activity	21
Omegas 3, 6, 7 and 9	Class IV	Homogenisation	Antiaging Regenerate Photo protection	22
Coenzyme Q10 Tocopherol Vitamin C derivative	Class IV	High Pressure Homogenisation	Collagen production Protects against photo aging; Antiaging	16
Lipophilic fraction of cocoa beans	Class IV	Spontaneous Emulsification	Antiaging	23
Quercetin	Class IV	Ultrasonication	Improved solubility and skin permeation Antiaging activity	24
Mangiferin	Class IV	Hyaluronic Acid	Increased permeability Anti-inflammatory activity	25

CHARACTERISATION OF NANOEMULSION [12]:

The absence of the internal phase, the elimination of flocculation, the elimination of microbial degradation, and the preservation of beauty in terms of appearance, colour, odour, and consistency are all characteristics of a stable nanoemulsion.

Flocculation and Creaming: When globules come together to create floccules, they go up or down in the emulsion more quickly as compared to the individual globules. This process is known as flocculation. Creaming is the process of dispersed globules rising or falling to create a concentrated layer. As a result, flocculation results in creaming.

Cracking: When an emulsion breaks, the dispersed phase separates as a layer. Emulsion cracks cannot be repaired; however, shaking a creamy emulsion is possible or stirred to recombine it. Cracking will be representing permanent instability.

Phase Inversion: It is physical process. It entails moving back and forth between o/w and w/o emulsions. Variations in temperature, the presence of electrolytes, and the stage volume fraction can all lead to phase inversion.

Miscellaneous Instability: If emulsions are kept at a temperature that is unusually high or low, or presence of light, they may start to degrade. Emulsions are therefore typically stored at a moderate temperature and packaged in coloured, airtight containers.

EVALUATION OF NANOEMULSIONS:

Drug Content [28]:Pre-weighed nanoemulsion is recovered by dispersing it in an appropriate solvent, and the extracted solution is then evaluated against a drug reference solution using a spectrophotometer or HPLC.

Dilution Test: This kind can be determined by diluting a nanoemulsion with water or oil. The test is predicated on the observation that a nanoemulsion can have more continuous phases added to it without having stability issues. A w/o nanoemulsion can be diluted with oil, but an o/w nanoemulsion can be diluted with water.

Viscosity Determination: The viscosity is determined using a rotational viscometer of the Brookfield type of nanoemulsions at various shear rates and temperatures.

Droplet Size Analysis [29]: Analyzer of the size of light-scattering particles counter, the LS 230, is utilized to evaluate the diffusion method's droplet size analysis of nanoemulsion. Correlation spectroscopy, which investigates the variation in light scattering brought on by Brownian motion, can also be used to measure it. Transmission electron microscopy (TEM) can also be used to analyse shrinking of the droplets in a nanoemulsion.

pH: A pH metre can be used to calculate pH of nanoemulsion.

Dye Test: An oil/water nanoemulsion absorbs the shade equally when a liquid dye is added to it. In contrast, The emulsion only absorbs the colour in the dispersion phase, and the colour is not uniform if the dye is water-soluble and the emulsion is typeless.. By inspecting the emulsion under a microscope, this is instantly discernible.

Refractive Index: An Abbes refractometer is used to calculate the nanoemulsion's reflectivity. The transparency of a nanoemulsion and how light passes through a substance are both described by the refraction. The ability to determine the medium's refractive index is based on the speed of the wave in the reference media (c) in relation to the wave's phase speed in the medium (vp) (n). i.e.n=c/vp. The nanoemulsion is classified as transparent if its refractive index is the same as that of water.

Zeta Potential: A device called the Zeta PALS, which is used to determine zeta potential. It is used in a nanoemulsion to establish the charge on a droplet's surface.

Polydispersity: It demonstrates that the droplet diameters in the nanoemulsion are uniform. In a nanoemulsion, the droplet size is less uniform the higher the pdi value. It is called as the standard deviation to mean droplet size ratio. To measure, a spectrophotometer is utilised.

Fluorescence Test: Many oils glow when exposed to UV light. Under a microscope, a field of w/o nanoemulsion fluoresces when it is subjected to fluorescent light. The o/w type nanoemulsion is used when the fluorescence is sporadic or spotty.

Conductance Measurement: The conductivity of a nanoemulsion is tested using a conductometer. In this test, an emulsion is put on two electrodes that are wired to an electrical component and a lamp. If the emulsion is of the o/w variety, water conducts the current, which results in a flow of current between the electrodes that illuminates the lamp. Because the oil in the outer phase does not conduct electricity, the light does not illuminate when the emulsion is not present.

Percentage Transmittance: The percentage transmittance of the nanoemulsion is calculated using a UV-visible spectrophotometer.

Filter Paper Test: The theory behind this experiment is that when put on filter paper, an oil-in-water nanoemulsion will quickly spread out. On the other hand, a water-based nanoemulsion will move very slowly. This method should not be used to cure very thick creams.

