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ENHANCEMENT OF THERAPEUTIC ACTION OF ANTI-HYPERLIPIDEMIC DRUGS BY USING A NOVEL NANOSUSPENSION-BASED APPROACH

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ABSTRACT: Hyperlipidemia is an elevated condition of lipid levels in the body and is known to speed up a process of atherosclerosis that may prove fatal in the development of various cardiovascular diseases. The figures of the patient with hyperlipidemia are constantly increasing which is rising a serious risk factor for a group of cardiovascular diseases. Although various pharmacotherapy for hyperlipidemia namely statins, niacin, fibric acid derivatives, cholesterol absorption inhibitors, and bioactive are available but suffer from various hurdles such as inadequate solubility and poor absorption leading to low bioavailability and ineffectiveness in lowering of cholesterol levels only up maximum 40%. Hence it is required to combat these hurdles associated with hyperlipidemia. Nanotechnology has provided revolutionary changes in medicine, providing a novel approach to treating hyperlipidemia. Various nanotechnology-based approaches include nanosuspension, nanoemulsion, nanoparticle, polymeric nanoparticle, dendrimer, polymeric micelle, *etc*. out of which nanosuspension has provided a strong background to combat the hurdles linked with pharmacotherapy due to possession of various benefits such as improved aqueous solubility, enhanced bioavailability, fast onset of action, reduced dosing regimen, enhanced dosing frequency, easy to prepare to contribute overall to patient compliance. Hence, this review provides deep knowledge about pharmacotherapy, bioactive used in hyperlipidemia, hurdles associated with drugs used in hyperlipidemia, the requirement of nanosuspension to combat these hurdles, recent research on nanoemulsion for anti-hyperlipidemic drugs along with patents and marketed formulations.

INTRODUCTION: Hyperlipidemia is a disorder wherein the concentrations of lipids, or fatty compounds present in the bloodstream are unusually high. Hypercholesterolemia or hyperlipoproteinem.

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The major cause of hyperlipidemia is an elevation in lipids such as cholesterol, LDL (low-density lipoproteins) and triacylglycerides (TGs) [1]. The major cause of hyperlipidemia is a lipid metabolic problem caused by low lipoprotein lipase (LPL) activity or a lack of surface apolipoprotein C-II.

Stressors, such as genetic defects and environmental elements, can also play a role [2]. It is the most common risk factor for atherosclerosis and associated disorders such as cardiovascular disease, peripheral arterial disease, ischemic

vascular disease and pancreatitis [3]. It has been established that high cholesterol and LDL in the blood are the primary causes of atherosclerotic arteries, while high concentrations of HDL in the blood are beneficial [4, 5]. The heart is impacted by elevated cholesterol and triglyceride disorders, resulting in cardiovascular disease, cardiac arrest, and stroke [6].

The prevalence of hyperlipidemia is relatively high throughout the world. According to a study, plasma LDL-cholesterol levels indicate a clear upward trend with socioeconomic progress. In 2019, high plasma LDL-cholesterol levels were responsible for 4.40 million deaths and 98.62% million disability-adjusted life years (DALYs).

As per a report in 2019, Ischaemic heart disease was the reason for deaths of 8.54 million, among 3.78 million were due to high plasma cholesterol levels, and ischaemic stroke was a reason for 2.73 million deaths, out of which 0.61 million were due to higher plasma cholesterol levels [7]. Various types of hyperlipidemia as a risk factor for cardiovascular diseases have been summarised in **Table 1.**

However, various therapeutic moieties are available to treat hyperlipidemia. Still, they are associated with some hurdles like inadequate solubility, poor absorption leading to low bioavailability, and ineffectiveness in lowering of cholesterol levels only up to a maximum 40%, higher adverse effects leading to ineffective treatment.

These hurdles have prompted to design and develop a novel approach that can enhance the effectiveness of the treatment by combating these hurdles. Nanotechnology has provided various novel approaches like nanosuspension, nanoemulsions, nanoparticles, polymeric nanoparticles, dendrimers, polymeric micelles, *etc* to overcome these hurdles associated with conventional therapeutic moieties [8].

