NANOEMULSION- AN INNOVATIVE DRUG DELIVERY SYSTEM TO IMPROVE WATER SOLUBILITY OF CLEVIDIPINE

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Abstract

Nanoemulsion is an advanced drug delivery system designed to enhance the solubility, stability, and bioavailability of poorly water-soluble drugs. Clevidipine, a third-generation dihydropyridine calcium channel blocker, is highly lipophilic and exhibits low aqueous solubility, limiting its therapeutic efficacy in conventional formulations. Nanoemulsion-based delivery systems offer a promising approach to overcome these limitations by dispersing clevidipine within a nanosized oil-in-water emulsion, improving its dissolution, absorption, and pharmacokinetic profile. The nanoemulsion formulation ensures rapid onset of action, controlled drug release, and enhanced stability while minimizing dose-related side effects. By leveraging biocompatible surfactants and stabilizers, nanoemulsions provide a scalable and efficient method for intravenous administration of clevidipine, optimizing its antihypertensive effects in acute settings. This innovative strategy not only enhances drug solubility but also improves therapeutic outcomes, making nanoemulsions a viable platform for the effective delivery of clevidipine in clinical applications.

Keywords: Nanoemulsion, Clevidipine, Drug Delivery System, Water Solubility, Bioavailability, Oil-in-Water Emulsion, Calcium Channel Blocker, Intravenous Formulation, Pharmacokinetics, Controlled Drug Release.

1. Introduction

The ultrashort-acting dihydropyridine calcium channel blocker clevidipine (Cleviprex) exhibits a quick onset and offset of action, effectively lowering blood pressure (BP) by diminishing arteriolar resistance while leaving venous capacitance vessels unaffected. This article examines the clinical effectiveness and tolerability of intravenous clevidipine in the management of BP within perioperative and intensive care environments, and also outlines its pharmacological characteristics. According to findings from the randomized, multicentre, double-blind, phase III ESCAPE-1 and ESCAPE-2 trials, intravenous clevidipine successfully managed preoperative and postoperative hypertension in patients undergoing cardiac surgery. The

randomized, open-label, multicenter, phase III ECLIPSE trials revealed that for maintaining systolic blood pressure within the desired range, clevidipine proved to be more effective than nitroglycerin or sodium nitroprusside during the perioperative period, and had comparable effectiveness to nicardipine after surgery in patients undergoing cardiac procedures. In smaller, double-blind studies involving individuals having coronary artery bypass graft surgery, perioperative clevidipine was shown to be noninferior to nitroglycerin, while postoperative clevidipine demonstrated similar effectiveness to sodium nitroprusside. Noncomparative research indicated that clevidipine achieved rapid blood pressure control in patients suffering from acute neurological conditions (such as intracerebral hemorrhage, subarachnoid hemorrhage, and acute ischemic stroke), and was largely not linked to 'overshoot' in most patients. Intravenous clevidipine was generally well accepted and typically did not cause reflex tachycardia or resulted in only minor increases in heart rate. [1].

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1.2 Nanoemulsion

A prospective solution to flaxseed oil's low oxidation stability is the nanoemulsion embedding system. Nanoemulsion is a significant type of oil in food. Researchers have worked to create efficient encapsulation technologies in recent years to address flaxseed oil's low oxidative stability. technologies based on nanoemulsions are especially well-suited for encapsulating and conveying lipophilic bioactive ingredients. A nanoemulsion is a dispersion system created by dispersing one or more substances into another liquid in the form of droplets, and it is a hydrophobic nucleus created by the creation of the tail group of a surfactant or cosurfactant

