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RESEARCH PAPER

Molecular Dynamic Approaches for Lipid Nanoparticle Development

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ABSTRACT

In the late ages, many diseases were discovered, and newly innovative drugs became resistant to the treatment of these diseases, the development in nanoscience and nanotechnology in the field of medicine will cause great progress in diagnosing the disease and its treatment. Newly developed drugs are available in the form of two oral and intravenous doses cannot be a good combination for each product. Trials to increase the solubility to improve bioavailability are illustrated by size reduction and increasing surface area through nanoparticles. It was found that proteins or nucleic acids like structure products may require a more convenient carrier system to support their efficacy and avoid degradation while a new disease has been found and needs new drugs. The choice of nanoparticles determines the physical and chemical constants that can be used in various ways to prepare nanoparticles as needed. This brief introduction explains the different types of lipids, the drug delivery system based on lipids and nanoparticles, their preparation and applications to pharmaceutical drugs products and possible aspects in the future. A comparison showed that nano lipid carrier is the best choice among other lipid - based formulation like solid lipid nano particles due to more stability and high loading capacity. This article will focus on silico methods adopted in lipid-based-drug-delivery-systems (LBDDS) development and choosing the optimum lipid - based invention, computational modelling for nanostructure formulation design, computational modelling of drug solubility in variety of lipid-based formulation and molecular dynamics as an approach to analyse the loading capacity of poorly water-soluble drugs in lipids nanoparticles.

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INTRODUCTION

In recent years, due to the emergence of new diseases and resistance of existing drugs, drug development has witnessed unprecedented growth in research and application [1]. In view of the emergence of new diseases, the availability of treatable drugs is very important in terms of low cost, high efficacy, availability, etc. [2]. Many new drugs have been developed to treat complex diseases effectively, but at the same time, some of the new drugs will have serious side effects, and the benefits cannot compensateriskthat will occur [3, 4]. Developed drugs play an effective role in in-vitro studies, and vice versa in in-vivo studies [5-7].The causes for their failure of in-vivo applications are unpredictable. And most of those causes are to define the goals of the drug, design, and bioavailability of drug molecules [8, 9].Therefore, there is still a great deal to improve drugs and their delivery systems and to aiming

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a specified area of drugs.The development of modern drugs should focus on their effectiveness and goals, the absence of side effects and their availability.Nanomedicineis anemanation field that musters nanotechnology with medicines and biomedicine to develop modern drugs that used to treat various diseases [10, 11].

Nanotechnology is associate enabling technology for numerous progressive and non-progressive innovations and its application has an extraordinary interest in drug manufacturing and therefore the therapeutic efficaciousness will be improved with aimed drug delivery to the specific disease position [12, 13].It is also noted that there is a simultaneous decrease in the dose of the drug with a decrease in toxicity.Nanoparticles are defined as three-dimensional nanoparticles on the nanoscale (size from 1 to 100 nanometers) and their longest and shortest axes do not vary greatly, noting a large difference, which makes it a factor of at least three [14, 15].Medicinal drugs that contain nanomaterials are applied to body internal or external part for diagnosis, treatment, and health benefit. The composed nanoparticles have wholly different mechanical, electrical, chemical, and physical properties in the field of drug delivery systems [16, 17]. It is noted that recent studies based on natural compound drugs and medicinal products which combined with nanoparticles have overcome their high crystallization, low solubility, and weak oral bioavailability [18]. The current review discusses the preparation of different types of lipid nanoparticles, the preparation methods of lipid nanoparticles and the formulation methods using nanoparticles with medicinal drugs, their advantages and future scope.

Lipids

Lipids are biomolecules which act as buildings blocks for the body's cell membranes. The lipids are soluble in non-polar solvents, essentially contain hydrocarbons in small hydrophobic or amphiphilic molecules. The amphiphilic nature may present as vesicles, liposomes, or membranes in aqueous field. The main role of lipid molecules is energy storage, and these nature molecules have considerable application in the food, cosmetics, and nanotechnology productions [19].

Classification of Lipids

Fatty acids are made up by a chain of hydrocarbons that ends with a group of carboxylic acids and these are water insoluble. The main basic group of biological lipids is fatty acids [20].

Glycerolipids consist of glycerols and structurally heterogeneous group of lipids in bacterial, plant, and animal membranes that play key structural and functional roles [21]. The triglycerides act as fat energy store in the body. Hydrolysis of triglyceride ester bonds in adipose - tissue represent the main part of metabolizing fat which liberate glycerol and fatty acids [22].

Glycerophospholipids are essential composition of cellular lipid - bilayer and piecesignificantcharacter in metabolism and signalling of the cell [23].

Sphingolipids are a class of lipids which contain a backbone of sphingoid bases, a set of aliphatic amino alcohols including sphingosine [24].These compounds play a key role in gesture transduction and cell credit. Such substances, especially categorized as phytosphingosine and dihydrosphingosine [25], are predominantly C18 substances and have slightly lower C20 bases. The sphingosine backbone is O-linked to a (normally) charged head group such as ethanolamine, serine, or choline [26].