But among these approaches, nanosuspension has drawn the attention of formulation scientists due to various benefits, improved aqueous solubility, enhanced bioavailability, fast onset of action, reduced dosing regimen, enhanced dosing frequency, improved drug loading, ease to prepare to contribute overall to patient compliance [9] **Fig. 1.**

TABLE 1: VARIOUS TYPES OF HYPERLIPIDEMIA [10]

Type	Generic name	Characteristic features	
		Lipoproteins	Lipids
Type I	Familial chylomicronemia	Elevated levels of chylomicrons	Elevated levels of triacylglycerols, cholesterols
Type II	Combined hyperlipidemia	Elevated levels of LDL, VLDL	Elevated levels of triacylglycerols and cholesterol
Type III	Dysbetalipoproteinemia/ Remnant hyperlipidemia	Elevated levels of β-VLDL/ LDL	Elevated levels of triacylglycerols and cholesterol
Type IV	Hypertriglyceridemia/Simple Hyperlipimia	Elevated levels of VLDL	Elevated levels of triacylglycerols
Type V	mixed hyperlipidemia/ Hypertriglyceridemia	Elevated levels of VLDL, chylomicrons	Excess triacylglycerols and cholesterol

Pharmacotherapy as Treatment for Hyperlipidemia: Numerous drug moieties belonging to different categories as viable treatment options are available to reduce the lipid profile in hyperlipidemia which includes HMG-CoA reductase inhibitors (statins), fibrates, acid-binding resins (cholestyramine, cholestipol), nicotinic acid (niacin) and cholesterol absorption inhibitors (ezetimibe) amongst HMG-CoA reductase inhibitors (statins) and fibrates are most important drug categories used as anti-hyperlipidemic drugs [10]. These drug moieties act *via* different pathways to reduce the lipid profile, which has been depicted in **Fig. 2**. Even though various drug moieties are available as anti-hyperlipidemic treatment, there are still a few hurdles with the currently available anti-hyperlipidemic drugs, which include poor aqueous solubility, low bioavailability due to possession of higher log P values, first-pass metabolism, higher adverse effects, drug interactions, *etc.* [11] which has been summarized into the **Table 2**.

These hurdles associated with anti-hyperlipidemic drugs must be overcome to improve the efficiency of available treatment for hyperlipidemia.

TABLE 2: PHARMACOKINETICS OF ANTI-HYPERLIPIDEMIC DRUGS

Category	Drugs	Log P value	Aqueous solubility	Bioavailability	Half-life	Active metabolite	References
HMG-CoA Reductase inhibitors	Atorvastatin	5.7	Insoluble	12%	14 hours	Yes	[12]
	Simvastatin	4.68	Insoluble	5%	3 hours	No	[13]
	Lovastatin	4.26	Insoluble	5%	5.3 hours	No	[14]
	Fluvastatin	3.69	Insoluble	24%	3 hours	Yes	[15]
	Cerivastatin	3.4	Insoluble	60%	2-3 hours	Yes	[16]
	Pravastatin	0.59	Soluble	18%	77 hours	No	[17]
	Rosuvastatin	1.47	Sparingly soluble	20%	19 hours	Minor	[18]
	Pitavastatin	3.75	Insoluble	60%	12 hours	Minor	[19]
Fibrates	Fenofibrate	4.86	Insoluble	Approx.. 30%	20 hours	Yes	[20]
	Gemfibrozil	3.61	Insoluble	Approx. 100%	1.5 hours	Yes	[21]
	Bezafibrate	3.97	Insoluble	Approx. 70%	1-2 hours	No	[22]

Drug Delivery Systems for Anti-hyperlipidemic Drugs: Drug delivery systems are the ways of delivering drugs to desired tissues, organs, cells, and subcellular organs *via* a variety of drug carriers for drug release and absorption [23]. Tablets, capsules, syrups, *etc*., are conventional drug delivery systems that are the first choice of scientists to deliver the drug to the body owing to various benefits like self-administration, accurate dose, ease of administration, low cost, and patient compliance.

But these drug delivery systems suffer from various hurdles like frequent administration for the drugs having low half-life, which increases the chances of missing the dose of the drug, fluctuations in steady-state drug plasma concentration, poor aqueous solubility, extensive first-pass metabolism leading to low bioavailability, lack of drug targeting, the prolonged onset of action, higher adverse effects, which enforced the modification in conventional drug delivery systems resulting in innovative drug delivery systems which mainly include nanotechnology-based drug delivery systems [24, 25].

1.4nanosuspension as Drug Delivery Systems for Hyperlipidemia: In the last few times, scientists have made multiple endeavors to design and test several innovative drug delivery systems that can help to overcome the hurdles of certain drugs and the conventional drug delivery systems associated with them [26].

These innovative drug delivery systems are mainly based on nanotechnology including nanoemulsion, nanosuspension, nanoparticles, polymeric nanoparticles, dendrimers, polymeric micelles, *etc* out of which nanosuspension is gaining more attention due to various attributes like improved aqueous solubility, enhanced bioavailability, fast onset of action, reduced dosing regimen, enhanced dosing frequency, improved drug loading, easy to prepare to contribute overall to patient compliance. Furthermore, nanosuspension is the only choice available when a drug candidate has many limitations, such as an inability to produce salt, a large molecular weight, a high dose, a high log P, and a high melting point.