and imbedded in the dispersed phase [3]. A popular delivery method utilized in a variety of industries, including food and drink, cosmetics, and medicines, is nanoemulsion. Nanoemulsion offers more application benefits than both regular emulsion and microemulsion. The nanoemulsion's particles are tiny. The tendency for particles to aggregate decreases with decreasing particle size, and flocculation, delamination, and other phenomena brought on by austenite solidification and gravity during the static phase are reduced. Numerous factors, including preparation technique, affect the stability of nanoemulsions [4]. Nanoemulsion preparation is dependent on external energy input and may be classified as either low-energy or high-energy based on the energy input technique. Spontaneous emulsification, phase transition, and other low-energy techniques are frequently employed and offer the benefits of minimal equipment needs, straightforward operation, and minimal heat production during the preparation phase. Poor stability of the prepared sample is the drawback. The widely used high-energy techniques were separated into phacoemulsification, high-pressure homogenization, microfluidization, and others. These techniques have the benefits of high sample stability and small emulsion particle size, but they also have the drawbacks of more complex equipment and significant heat generation during the preparation process. The kind of emulsifier also has a significant impact on the physical and chemical stability of the nanoemulsion. The size of the droplets created during homogenization and their resilience to ensuing environmental changes are both significantly influenced by the type of emulsifier used [5]. Consequently, choosing the best emulsifier for the creation and stability of a nanoemulsion is crucial. Proteins, phospholipids, and polysaccharides are currently often utilized as food emulsifiers in the food business due to their wide dispersion, environmental stability, biocompatibility, and friendliness. [6].

1.2.1 Advantages of Nanoemulsion:

- It's a strategy to increase the bioavailability and water solubility of lipophilic medications.
- Assists in taste masking and stabilizing lipophilic medications.
- Because the medicine is encapsulated in oil droplets, it is protected against oxidation and hydrolysis.
- Increase the drug's ability to penetrate the skin.
- Because droplets are nanoscale, their area is large, which speeds up absorption and lowers variability, improving the drug's bioavailability.

- They must be able to transport peptides that the GIT's enzymes can hydrolyze.
- The employment of Nanoemulsion as delivery methods can increase the effectiveness of a medicine, allowing the full dose to be lowered and therefore decreasing adverse effects.[7]

1.2.2 Disadvantages of Nanoemulsion:

- Large concentrations of surfactant and co-surfactant are required to stabilize the nanodroplets;
- preparation calls for specialized equipment; the solubility of top melting substances is limited;
- The surfactant must be nontoxic for pharmaceutical use;
- Environmental factors such as pH and temperature affect NE stability. [8]

1.2.3 Advantages over other Dosage Forms

- A higher absorption rate and less absorption variability.
- Defense against hydrolysis and oxidation in O/W nanoemulsions.
- Delivery of lipophilic medicines following solubilisation.
- Aqueous dosage form for medications that are insoluble in water.
- A number of medications have improved bioavailability.
- Ability to contain both lipophilic and hydrophilic medicines.
- Delivery methods to increase effectiveness while lowering dosage and adverse effects.
- As non-toxic and non-irritant vehicles for skin and mucosa administration and release control via penetration of medication through liquid film, whose hydrophilicity or lipophilicity aswell as thickness are typically accurately regulated.
- Because nanoemulsions are thermodynamically stable, they can self-emulsify systems whose characteristics aren't conducive to the strategy being used.
- Increase a drug's effectiveness so that the whole dosage can be lowered, reducing adverse effects.

1.2.4 Types of Nanoemulsion

- **Water in oil (W/O) Nanoemulsion:** During which droplet of Water was dispersed in continuous phase oil. [9]

- **Oil in water (O/W) Nanoemulsion:** During which Oil droplet was dispersed in continuous phase Water.
- **Bi-continuous Nanoemulsion:** During which Surfactant was soluble in both oil as well as water Phase, and droplet was dispersed in both oil also as water phase. [10]