Sterols, also known as steroidal alcohols, are a steroid subgroup, and an essential organic molecular class. They 're lipid sort. They exist naturally in plants, animals, and fungi, and may also be produced by certain bacteria (But maybe with different functions). Cholesterol, which is important to the structure of cell membranes, is the most familiar type of animal sterol and acts as a precursor to fat-soluble vitamins and steroid hormones [27]. Steroids play a role in hormones and molecular signalling [28].

Prenol was formulated from the carbon precursors which generated primarily through the mevalonic acid the pathway (MVA). By successive addition of C5 units, simple isoprenoid is formed (linear alcohol, di-phosphate, etc.) and may be classified conferring to the numeral of turbines pieces patterns named polyterpenes [29, 30].

Saccharolipids are fatty acids, i.e., they are directly linked to a backbone of sugar, forming structures compatible with bilayers of membrane. The most acquainted saccharolipids in Gram-negative bacteria are the acylated glucosamine predecessors of the Lipid A module of lipopolysaccharides [31].

Polyketides are periodic molecules supplementaryrevised by glycosylation,

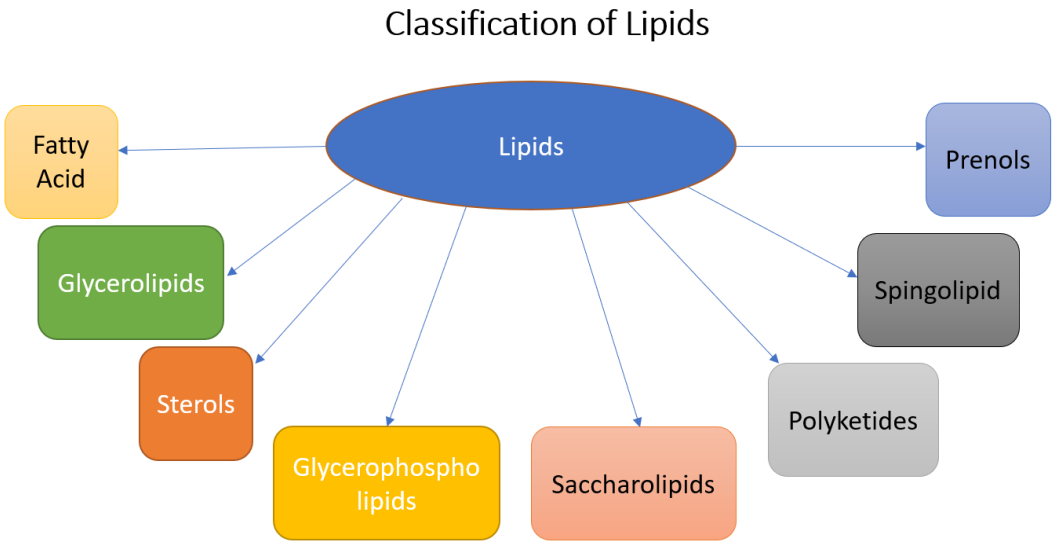

Fig. 1. Classification of Lipids

methylation, hydroxylation, oxidation, and so on. Polyketides or polyketide derivatives, such as erythromycins, avermectins, tetracyclines, and anti-tumor epothilones utilized in microbial, parasitic, and cancer therapy [32, 33].

Selection of lipid excipients to formulate LBDDS

The excipient is a material that is manufactured in a combination with the active ingredient in a product, that used for long-term stability purposes [34], solid structures which hold active moiety in limited doses or providing the active ingredient a medicinal boost in the final dosage shape, such as enabling the absorption of drugs [35], decreasing viscosity or enhancing solubility. Although excipients are inactive, they play an essential role in dosage behavior with no effect on pharmaco-dynamics and pharmaco-kinetics.Low-soluble drugs in water are a kind of challenge for scientists regarding solubility and bioavailability [36]. The efficient size-dependent properties of lipid-based drug delivery systems have been demonstrated and they have gained much interest. Lipid-based drug delivery systems held the lead due to apparent benefits of better biocompatibility and flexibility. Lipid-based drug delivery systems held the lead due to apparent benefits of better biocompatibility and flexibility. Those kinds of techniques are commercially feasible in formulating pharmaceuticals for the delivery of topical, dental, respiratory, or injectables. A product can be modified through combination with lipids to satisfy the disease case, route of delivering dose, stability, safety and efficacy of the product. Lipid carriers are effective, thereby proven to be desirable choices for prescription formulations, as well as vaccines, diagnostic tests, and nutraceuticals. Type I assortment consists of triglycerides (oils); Type II adds water-insoluble and dispersible surfactants to the oils; Type III comprises water-soluble surfactants and hydrophilic cosolvents; and Type IV comprises no oils and entails exclusively of surfactants and hydrophilic co-solvents. Different factors in the composition of active pharmaceutical ingredients affect lipid isolation as excipients. Solubility, dispersion, digestion and absorption are the most essential properties to be tested when choosing appropriate lipid excipients [37].