APPLICATIONS OF NANOEMULSION IN ADVANCED DRUG DELIVERY: -

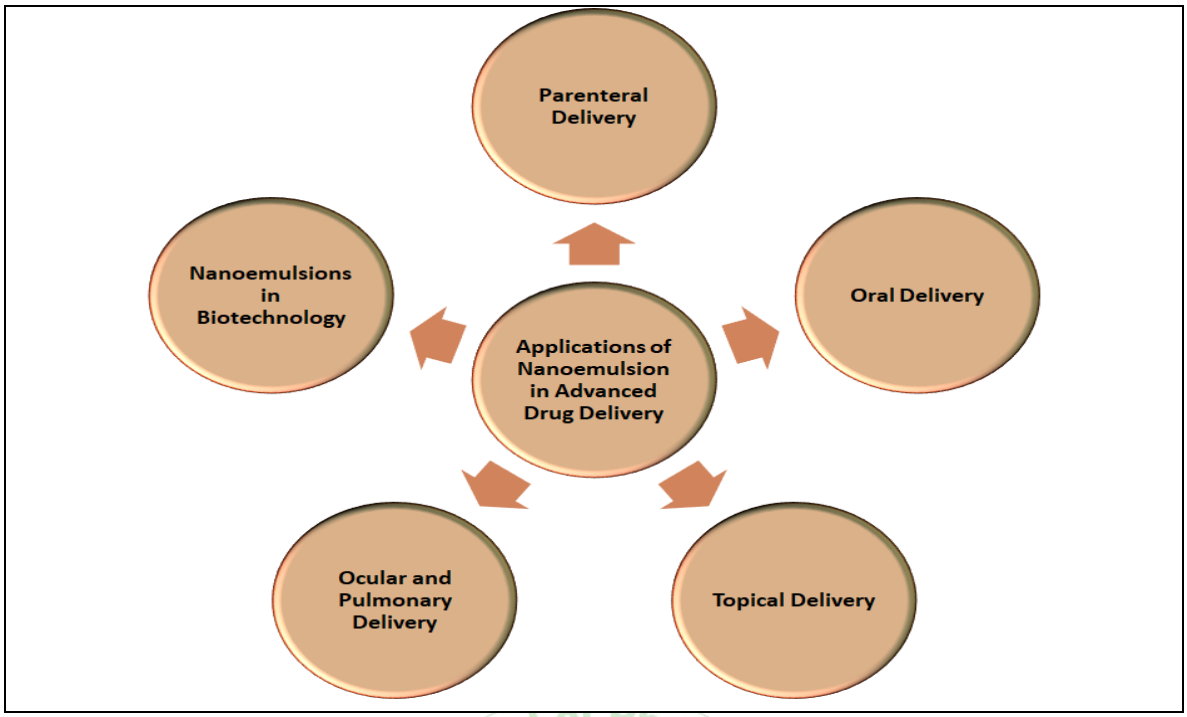

Figure 2: Applications of Nano emulsions

Parenteral Delivery: Parenteral administration of medications with restricted solubility (particularly via the IV route) is a significant concern in the business due to the highly poor drug delivery to a specific spot. Nanoemulsion formulations differ from macroemulsion systems when administered parenterally because nanoemulsions of small particles are excreted from the body slower and more gradually than emulsions of large particles and stay there for a longer period of time. Parenteral delivery can be performed using either o/w or w/o nanoemulsion. Several of the nanoemulsion systems described in the literature can be employed for parenteral administration due to surfactant toxicity and parenteral use. By substituting parenterally acceptable co-surfactants, such as polyethylene glycol (400)/polyethylene glycol (660)/12 hydroxystearate/ethanol, for C3-C4 solvents, Von Corsewant and Thoren were able to create an almost balanced middle phase nanoemulsion while maintaining a versatile emulsifier film and impulsive curvature close to zero. The intermediate phase formation was selected for this application because it could integrate substantial amounts of water and oil with only a small amount of surfactant.

Oral Delivery; For oral delivery, nanoemulsion formulations provide a number of advantages over traditional oral formulations, including increased clinical potency, improved absorption, and reduced drug toxicity. Therefore, it has been suggested that nanoemulsion is the good delivery system for medications like steroids, hormones, diuretics, and antibiotics. Pharmaceuticals using peptides and proteins have very high potencies and are very targeted in their physiological effects. The majority, though, are challenging to provide orally. They are typically not therapeutically active when administered orally since their oral absorption in conventional formulations—those that don't include nanoemulsions—is below 10%. The majority of protein medicines are only offered as parenteral formulations the result of their negative oral bioavailability. However, because parenterally given peptide medications have a very short biological half-life, several doses are necessary. Neoral®, a cyclosporine nanoemulsion preparation, has taken the place of Sandimmune®, a mediocre cyclosporine oil-in-water emulsion preparation. Due to its increased dispersion, Neoral® absorbs more quickly, reliably, and with less fluctuation between and within individuals.