Nanosuspensions can tackle such unique drug delivery difficulties by preserving the active pharmaceutical ingredients (API) in a crystalline state while allowing for greater drug loading during formulation development.

Because of the reduced usage of toxic non-aqueous solvents and extreme pH, accommodating a big medication amount with a small dose volume provides further benefits in parenteral and ophthalmic drug delivery systems. Enhanced stability, extended drug release, increased efficacy through tissue targeting, minimal first-pass metabolism, and deep lung deposits are among the other benefits [27].

Nanosuspension is a heterogeneous mixture of drug molecules stabilized using surfactants [28, 29]. A pharmacological nanosuspension is a finely distributed submicron size drug particle in a liquid suspension for oral, topical, and injectable application, as well as pulmonary delivery [30].

The size of drug particles in nanosuspension is generally smaller than 1μm (typically around 200nm and 600nm). Various anti-hyperlipidemic drugs formulated as nanosuspension have been summarized in **Table 3.**

TABLE 3: VARIOUS ANTI-HYPERLIPIDEMIC DRUGS FORMULATED AS NANOSUSPENSION

Drug candidate	Polymer	Outcomes	Reference
Atorvastatin calcium	Polyvinyl pyrrolidone	The improved dissolution rate of formulation than the pure drug	31
Simvastatin	Soluplus	Improved cytotoxic effect was found in pure drug	32
Simvastatin	PVPK-30, Sodium lauryl sulphate	Improved dissolution rate and particle size using a higher concentration of PVPK-30 than a higher concentration of sodium laurl sulphate	33
Fluvastatin	Cyclodextrin, poloxamer 407	2.4 fold improvement in bioavailability using formulation than capsules of the drug	34
Lovastatin	HPMC K15M, PVP K-30, N-CMC	Formulation having 1% w/v PVP K-30 provided improved biovailability than conventional tablets	35
Fenofibrate	Poloxamer 188, PVP-K30, Polysorbate 80	Nanosuspension provided a higher mean Cmax (82.63%), AUC0–36h (69.34%), shorter Tmax (51.46%), and shorter MRT (11.92%) than drug suspension indicating easier absorption of nanosuspension	36
Fenofibrate	Poloxamer 188, PVP K-30	Improved AUC0–36 h and Cmax of nanosuspensios than reference formulations	37
Rosuvastatin	HPLMC, PVPK-30, Pluronic F-127, PEG 6000, Tween 80	C_{max} and AUC increased significantly by 8.2-folds and 21.1-folds from rosuvastatin nanosuspension prepared by 10% PVP than conventional rosuvastatin	38
Ezetimibe	Tween 80	3-fold higher C_{max} was found using ezetimibe than conventional suspension on oral administration	39

Adverse Effects Associated with Statin Therapy: As a result, liver impairment is a potential factor for myopathy caused by statin therapy, as well as many other serious conditions such as myopathy, rhabdomyolysis [40] broken heart syndrome, idiopathic inflammatory myopathy (IIM), myalgia and arthralgia and so on [41, 42] and all physicians advise caution while recommending statin drugs. Long-term administration typically results in excessive concentrations of liver function tests that could lead to significant liver damage. Some statins, such as lovastatin and Simvastatin, penetrate the blood-brain barrier (BBB), raising the risk of neurotoxic effects **Fig. 1**. Lovastatin can pass the placenta and has the potential of harming the fetus. Hyperglycemia and gastrointestinal disorders have also been reported [43].