Because of their hydrophilicity, the solubility property is very significant for preparing various formulations using lipids. Whereas formulating, supernatants (hydrophilic cosolvent) are required by the lipid derivatives to improve solubilization and dispersion [38].

The correct formulated medication with lipid molecules should be dispersedequally without creating any emulsification during digestion.

Light scattering applied to calculate the emulsion particle - size by laser technique to choose the proper formula [39].

The formulated drugs with specified lipid carrier should be easily digestible by the digestive enzymes. The goal of formulations based on lipids

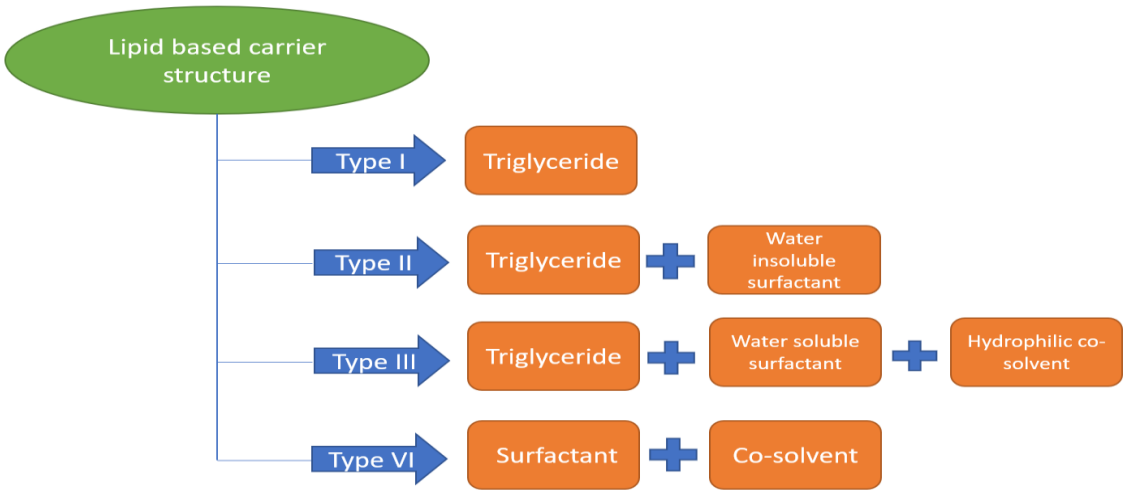

Fig. 2. Types of lipid-based carrier structures

is for optimum product absorption (bioavailability). Therefore, in lipid structures the collection of lipids dependent on these properties is very necessary. In addition to this, toxicity, solubility capability, cost, lipid behavior at temperatures, purity, chemical stability is also important when selecting lipids for the production of formulations [37].

Various approaches used in the development of LBDDS

A wide-ranging study is under way around the world to overrule the weakness of drug bioavailability. Different approaches of formulations have tried to make medications obtainable through their metabolisms. The lipid-based drug delivery mechanism is also such a thing that provides the active pharmaceutical component with lipid excipients in formulations. Various routes are useful for lipid-based drug delivery system, such as oral, parental, ocular, dermal, intranasal et. Every route of administration should ensure the drug's optimum bioavailable [40].

Molecular techniques in LBDDS

It is necessary to note that the prepared nanoparticles and their formulated substance that show the nature, protection, and efficacy requirements of any nano pharmaceutical should be determined according to factors like physicochemical composition, biological structure, distribution, bio - availability, interaction with the biological system, therapeutic indication, administration route and expected therapy length. Also, for the preparation of nanoparticles, various types of matrix materials have been used, such as natural or synthetic polysaccharides and proteins. The selection of appropriate matrix is very essential in providing them.

Some of these are including basic nanoparticle size, the permeability and surface charge of nanoparticles, biocompatibility and biodegradable composition, the matrix must not be poisonousand immunogenic, the nature of solubility in formulation not impacting the stability and nature of desirable and release of drug capability should be desired.

There have been various methods used to manufacture lipid nanoparticles. Hot pressure homogenization, microemulsion, solvent emulsification-evaporation, solvent emulsification-diffusion, ultrasonication or high velocity homogenization, hot melt encapsulation, dual emulsion, membrane contactor, supercritical fluid and spray drying are the main techniques.

Each approach has its own benefits and drawbacks in lipid nanoparticles preparation. In this homogenization technique, hot pressure homogenization can be accomplished at elevatedtemperature or below room temperature and high-pressure application, and then lipids are forced into a small gap of few micron ranges with high pressure (100-200 bar).