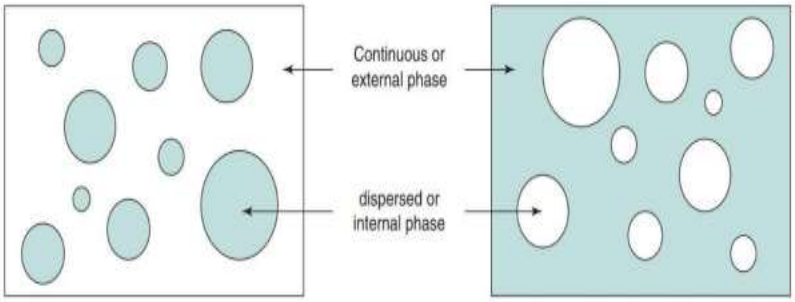

Figure 1: Oil in Water (O/W) and Water in Oil (W/O) Emulsion

1.2.5 Component of nanoemulsion

- **Oil**

For the chosen drug candidate to have the maximum solubilizing potential for nanoemulsion formulation, the oil is essential. With its great drug loading capacity, this is frequently the most important strategy. Triglycerides are found in long-chain fatty acids and are found in both naturally occurring and artificially produced oils and fats. Triglycerides are within the short-chain category. Twelve-carbon triglycerides are essential for reducing the level of unsaturation and halting oxidative deterioration. The power of the solubilized drugs is what determines which oil phase is best for the nanoemulsion. The oil is critical to increases friction to maneuver of drug into intracellular compartment is critical to increases water solubility of less water-soluble drug. For example, the combination of fatty oils and medium-chain triglycerides (MCTs) plays a crucial role in achieving an optimal balance between drug loading capacity and the efficiency of emulsification or nanoemulsification [11]. The selection of long-chain and medium-chain triglyceride oils with varying degrees of saturation is essential in designing Self-Microemulsifying Drug Delivery Systems (SMEDDS). Triglycerides, being highly lipophilic, serve as effective solvents for drugs, with their solubilization capacity largely influenced by the concentration of ester groups. Compared to long-chain triglycerides, MCTs exhibit a higher solvent capacity and greater resistance to oxidation, making them a preferred choice for enhancing drug solubility and stability. The water solubility of poorly soluble drugs is influenced by MCT, which is now replaced by novel semi-synthetic MCT. Oils, whether digestible or not, and fats such as olive, palm, corn, sesame, soybean, and hydrogenated oils, as well as oleic acid, alter oil phases to improve solubility [12]

- **Surfactant**

The term "surfactant" refers to molecules and ions that are adsorbed at the contact. It can provide interfacial tension and prevent the interfacial nature phenomena. It is a key ingredient in the creation of nanoemulsion. Its action has self-Drugs that are poorly soluble in water can be dissolved by using self-emulsifying, self-nanoemulsifying, and self-micro emulsifying agents. For the purpose of creating an emulsifying system, the majority of chemicals possess the characteristics of surfactants [13]. It is okay to take the restricted surfactant unit orally. Hydrophilic and Lipophilic Balance (HLB) is high in non-ionic surfactants. Although a large amount of surfactant might be chemically harmful, the ideal amount is used to make nanoemulsions. The selection of surfactants is a critical factor in formulation design, with safety being a major consideration. Surfactant molecules can be derived from both natural and synthetic sources, but they possess a limited capacity for self-emulsification. Non-ionic surfactants are generally preferred over ionic surfactants due to their enhanced stability, non-toxic nature, and thermodynamic compatibility. The concentration of surfactants plays a key role in determining droplet size during emulsification and nanoemulsification processes, as it directly influences the stabilization of oil droplets within the surfactant system [14]. Notably, an increase in surfactant concentration typically leads to an increase in droplet size, which can impact the overall stability and performance of the formulation. It’s vital component of preparation of Nanoemulsion system for improving the solubility of poorly water-soluble drugs [15]

- **Co-surfactant**

The function of a co-surfactant is comparable to that of a surfactant unit. In order to boost the surfactant's ability to improve the water solubility of drugs that are not very water soluble, co-surfactant was added either in combination with or in addition to the surfactant unit. To stop interfacial fluidity, the cosurfactant, which is a single chain surfactant unit, is prepared. The monomolecular layer of the surfactant molecule can separate the co-surfactant molecule from the surfactant, oil, and water. The surfactant molecule's monomolecular layer is known as the liquid crystal formation layer. In self-nanoemulsifying drug delivery systems (SNEDDS), the primary use of co-surfactants is to prevent the natural interfacial phenomena between the water and oil interface. cosurfactant such as propylene glycol, ethanol, methanol, pentanol, and glycol [16]