Topical Delivery [37]: The avoidance of the drug's hepatic first pass metabolism and associated adverse consequences is just one of the benefits of topical drug administration over other approaches. Another is the drug's capacity to distribute itself straight on the skin or eyes that are afflicted. For the administration of prostaglandin E1, In a hairless mouse model, both o/w and w/o nanoemulsions have been tried. The nanoemulsions were built on oleic acid, or Gelucire 44/14, and stabilised with a mixture of Labrasol (C8 and C10 polyglycolysed glycerides) and PlurolOleique CC 497 as a surfactant. Regardless of the O/W nanoemulsion. there were observed delivery rates to be boosted, the authors came to the conclusion that neither system's penetration rates were sufficient for practical application. It has also been claimed to use a lecithin/IPP/water nanoemulsion to deliver indomethacin and diclofenac transdermally. As per FTIR spectra and differential scan calorimetry (DSC), after a day of incubation, the IPP organogel had changed the lipid composition in the mammalian stratum corneum. It has also been investigated how the hydrophilic drug diphenhydramine hydrochloride is distributed transdermally into excised human skin from a w/o nanoemulsion. The formula was created using Tween 80 and Span 20 in combination with IPM. However, two other formulations

that contained oleic acid and cholesterol, respectively, were evaluated. Although oleic acid had no detectable effect and cholesterol improved medication penetration, scientists have shown that compositional choices can change the parameters of penetration.

Ocular and Pulmonary Delivery: The majority of drug delivery to cure eye disorders occurs topically. For ocular delivery, poorly soluble drug dissolution, increased absorption, and prolonged release profiles of o/w nanoemulsions have been studied. Lecithin, propylene glycol, and PEG 200 were used in the formulation of the pilocarpine-containing nanoemulsions, with IPM serving as the oil phase. The formulations' a favourable refractive index and low permeability made them suitable for ophthalmologic uses. a non-ionic fluorocarbon surfactant that stabilises a water-in-HFA propellant nanoemulsion that is meant for pulmonary distribution.

Nanoemulsions in Biotechnology: Aqua-organic or purely organic media are used for many enzymatic and biocatalytic processes. These kinds of reactions also include biphasic media. Biocatalysts' denaturation is caused using only pure polar media. The usage of water-resistant media has some advantages. Low water content enzymes detect and have-

- An increase in solubility in reactants that are non polar.
- Thermodynamic equilibrium modifications that would encourage condensations.
- Improvements in the enzymes' thermal stability make it possible to conduct reactions at high temperatures.

Numerous enzymes typically function in hydrophobic environments within cells, including hydrolytic enzymes, esterases, aldehyde dehydrogenases, and oxidases. In biological systems, many enzymes function at the interface where the hydrophilic and hydrophobic domains converge. Polar lipids and other naturally occurring amphiphiles often serve to stabilise this interface. Enzyme catalysis has been employed in nanoemulsions for a number of reactions, including the production of esters, peptides, and sucrose acyl transesterification; various degradation processes; and the modification of steroid molecules. The lipase family of enzymes is the one that is most frequently used in microemulsion-based processes.

Formulations based on Drug Delivery System:

Table 2: Formulations Based on Drug Delivery

Drug	Microbes	Formulation	Bioactivity	Reference
Zidovudine	HIV	Stearylamine (SA) &Dicetyl Phosphate	ZDV targets lymphatics more effectively.	38
Amphotericin B	Aspergillus fumigates	Hydrogenated soy phosphatidylcholine, cholesterol, and distearoylphosphatidy-lglycerol (DSPG)	medication delivery with specificity to the infected location	39
Econazole nitrate	Fungi	Glycerol Palmitostearate	increased medication penetration and high encapsulation efficiency	40
Ciprofloxacin Hydrochloride	Gram negative, gram positive and mycoplasma	Stearic acid, soy phosphatidylcholine, and sodium taurocholate	Prolonged drug release	41
Beta-lactam / Ciprofloxacin	Staphylococcus aureus, Bacillus anthracis	Glycosylated polyacrylate Nanoparticles	enhanced bioavailability and increased therapeutic effectiveness	42
Rifampicin, isoniazid, pyrazinamide	Mycobacterium Tuberculosis	Alginate nanoparticles	Higher therapeutic efficacy, enhanced pharmacokinetics, and increased drug payload	43
Saquinavir	HIV	Polyethylene oxide (PEO) modified poly (epsilon carprolactone) (PCL) Nanoparticles	Defend against cytochrome C metabolism and avoid P efflux pump while using the medicine.	44
Sulfamethoxaz-ole	Strep throat, Staphylococcus infection, and flu	Polyamidoamine (PAMAM) dendrimers	Increased antibacterial activity, sustained drug release	45

CONCLUSION:

Nanoemulsions are translucent, isotropic fluid mixtures of surfactant, co-surfactant, and oil that are stable from a thermodynamic perspective. It is the most efficient dosage form for labile drug protection, drug release control, boosting low-water soluble drug solubility, improving bioavailability, and decreasing patient variability. Today, nanoemulsion can be created for a number of administration routes. A nanoemulsion formulation can be considered an effective, secure, and patient-compliant pharmaceutical delivery method. The stability of the formulation might be increased by controlling factors including the kind and amount of surfactants and co-surfactants, the variety of oil phases, the techniques used, and the variables in the process.

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