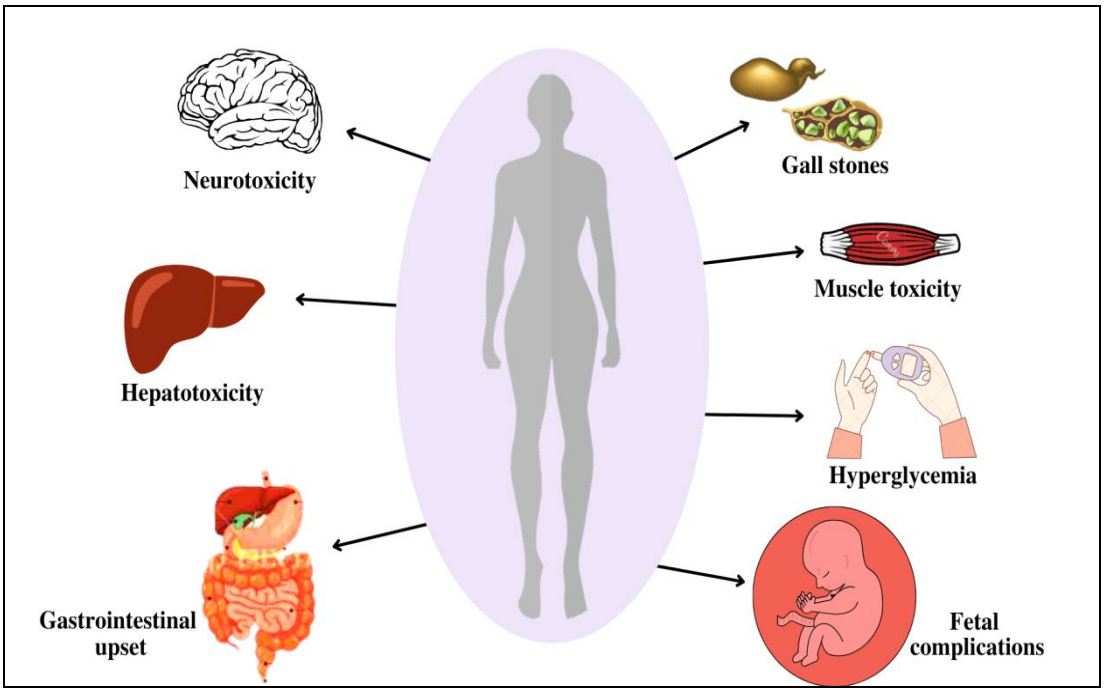

FIG. 1: ADVERSE EFFECTS ASSOCIATED WITH STATIN THERAPY

Muscle inflammatory conditions, such as myositis and rhabdomyolysis, are the most common adverse effect of fibric acid derivatives. Gallstones and increased liver function tests are the most dangerous, culminating in cholecystectomies and serious liver problems, respectively [44]. The side effects of different anti-hyperlipidemic drugs are tabulated in **Table 4.**

TABLE 4: ADVERSE EFFECTS OF DIFFERENT CLASSES OF ANTI-HYPERLIPIDEMIC DRUGS

Anti-hyperlipidemic Drugs Class	Examples	Adverse effects	Reference
HMG CoA Reductase inhibitors (Statins)	Ex: Atorvastatin, Lovastatin, Rosuvastatin, Simvastatin etc	Muscle aches, tenderness, or weakness (myalgia) Drowsiness. Dizziness	[45, 46]
Fibric acid derivatives	Clofibrate, Ciprofibrate, Fenofibrateetc	Nausea, stomach upset, and sometimes diarrhea, liver inflammation	
Bile acid binding resins	Ex: Cholestyramine, Colestipol, and Colesevelam	Abdominal pain, Bloating, Constipation, Flatulence, Gallstones, Heartburn, Vomiting, Weight loss	
Cholesterol absorption inhibitors	Ezetimibe,	Stomach pain, diarrhea, fatigue, headache, muscle soreness; contradicted in pregnancy and lactation	
Niacin derivatives	Niacin, Nicotinic acid	Flushing of the face, neck, and chest, nausea, vomiting, headache, abdominal pain, dyspepsia, diarrhea, rhinitis, rash, and pruritus	

Nanosuspension-Based Therapeutic Approach: Nanosuspensions use a variety of approaches to reduce the size of the drug particles to the nanoscale, which helps to enhance drug solubility owing to the smaller particle size [47]. The various methods used to prepare nanosuspensions are shown in **Fig. 2**.

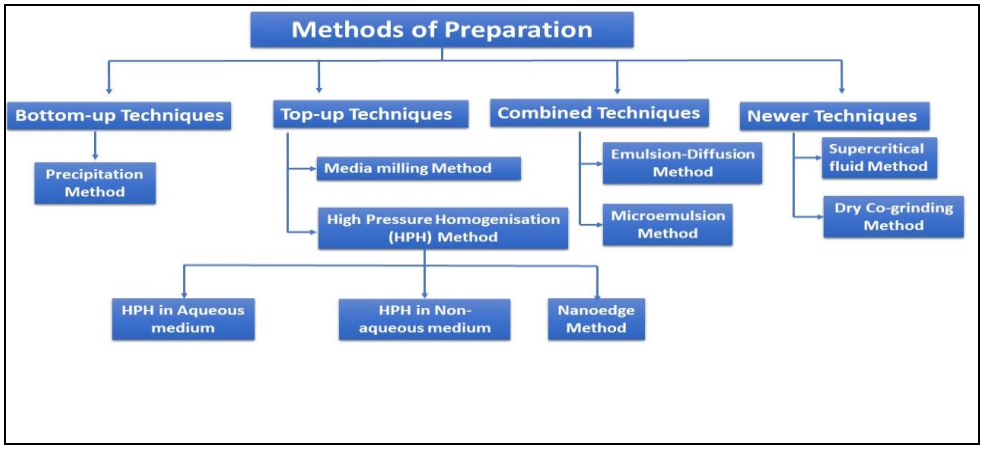

FIG. 2: METHODS OF PREPARATION OF NANOSUSPENSION

Nanosuspensions are synthesized into numerous dosage forms through post-production procedures. Because of the finer particle size and increased surface area, nanosuspension improves medication solubility and uptake [48]. Some of the FDA-approved nanosuspension-based drug formulations are given in **Table 5.** Various route of administration used for drug delivery and the mechanism of nanosuspension is explained in **Fig. 3.**