1.2.6 Method of Preparations

High-energy stirring, ultrasonic emulsification, high homogenization, including micro fluidics, and membrane emulsification are among the high-energy methods for preparing nanoemulsions; the phase inversion temperature method, the emulsion inversion point method, and consequently the spontaneous emulsification are among the low-energy emulsification methods; and it is possible to organize reverse nanoemulsions in highly viscous systems by using a combined method that combines the high-energy and low-energy emulsifications. Potential areas of nanoemulsion applications are taken into consideration after discussing the main benefits and drawbacks of various nanoemulsion preparation techniques. [17]

1.2.6.1 High Energy Methods

- **High-Pressure Homogenization**

Using a high over the system that contains an oil phase, an aqueous phase, and a surfactant or co-surfactant is how this process is carried out. A homogenizer is used to help apply the pressure. Poor productivity and component breakdown that produces a lot of heat are some issues with homogenizers. Only Oil in Water (O/W) liquid nanoemulsions with less than 20% oil phase are often made using this technique; cream nanoemulsions with high viscosity or hardness and a mean droplet diameter of less than 200 nm cannot be made. [18]

- **Micro fluidization**

The "MICRO FLUIDIZER" is a tool used in micro fluidization technology. A high-pressure positive displacement pump (500–200 PSI) is used in this device to push the product into the interaction chamber, which is made up of tiny channels known as microchannels. After passing through the microchannels, the goods reaches an impingement region where it is reduced to extremely tiny particles in the submicron range. To create a course emulsion, the two solutions—the oily phase and the aqueous phase—are mixed and run through an inline homogenizer. To create a stable nano emulsion, the course emulsion is passed through a micro fluidizer for further processing. [19]

- **Ultra-sonication**

When it comes to cleaning and operation, ultra-sonication is superior to other high energy techniques. Ultrasonic waves create cavitation forces in ultrasonic emulsifications, which cause the macroemulsion to split into a nanoemulsion. This technique makes use of ultrasonicators, which have a search that produces ultrasonic waves. It will accomplish the desired particle size

and stability of the nanoemulsion by adjusting the ultrasonic energy input and duration. The technique of acoustic cavitation in particular provides physical shear in ultrasonic emulsification. Cavitation is the process via which microbubbles develop, expand, and ultimately collapse; it is brought on by variations in the sound wave's pressure. When microbubbles collapse, there is a great deal of turbulence, which leads to the creation of nanodroplets. When ultrasonic radiation is applied to an oil and water system, cavitation forces are created, and surplus energy is supplied to create brand-new interface structures and nano-sized emulsion droplets. Nanoemulsions are frequently created by ultrasonication without the use of surfactants. A recent study shown that the intensity, duration, and kind of surfactant all affect how well ultrasonic emulsification works. Ultrasonication has been widely employed to create food and pharmaceutical component nanoemulsions. Compared to previous high-energy methods, food-grade ultrasonication nanoemulsion exhibits superior stability, smaller droplet sizes, and needs less energy input [20].