The technique of microemulsion is the use of low melting fluid, emulsifier and water are melded in typical ration to get the fine particles smaller than 100 nm. This method is highly sensitive and requires more labor works. The solvent

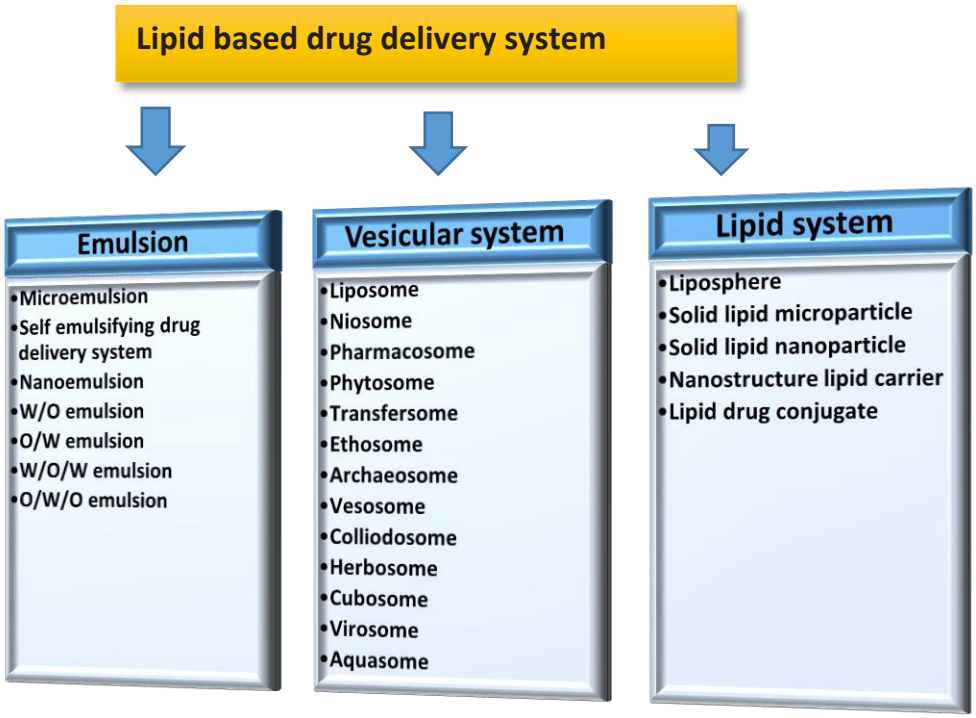

Fig. 3. Different Lipid based drug delivery systems

emulsification-evaporation is required the use of various miscible solvents in water, which then melt the lipid and then emulsify it at elevated temperatures with solvent-saturated aqueous surfactant solution. The ultrasonication or high-speed homogenization requires stirring at high speed and supersonic at high temperature [41].

The double emulsion requiresthe drug being encapsulated with a stabilizer to avoid drug partitioning to the process of external water during solvent evaporation in the process of external water of water/oil/water double emulsion. The liquid phase membrane contactor technique was pushed through the membrane pores at a temperature above the lipid melting point for the formation of small droplets. Droplets were constantly mixed in the membrane and cooled to room temperature and nitrogen was used to produce pressure for the liquid aspect to produce the final solid lipid SL. The supercritical fluid technique used in the preparation of powder and nanoparticles by adding moderate pressure and temperature conditions while using supercritical carbon dioxide solutions. The spray drying utilizes lyophilization to turn a dispersion of aqueous lipid nanoparticles into a drug component [42].

They will be filled with active pharmaceutical drugs after the nanoparticles have been prepared. A nanoparticle is a nanomaterial that plays an important role in transporting substances such as medicine. Lipid carriers, micelles and polymeric nano particles can be utilized to fill and encapsulate drugs like Amphotericin B and Paclitaxel [43].

Because of their tiny size, nano carriers carry drugs to inaccessible areas in the body. They also deliver drugs to targeted sites. Nanoparticles are designed in the field of cancer nanomedicine to exploit the Enhanced Permeability and Retention (EPR) effect in tumours through boosting the therapeutic range and reducing toxicity. In some cases, the drug material is also converted into nanomaterial. Some conventional medications can be transformed into nanocrystals to increase dissolution and bioavailability like cyclosporine and griseofulvin. Regulatory requirements and limitations on the implementation of molecular concepts in the development of drug delivery systems that based on lipids. The development of lipid formulation will boost drugs bioavailability, and the preparation of formulations for lipids has some essential guidelines [44]. These guidelines ensure drug solubility during preparations, dispersion, and digestion. In general, high percentage lipids (>60 percent) with lower