TABLE 5: CURRENTLY USED MARKETED NANOSUSPENSION-BASED DRUG FORMULATIONS

S. no.	Drug	Brand name	Disease/Disorder	References
1	Dexmethylphenidate HCL	Focalin® XR	Attention deficit hyperactivity disorder (ADHD)	[49]
2.	Fenofibrate	Triglide®/TriCor®	Hyperlipidemia	
3	Methylphenidate HCL	Ritalin® LA	ADHD	
4	Nabilone	Cesamet®	Antiemetic	
5	Finofibrate	TriCor®	Hypercholesteremia	
6	Finofibrate	Tridlide®	Hypercholesteremia	

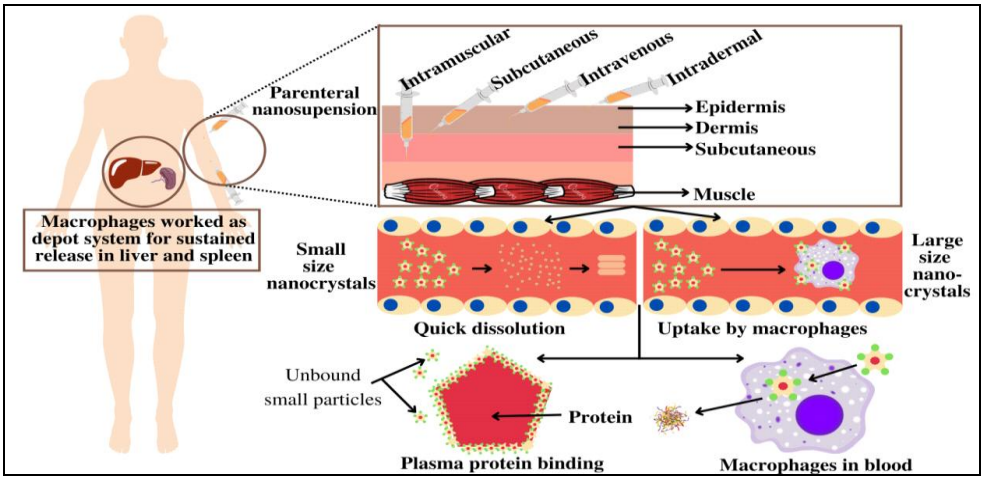

FIG. 3: MECHANISM OF NANOSUSPENSION DRUG DELIVERY IN THE BODY

Advantages of Nanosuspensions over Other Nanoparticles: Unlike solid lipid nanoparticles (SLN) that are lipid-based nanocarriers, nanosuspensions are polymeric colloidal carriers of drugs [50]. Compared to other nanotechnology drug delivery systems, where the drug is constrained to a cavity enclosed by a polymeric film or physically scattered in the matrix, nanosuspension incorporates drug nanoparticles scattered in a liquid media with no film or matrix [51]. They do not penetrate hair follicles in a size-dependent manner, unlike other nanostructures [52]. They can immediately begin to migrate through the cell wall into the cytoplasm without being entrapped inside the lysosomes, in an energy-dependent fashion [53]. About more than 40% of new chemical moieties are discovered under various innovations for lipophilic or poorly water-soluble compounds. Different formulation approaches are available to soluble solve the problems of low solubility and low bioavailability of drugs. Conventional approaches included micronization, use of fatty solutions, use of penetration enhancers or cosolvent, surfactant dispersion method, salt formation, *etc* but still these techniques have limited capacity for solubility enhancement of poorly soluble drugs. Other than these beneficial approaches are liposomes, dispersion of solids, emulsion and microemulsion method, and inclusive complexes with cyclodextrin. Comparison of various routes of administration with conventional formulation and nanosuspension

TABLE 6: REASONS FOR SELECTION OF NANOSUSPENSION ROUTE OF ADMINISTRATION [54]