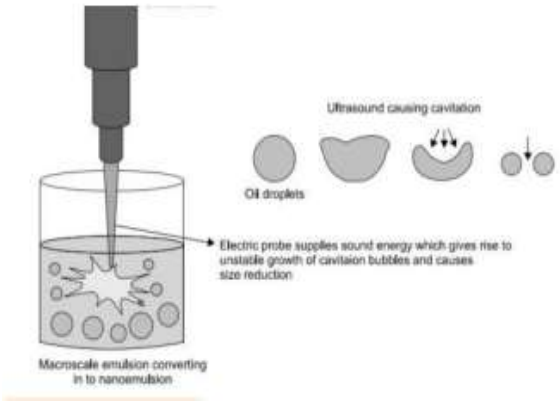

Figure 2: Ultrasonication

1.2.6.2 Low Energy Methods

- **Phase Inversion Emulsification Method**

During the emulsification process, this method's phase shift is caused by the surfactant's spontaneous curvature. Changes in temperature, composition, and other factors can alter the surfactant's spontaneous curvature. Phase inversion emulsification techniques come in two varieties: TPI techniques, which use PIT and PIC, and CPI techniques, which use EIP. When the surfactant's spontaneous curvature or affinity varies in response to variations in variables like temperature and composition, transitional phase inversion occurs [21]. On the other hand, CPI happens when dispersed particles are constantly introduced until their drops coalesce to form bicontinuous/lamellar structural phases. A catastrophe occurs when a system's behavior abruptly changes as a result of shifting circumstances. It is crucial that the surfactant is mostly

present in the dispersed particles for catastrophic phase inversion to occur; this causes a high rate of coalescence, which in turn causes fast phase inversion. The spontaneous curvature or surfactant affinity is altered during transitional phase inversion, whereas it remains unchanged during catastrophic phase inversion. [22]

A. Phase Inversion Temperature (PIT)

The Hell method uses temperature changes to inverse the spontaneous curvature of surfactants. The POE groups of polyethoxylated surfactants are dehydrated in non-ionic surfactants, such as polyethoxylated surfactants, making the surfactant more lipophilic and changing its curvature. Thus, phase inversion occurs and nanoemulsion is created [23]. This process creates oil-in-water (O/W) emulsions by mixing water, oil, and non-ionic surfactants at a certain temperature. The surfactant POE groups then undergo dehydration as a result of the temperature progressively rising, making the surfactant more lipophilic and beginning to exhibit a greater affinity for the oily phase. Through intermediary liquid crystalline or bi-continuous structures (such as the lamellar phase), this results in a phase inversion from the beginning of the O/W emulsion to the water-in-oil (W/O) nanoemulsion. The non-ionic surfactant has zero curvature and has the same affinity for the aqueous and oily phases at hydrophile-lipophile balance (HLB) temperatures, which are intermediate temperatures. Rapid cooling or heating of HLB (to produce O/W or W/O emulsions, respectively) is necessary for effective phase inversion. Kinetically stable nanoemulsion is produced by rapid heating or cooling [24]

B. Phase Inversion Composition (PIC):

Similar to the PIT method, the phase inversion composition, or PIC, approach achieves phase inversion by altering the composition of the system rather than the temperature. PIC involves adding one of the ingredients, such as water, to a combination and either adding oil to the water-surfactant mixture or adding oil to the water-surfactant mixture. Although various kinds can be employed, POE type non-ionic surfactants are often used in the PIC technique to create nanoemulsions. Surfactant POE chain hydration happens when water is gradually introduced to the oil phase and the amount of the water fraction rises [25]. The water phase's hydrophilic-lipophilic surfactant characteristics will be balanced, and the surfactant's spontaneous curvature will decrease to zero, nearly identical to the HLB temperature within the PIT. During this transition, a bi- continuous or lamellar structure is made. When additional water is added the transition composition is exceeded, and therefore the structures of the surfactant layer with zero

curvature change to having high positive curvature [26]. This alteration in curvature results in phase inversion and causes nano-size droplet formation. Thus, changing the composition of the system causes phase inversion. Similarly, other composition parameters, like the addition of salt and pH. Figure 5 Phase Inversion Emulsification Techniques changes, also cause nano-size emulsion droplets by transitional phase inversion [27].