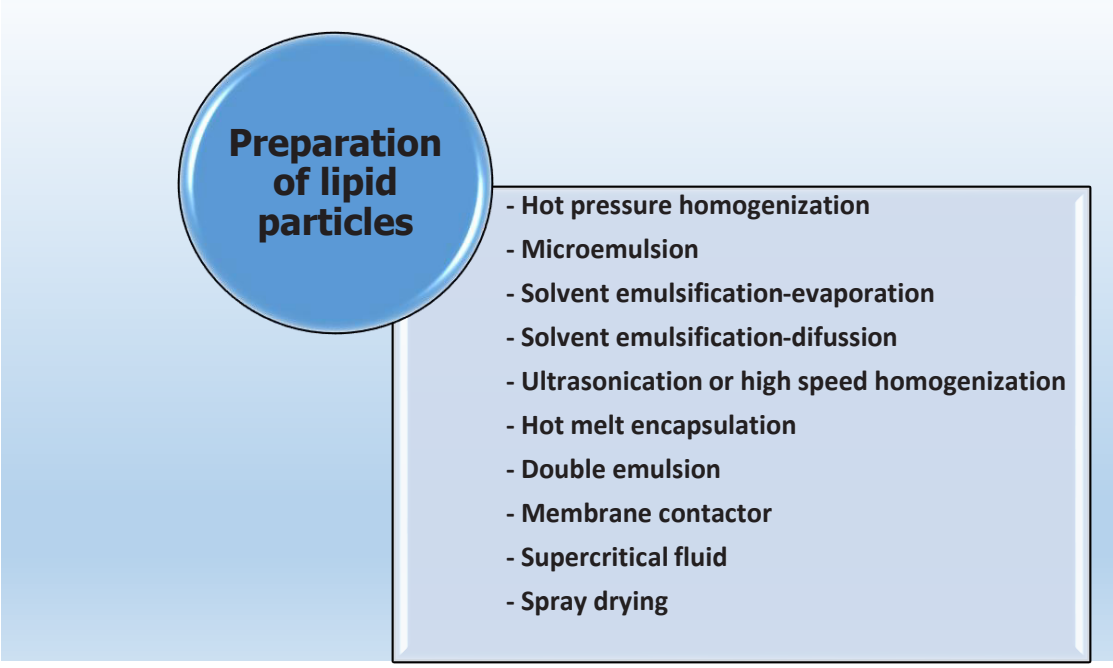

Fig. 4. Different types of methods for lipid nanoparticles preparation.

surfactant (<30 percent) and co-solvent (<10 percent) improve drug dilution and solubilization. Medium-chain triglycerides provides higher drug solubility and formulation stability while long-chain triglycerides may tolerate greater bioavailability. Type III of the self-microemulsifying drug delivery system provide tiny droplet dispersion. Type IV of dispersion formulations (surfactant / cosolvent) dispersion formulations. Type IV formulations give greater drug solubility but must be carefully formulated to avoid drug precipitation after dispersion [45].

Different silico methods adopted in lipid nanoparticles development

Among the most critical conditions for good lipid-based formulation (LBF) is that it must be effectively dissolved within the lipid framework used [46]. The stage diagrams were conventionally used to constitute miscible formulations, thus determining the LBF's loading capacity [47]. The log-linear model was used to estimate loading capacity of co-solvent for drugs [48]. This model shows the exponential increment of non-polar drugs solubility with co-solvent concentration in linear manner [49].

This principle was used to estimate drug solubility in lipid mixtures [50]. This technique needs experimental tests which considered as main disadvantage restricting its applicability. Therefore, statistical analyses of drug solubility putted in the scope to reduce the costs of producing LBF [51]. Some theories like optimal solubility and standard solution fails to offer exact forecast of drug solubility in polar-lipid solutes and solvents [52]. This is essentially a result of the nonattendance of experimental molecular interactions. Multivariate data analysis techniques like partial minimum square projection to latent structures (PLS) successfully used in envisaging drug dissolve in water-based structures and therefore utilized to predict drug solubility in individual excipients [53, 54].

By applying a similar method to the log-linear model (Alskär et al., unpublished), a computationally solubility estimation based on molecular descriptors and solid-state like melting point and fusion entropy can predict LBF'sloading capacity for API [55]. Currently no validated computational models can be utilized to express molecular interactions between API and LBFs or colloidal systems formed after LBFs digestion in GIT.

This will provide in-vivo information about

formula solubilization and precipitation influencers

along with population performance and inter-individual variability through calculating free solvation energy utilizing molecular-dynamic-simulation (MDS)principle [56].

MDS commonly used for revealing interactions with biological sites in the drug development process [57]. Major efforts have been made to use MDS in exploring biological membranes particularly the hydration of different phospholipids with the goal of educating the transport mechanisms in human cells [58].

A few information provides randomly aggregated data on lipid-based pharmaceuticals and excipients [59]. The simulations correctly illustrated three phases (micellar, hexagonal, lamellar) that were observed experimentally. There is the computational ability to model complex structures and there are possibilities for MDS of LBF excipients systems [60].

Computational modelling for nanostructure formulation design

Nanotechnology provides new possibilities to produce new materials and the advancement of novel ways of pharmaceutical dosing and drug delivery systems. Nanoparticles capable of encapsulating active pharmaceutical ingredients (APIs) within dimension of 1–100 nm [61]. Nanotechnologies have been used to boost APIs and excipient features by managing particle size through crystallization milling to produce the desired size which improve dissolution and absorption of oral APIs [62]. Nanoparticles increase the parenteral volume of distribution containing nano-suspensions and modify their pharmaco-kinetic properties [63]. Computational models explore the solubility along with various factors and interactions at the atomic level [64]. However, at laboratory level, solubility need to be assessed experimentally rather than measured using statistical methods which consume more costs [65].