Oral Route	The main disadvantage of the conventional formulation is a slow onset of action /poor absorption in comparison to this if we give nanosuspension with an oral route it will show the rapid onset of action /improved solubility so it will enhance bioavailability
Occular Route	The main disadvantage of a conventional formulation is lacrimal wash-off/low bioavailability. The benefits of nanosuspension over it are higher bioavailability and lesser irritation
Intravenous Route	The main disadvantage of the conventional dosage form is poor dissolution /non-specific action and the benefit of nanosuspension is rapid dissolution/tissue targeting prolonged retention time in the systemic circulation
Intramuscular Route	The main disadvantage of the conventional formulation is low patient compliance due to pain and the benefit of nanosuspension is reduced tissue irritation and high bioavailability. Rapid onset of action
Inhalation	The disadvantage of conventional is found to be low bioavailability due to low solubility and the benefits of nanosuspension are rapid dissolution /high bioavailability of dose regulation

Applications of Nanosuspension to Antihyperlipidemic Drugs: Nanosuspension is a heterogeneous mixture of drug with appropriate stabilizer(s) that has particle sizes under 1 µm, which helps to sustain long-term physical and physicochemical stability [55, 56]. To improve the oral administration of atorvastatin, Hashem *et al.* created solid nanosuspensions and compared them with self-nano-emulsifying drug delivery systems (SNEDDS). C_{max} of atorvastatin in nanosuspension and SNEDDS systems was 5,909.89 and 8,099.21 ng/mL, respectively. The optimized SNEDDS and nanosuspension formulation bioavailabilities were significantly improved with $AUC_{[0-\infty]}$ values of 170.28 percent and 71.80 percent, respectively.

The overall pharmacokinetic profile of SNEDDS and nanosuspension were improved by 93.81 percent and 55.31 percent, respectively. Thus, the findings showed that optimized nanosuspension preparations enhanced the poorly soluble medication atorvastatin's overall pharmacokinetic characteristics [57]. The noticeable decrease in particle size alongside larger surface area, better solubility and unstructured form of the drug in the suspension are all factors that contribute to nanoparticles' capacity to improve dissolving rate and, as a result, bioavailability.

Pharmacokinetic parameters of ezetimibe, a cholesterol absorption inhibitor, were improved by formulating into nanosuspension [58, 59]. With particle sizes smaller than 200nm and greater zeta potential, an improved formulation of gemfibrozil nanosuspension was effectively created. When compared to gemfibrozil medication, nanosuspensions showed a significantly improved solubility and dissolution rate [60].

Nanosuspensions of Natural Antihyperlipidemic Products: As previously stated, hyperlipidemia leads to atherosclerosis. Curcumin has been proven to have a therapeutic impact on atherosclerosis in the past few years; however, its lipophilic nature severely decreases its absorption and restricts its use in clinical treatment. Curcumin nanosuspension was discovered to be a better and more efficient technique to slow atherogenesis [55, 56]. The lowering of vascular cell adhesion molecule-1 (VCAM-1) and interleukin-6 (IL-6) levels is one proposed mechanism [61]. The research was conducted to create a nanosuspension of flavonoid-rich fraction obtained from *Psidium guajava* leaf extract.

The designed nanosuspension had optimal physical characteristics, such as nano-sized particles and a negative surface charge, inferring a stable nanosuspension and a pharmacokinetic profile, such as better absorption and continual flavonoid circulating levels, facilitating antihyperglycemic activity [62]. Berberine nanosuspensions with particle sizes as minute as 107.4 nm were also made, and their hypolipidemic action in diabetic mice was validated [63]. Resveratrol, another natural hypolipidemic, was formulated as nanosuspension using a quality by design (QbD) method and precipitation method [64]. Nanosuspension of ursodeoxycholic acid, a natural cholesterol-lowering agent, and rutin have also been developed. As a result, nanosuspension technology can also be used for natural chemicals that have poor dissolution or absorption [65].

Factors Affecting the Efficacy of Nanosuspensions: There is currently a large amount of evidence demonstrating nanosuspension technology's viability and efficacy in enhancing drug efficacy. However, nanoparticles' inconsistency and distinctive features, particularly customized nanosuspensions, may come with unintended safety and health risks. Utilizing animal and *ex-vivo* models, a massive portion of studies have been conducted on nanosuspension synthesis, pharmacokinetics, and biological properties. Unfortunately, the parameters that affect safety have not been thoroughly investigated. Particle size and surface area, zeta potential, and the nature of the stabilizer chosen are all likely to have a role in nanosuspension tolerability or toxicity **Fig. 4**.