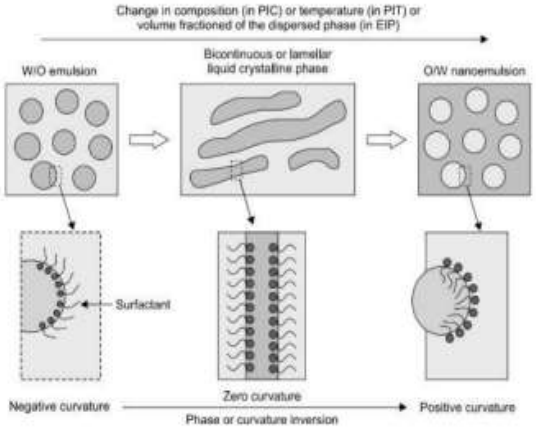

Figure 3: Phase Inversion Emulsification Techniques

C. Emulsion Inversion Points (EIP)

Phase inversion in the EIP approach happens via CPI processes. Instead of altering the surfactant characteristics, the fractioned volume of the dispersed particles is changed to cause the Catastrophic Phase Inversion (CPI). The system begins to function as a W/O nanoemulsion because the water phase is introduced into the oilsurfactant mixture [28]. Water droplets merge with one another when increasing volumes of water are added over a certain water content while stirring continuously; this results in the formation of bi-continuous or lamellar structures. Through an intermediate bi-continuous microemulsion, further dilution with water results in phase inversion from a W/O to an O/W system. The procedure factors, such as the rate at which water is added and, therefore, the rate at which stirring occurs, determine the sizes of the nanoemulsion droplets that are created. The surfactant must be mostly present in the scattered particles for catastrophic phase inversion to occur; as a result, there is a high rate of coalescence and fast phase inversion [29]. When it comes to catastrophic phase inversion, small molecule surfactants are frequently used. Both W/O and O/W emulsions can be stabilized with these surfactants. Initially in catastrophic phase inversion, the surfactant is especially present within the dispersed particles, thus it behaves as an abnormal emulsion (unstable emulsion) which doesn't obey Bancroft's rules. Consistent with Bancroft's rules, for a stable emulsion (normal emulsion) emulsifier should predominantly present within the continuous phase. Therefore,

catastrophic phase inversion occurs from the abnormal emulsion to make a more stable normal emulsion.[30]

1.2.6.3 The shelf-nano emulsification method

The self-emulsification approach creates nanoemulsions without altering the surfactant's spontaneous curvature. Turbulence and nano-sized emulsion droplets are produced when surfactant and/or co-solvent molecules quickly diffuse from the dispersed phase to the continuous phase [31]. Because of the spontaneous emulsification process, the self-emulsification method is also cited. SNEDDS have a reduced lipid content, more hydrophilic surfactants or co-surfactants (co-solvents), and facilitate the self-emulsification process.xxiii An isotropic combination of an oil, surfactant, co-surfactant, and medication is a common definition of SNEDDS. Due to the mild agitation caused by the stomach and intestine's digestive motility, this combination produces a thin and optically transparent O/W nanoemulsion when diluted by aqueous fluids in vivo. Diffusion of the hydrophilic co-solvent or co-surfactant from the organic phase into the aqueous phase and the production of nanoemulsion negative free energy at transitory negative or ultralow interfacial tensions are the two most often documented processes of nanoemulsion generation from SNEDDS. The most widely used and promising method for delivering hydrophobic medications with limited bioavailability is SNEDDS. Bioactive food ingredients have also been delivered via SNEDDS. [32].

1.2.7 Applications

One extremely intriguing use of nanotechnology may be the cell-specific delivery of medications. By encapsulating toxic agents and reducing off-target interactions, delivery vehicles made of smart materials with adjustable physical and biological properties will enhance current therapeutic approaches. They will also increase the bioavailability of poorly soluble drugs, giving them tissue or cell specificity, and facilitating or enhancing intracellular delivery.[33] Colloidal dispersions known as nanoemulsions are made up of an oil phase, an aqueous phase, and surfactant and co-surfactant in the proper proportions. in contrast to coarse emulsions that have been micronized using external energy. Low interfacial tension supports nanoemulsions. This is frequently accomplished by the addition of a co-surfactant, which causes a thermodynamically stable nanoemulsion to develop spontaneously [34]. Emulsions with internal phase droplets smaller than 1000 nm are commonly referred to as nanoemulsions. Mini emulsions, ultrafine emulsions, and submicron emulsions are other names for the