It should be emphasized that although the solid properties are often harder to study with simulation models. Calculation of solubility in new solvent could be anticipated by knowing relative solubility, solvation-free energies and experimental solubility data in one reference environment [66].

Formulation design is an essential step of the production of drugs. However, this process requires exhaustive experimental research at an experimental stage. The basic data essential for formulation design includes excipient selection, solubility prediction, encapsulation quality, release, absorption and stability. The use of numerous analytical methods, countingquantifiableedifice – activity associations, molecular, physics, detacheddivision, finite-element progression, computational fluid dynamics and physiologically grounded pharmacokinetics, help recognize inadequacies in drugmerchandise and propose understanding complex formulations in reduced time [67].

Designing pharmaceutical formulations involve the drug blending with various excipients to form a pharmaceutical formula to enhance drug solubility, absorption, and stability. The physicochemical properties of drugs are essential criteria for selecting suitable excipients for formulation. The experimental method is used for predicting the appropriate excipient for the drug formulations development; however, it is time-consuming and expensive [68].

Computational methods play in resolving the hitches raise thru drug enterprise including stability, solubility, tensile strength, porosity, and dissolution behaviourin-vivo [69].

Quantitative structure activity relationship (QSAR) applied for distinctive drug-like molecules from non-drug, physic-chemical and PK properties [70]. Quantitative structure property relationship (QSPR) expose similarity between the signifierassets like Log-P and pKa of the drug molecule [71]. MDS offers dynamic creation of a system through which molecules interact for specified time [72]. This approach is useful in nano-based carriers design and excipients selections [73].

QSPR were created to study drug cargodimensions of polymer micelles throughrelation between the polymer erection and micelles effectiveness, QSAR was used to measure the suitable descriptors [74]. The relation between cargo capacity and micro-structure could be simulated through calculating quantitative estimation of polymer loading capacity for drug [75].

MDS was used to explore drug interaction with SL and requisiteenergy estimated by molecular docking to compare the capability of entrapment [76]. MDS used to figure out the liquid phase behaviour of GI products, lipid creations and drugs

partitioning into formulations scattering and after assimilation [77, 78].

Lipid formulations utilized to increase the bioavailability of poorly water-soluble drug molecules by solubilize the drug in a colloidal system ducking the crystalline form [79]. Lipid formulations are distributed within the aqueous GI fluid and digested subsequently through which drug solving chattels of the devising may revolution. Throughout these changes, the solving property may impact leading to precipitation [80].

It was found that molecular interaction results may not be accurate when applied to several liquid phases to accurately expect actions through the observed phases [78, 81].

A force-field is required to perform MDS, the parameters include bonded and unbonded interactions and electrostatic interactions using Coulomb-law. A crucial factor for using MDS to predict solubility is knowledge of system physics including the inter- and intra-molecular forces [82].

Computational modelling for determining the drug solubility using lipid-based formulation (LBF)

Due to the many new candidate drugs, poor solubility is a major impact on drug absorption window in GI fluid with an estimated solubility-limited absorption of 70-90% of all discovery compounds [83].

Erratic absorption increases safety issues because unreproductive reactions can lead to adverse drug reaction leading to expensive and late termination of the project. The dosage type used to administer the medication for poorly soluble drugs made the selection of the optimum formula for such drugs to improve their absorption is very critical, therefore, finding a proper tool to anticipate the best formula and avoid loss of time and money consumed by trials will be valuable such as LBFs [84, 85].

LBFs provide the drug in soluble state rather than solid in conventional tablets. In addition, LBFs sustain a super-saturated state in the GI fluid by increasing the API concentration at the site of absorption. These formulas contain oil: surfactant/co-surfactant: water-soluble organic solvents in dissimilar magnitudes liable on API nature and way of delivery like oral, transdermal or injectable [86]. Tolerable drug solubility inside lipid structure castoff [87] is one of the most critical requirements for effective lipid formulation. Therefore, efforts to promote the computational prediction are warranted and decrease the cost of developing LBFs [88].

However, recent developments in computational technology have facilitated the creation of more intricate in silico simulations, and taking into consideration molecular structure, physiochemical properties and particular solvent-solvent interactions. For example, it was found that using MDS of Caprylin mixture will offer the drug in either lipid/or/aqueous/or/interface. Computations that based on assessment of solubility in each excipient shown promising results [89].

In order to apply these computations on wide range of products, a lot of experimental work need to be tested and collect the results of solubility in different excipients [90].

Molecular dynamics as a promising model for analysing the capacity of poorly water-soluble drugs in lipids nanoparticles

In new fields, molecular modelling is extremely effective where new theoretical principles participate in the development of new nanomaterials for drug delivery systems [91]. The goal of these nanomaterials is to solubilize non-soluble API and provide vehicle that maximizes efficacy by delivering the active ingredient to target tissue [92]. This may provide useful in design of new materials rationally [93, 94].