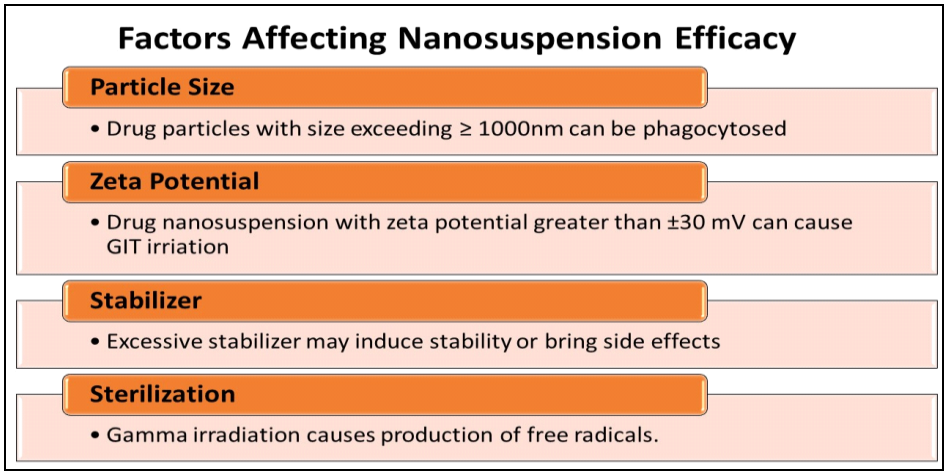

FIG. 4: CRITICAL FACTORS INFLUENCING NANOSUSPENSION EFFICACY

The ideal size range is 100-800nm; for parenteral administration, a size range of ≤ 100nm is suggested; particles larger than 1000nm can be engulfed. Particle size requires a zeta potential of less than ± 30 mV. The greater the value of zeta potential, the more stability and the more toxicity, producing gastrointestinal irritation. Natural stabilizers are less harmful than synthetic stabilizers, such as phospholipids or poloxamer, which are safer than HPMC or SDS. An excess stabilizer can either cause stability or cause negative effects. Filtration sterilization is superior to thermal sterilization in terms of stability, but thermal sterilization may kill microbiological organisms; gamma irradiation has strong antibacterial properties, but free radicals must be formed [66].

Patent: Several nanonization techniques have recently evolved to improve the dissolution rate and bioavailability of a variety of medications that are poorly soluble in water, and several drug nanoformulations have been clinically authorized or are under clinical evaluation during the last decade. The given **Table 7** contains the patent of nanosuspension.

TABLE 7: RECENT PATENT ON NANOSUSPENSION [67]

Patent Number	Patent description	Publication year
WO2016135753Al	Through the use of milling, this patented work develops a system for topically applied nanosuspension	Sep1, 2016
WO2016081593Al	The nanosuspension made with a potent therapeutic moiety is described in the patented invention. An active nutraceutical with a poor solubility profile makes up this moiety	May 26, 2016
US20160317534A1	This patent describes a medication that has been lyophilized and used to create a nanosuspension. This nanosuspension was stable enough to be stored for an extended period time	Nov. 3, 2016
US20160206577	This patented study demonstrates the approach of making an antibacterial moiety in nanosuspension, which increases medication stability and decreases toxicity	Jul. 21, 2016
US20150238446A1	The invention of stable hexaflumuron nanoparticles that may be injected into fish to treat sea lice was announced by the researchers	Aug. 27, 2015
CN105708844A	The method for creating an ocular nanosuspension of tobramycin and dexamethasone is described in this patented work. The procedure was discovered to be repeatable, efficient, stable and practical	June 29, 2016
CN105315249A	This invention relates to a technique for creating simvastatin nanosuspensions that will improve the effectiveness of drug delivery systems	Feb. 2, 2016
CN105534947A	The process for creating a celecoxib nanoparticulate capsule that can be freeze-dried into solidified powder is covered by the patent	Feb. 16, 2016
CN104814926	According to this innovation, lurasidone nanosuspension was created by combining the high-pressure homogenization method with nano-precipitation	Aug. 5, 2015
US9023886B2	The patented idea shows how to utilize microfludization technology to create nanosuspensions out of ineffective water-soluble drugs	May 5, 2015
CN111759810A	The dissolution and release are fast, the gastrointestinal transmembrane transport capacity of fenofibrate is greatly improved, and the absorption of fenofibrate is promoted	Aug 6,2020
US 10,617,668 B2	The dissolution and release are fast, the transport capacity of simvastatin is greatly improved, and the absorption of simvastatin is promoted	Apr 14, 2020
WO2016081593A1	The dissolution and release are fast, the gastrointestinal transmembrane transport capacity of simvastatin is greatly improved and the absorption of simvastatin is promoted	May 26, 2016

List of Herbal Drug Nanosuspension Formulations: In **Table 8**. It contains list of herbal drug nanosuspension; this nanosuspension formulation enhances the bioavailability of a drug.