nanoemulsions. Phase behavior investigations have demonstrated that the surfactant phase structure (bicontinuous microemulsion or lamellar) at the inversion point caused by either composition or temperature controls the droplet diameter. Regardless of whether the initial phase equilibrium is one or multiphase, research on nanoemulsion creation using the phase inversion temperature approach has demonstrated a correlation between the minimal droplet size and full oil solubilization during a microemulsion bicontinuous phase. Because of their small droplet size, nanoemulsions are stable against creaming or sedimentation, and the most common process of nanoemulsion breakdown is Ostwald ripening. [35]The primary distinction between an emulsion and a nanoemulsion is that the former is hazy in appearance, while the latter is kinetically stable but thermodynamically unstable. Vaccine delivery, cancer treatment, pulmonary drug delivery, nontoxic disinfectant cleaner, cell culture technology, formulations for better oral delivery of poorly soluble drugs, ocular and optic drug delivery, intranasal drug delivery, parenteral drug delivery, cosmetics, and transdermal drug delivery are just a few of the applications for nanoemulsions.[36]

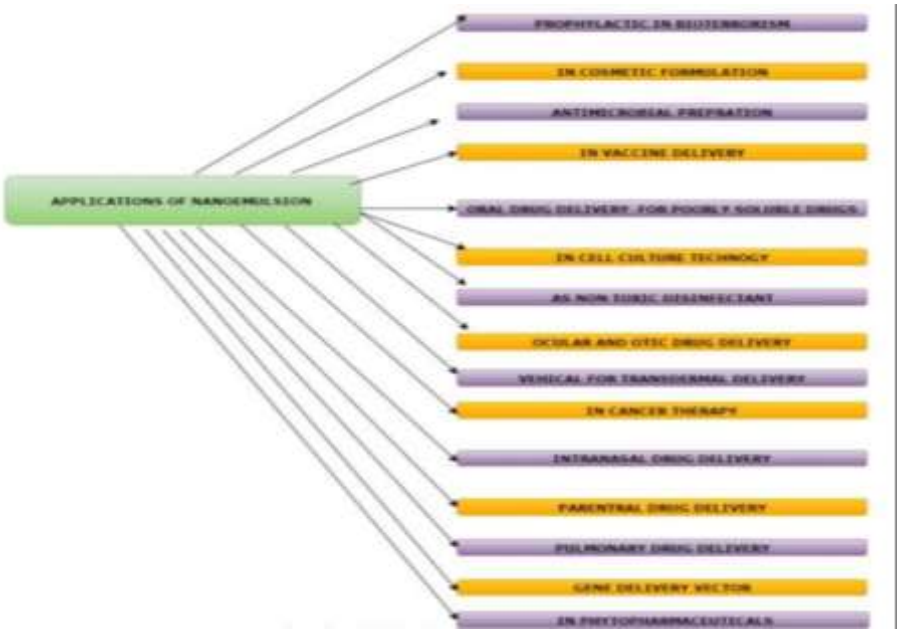

Figure 4: Application of Nanoemulsion

2. Conclusion

In conclusion, nanoemulsion-based drug delivery systems offer a promising approach to enhancing the water solubility and bioavailability of poorly soluble drugs like clevidipine. Clevidipine, a short-acting calcium channel blocker used for hypertension management, faces

solubility challenges due to its lipophilic nature. Nanoemulsions, with their nanoscale droplet size, high surface area, and efficient drug encapsulation, provide an effective means to improve its aqueous dispersion, stability, and rapid onset of action. This novel formulation not only enhances drug solubility but also ensures better pharmacokinetic performance, controlled drug release, and reduced variability in therapeutic response. Therefore, nanoemulsion technology holds great potential in optimizing clevidipine's clinical efficacy, making it a valuable strategy for improving treatment outcomes in hypertensive emergencies.

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