Nowadays nanocarriers based on lipids have received extensive attention from scholars and researchers as desirable delivery systems. SL in which lipid matrix consists of one or mixtures of solid lipid were developed for encapsulation and controlled release of lipophilic pharmaceuticals [95, 96]. It can be effective in protecting unstable substances from degradation [97], there are also drawbacks associated with SL, including recrystallization after cooling leading to poor encapsulation, un-controlled release, and instability [98, 99].

Consequently, nano-structured lipid carriers (NSLC) were developed with solid and liquid lipid matrix ratio between 70:30 and 99.9:0.1 [100]. The presence of liquid lipid within the matrix was expected to inhibit recrystallization foremost to enlarge drug size and solubility [101].

The increased interest for NSLC was due to the privilege of increased loading capacity

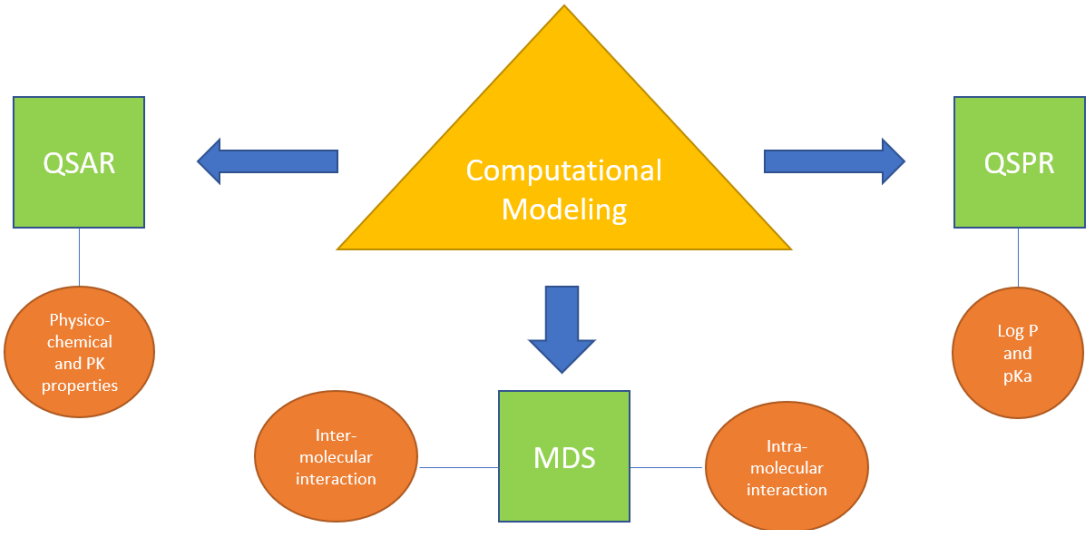

Fig. 5. Computational modelling for formulation design

[102], controlled release, stability [103] and biocompatibility [104]. So far, several studies have been carried out into the physicochemical properties of SL and NSLC. It was found that using NSLC with Precirol base enhance lovastatin absorption by mouth compared to SL [105]. Accordingly, NSLC entire structure determines the efficiency of those carriers [106].

No clear technique available for such purpose. Contempt the deficiency of suitable trial apparatus and procedures, some hypothesis recommended various longitudinal measures in NSLC for the solid and liquid. The obtained experimental information on the physicochemical properties of SL and NSLC with glyceride base showed no spherical droplets of NSLC analogous to SL but observed them as lipid sheets on the surface with tacky ads of oil. NSLC with crystalline induced low drug linkage due to increased water-lipid interfaces in comparison to SL [107]. Fluorescence imaging was used to measure the distribution of a trapped lipid dye in both SL and NSLC and the results showed that the trapped dye was expelled into the aqueous process due to a solidification of lipids in SL while NSLC prevented the exclusion of encapsulated dye [108, 109].

In another example, three different lipid structures were compared. Solid lipids and liquid lipids are combined in structure one, creating highly disordered constructions of defective lipid matrixes. Structure 2 has tremendous oil constitution in which a homogeneity fissure occurs during chilling across solid-lipids and liquid-lipids leading to phase separation. Drug may be put in the solid part but may be dispersed in the oily sections of the structure under excess solubility. Finally, the third structure was composed of amorphous solid and liquid lipids which prevented expulsion of drugs [110, 111]. Internal structure of lipid carriers is supposed to be predicted by different excipients and production method experimentally. The hypothesis predicts identical allocation of lipids (liquid and solid) inside the texture, a diversified temple that are identical to lipid bilayers, a liquid phase will be in the core and solid shape on the superficies [112]. In addition, MDS is a technique providing detailed information on functional species belongs to carriers and API localization. Studies concentrate on lipid distribution used the coarse-grained MDS approach to describe the structure of lipid droplets consisting of triolein and cholesteryl oleate with different bits. These droplets were wrapped by a mono layer of phospholipid, the results showed that cholesteryl oleate molecules are often located within the hydrophobic part with little monolayer penetration ability [113].