Nano-suspension is a biphasic system comprising drug particles smaller than 1um in size and suspended in the solution. Surfactant or polymer present.

Saturation increases solubility and solution velocity; poorly soluble drugs' bioavailability and solubility reduce the particle size to nanometers (1-1000 nm wavelength range).

TABLE 8: LIST OF NATURAL HERBAL DRUG NANOSUSPENSION FORMULATION

S. no.	Herbal drug	Dosage Form	Therapeutic effect	Reference
1	Silybummarianum, Elettariacardamomum and Coriandrumsativum	Nanosuspension	Enhanced the antiradical potential as compared with their crude extracts.	68
2	Vasicine	Nanosuspension	Enhanced the bioavailability of vasicine nanosuspension by reducing particle size	69
3	Curcumin	Nanosuspension	to improve the bioavailability of curcumin (CUR) by decreasing its particle size	70
4	Piper Nigrum	Nanosuspension	Using a nanosuspension technique, increase the medicinal potential and oral bioavailability of piperine, the bioactive ingredient of Piper nigrum.	71
5	Phyllanthusamarus	Nanosuspension	Nanosuspension of Phyllanthusamarus extract for improving oral bioavailability and prevention of paracetamol-induced hepatotoxicity in Sprague–Dawley	72
6	Terminalia arjuna bark	Nanosuspension	Nanosuspension enhances dissolution rate and oral bioavailability of *Terminalia arjuna* bark extract *in-vivo* and *in-vitro*	73
7	Silymarin	Nanosuspension	Formulation and optimization of lyophilized nanosuspension tablets for improved physicochemical characteristics and silymarin release	74
8	Kaempferiaparviflora	Nanosuspension	Kaempferia parviflora Nanosuspension Formulation for Scalability and Improvement of Dissolution Profiles and Intestinal Absorption	75
9	Psidiumguajava Linn	Nanosuspension	Nanosuspension of flavonoid-rich fraction from Psidiumguajava Linn for improved type 2 diabetes potential	76
10	*Ginkgo biloba*	Nanosuspension	An Optimized Piper nigrumNanosuspension Increased Oral Bioavailability of Piperine	77
11	*Allium cepa* peel extract	Nanosuspension	Enhance the pharmaceutical potential and oral bioavailability of quercetin contents of Allium cepa peel extract by novel nanosuspension technology	78
12	Quercetin	Nanosuspension	Enhance the bioavailability	79
13	Gemfibrozil	Nanosuspension	Gemfibrozil is a lipid regulating agent that decreases serum triglycerides and very low-density lipoprotein cholesterol and increases high-density lipoprotein (HDL) cholesterol	80
14	Ezetimibe	Nanosuspension	Enhance the solubility of ezetimibe by formulating it into nanosuspension	81
15	Rosuvastatin	Nanosuspension	Rosuvastatin formulated as a nanosuspension formulation can enhance dissolution and bioavailability	82
16	Felodipine	Nanosuspension	The nanosuspension of felodipine may improve the drug's oral bioavailability by increasing its dissolving rate	83

Future Prospects: In the future, it is anticipated that nanosuspensions will be extensively utilized for various drug dosage forms, with lower toxicity and the least safety concerns in the pharmaceutical sector.

To begin, selecting an appropriate preparation procedure for nanosuspensions is critical because the particle size is directly determined by it. Conversely, varying particle sizes might affect drug delivery and cause adverse effects. Stabilizers are also important for nanosuspension stability, production and release. During the synthesis of nanosuspensions, a large variety of organic solvents for poorly soluble or insoluble medicines might be disregarded. Sparingly water-soluble compounds produced as nanosuspensions might increase bioavailability *via* i.v. infusion when compared to other administration routes. As a result, the best drug delivery techniques for nanosuspensions should be carefully selected.

CONCLUSION: This review highlighted the application of nanosuspension technology in developing anti-hyperlipidemic medications. Nanosuspension appears to be among the highly efficient delivery methods for anti-hyperlipidemic medications since it is simple to create and does not demand expensive polymers, making it both therapeutically and economically advantageous. Nanosuspensions have been used in pulmonary and ocular administration, and their uses in oral and parenteral routes have also been thoroughly examined.

But, their use in buccal, nasal, and topical administration is currently being researched. Other innovative drug delivery technologies can potentially be employed to boost the efficacy of traditional medications. However, nanotechnology and discoveries related to it must be investigated deeper since they appear to be among the most viable alternatives for overcoming drug and dosage form restrictions. Nanotechnology will pave the way for technological innovation and development. It will be the most effective means of overcoming the drawbacks and adverse effects of traditional anti-hyperlipidemic drugs.

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