Researchers used MDS to investigate excipients impact on droplet structure and location of drugs within the self-emulsifying drug delivery systems containing capric triglycerides and cyclosporine [114]. A drug located in aqueous solution to explore the impact of API, FA chain length and surfactant amount/type on droplet texture. Results showed

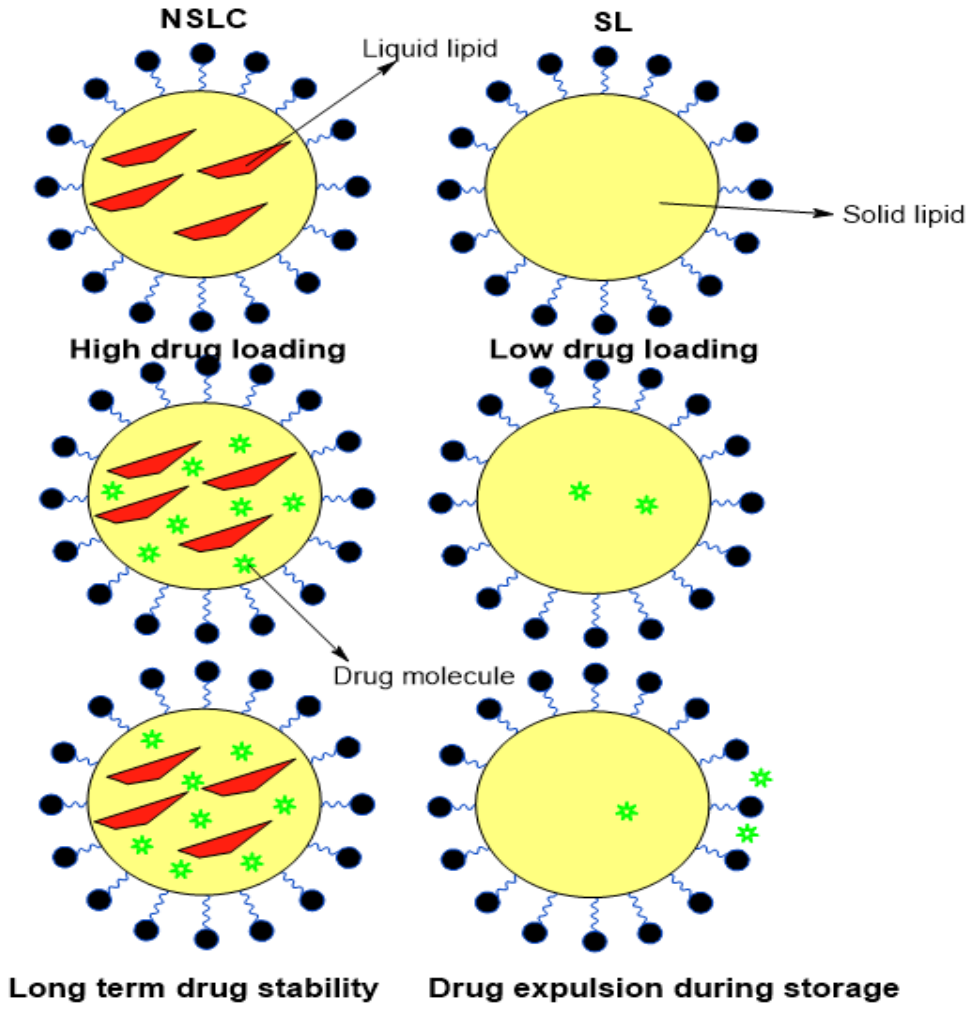

Fig. 6. Comparison of drug loading capacity and stability on storage between NSLC and SL

that the modification of FA chain lengths led to the creation of various decorations such as lamellar or vesicle [115].

Optimization tools for lipid nanoparticle-mediated delivery of RNA

Nanotechnology utilized in up-to-date vaccine enterprise like COVID 19 vaccines since nanomaterials are supreme for antigen transport as imitators of viral structures. Vaccine candidate tossed for clinical trials is an mRNA vaccine carried through lipid nanoparticles.

The diminished viral vaccines are considered as nanocarriers which encapsulate or encode antigen nucleic acid. These carriers offer stability, targeting of these payloads to antigen donating cells. Synthetic nanocarriers as well as cationic liposomes used for the transport of DNA vaccines crosswise cell membranes achieving the aimed targeting. For example, Moderna's mRNA vaccine which was developed for CORONA is built on a lipid nanoparticle. Cationic nano emulsions and liposomes labouring for enlightening the stability and conveyance of mRNA constructed vaccines [116]. NL have the budding to enhance the stability oof the entire RNA which facilitate the transport across membrane and draw out circulation time [117].

Since NL contains cationic lipids, they engage with negative charged genetics and backing endosomal escape. Moreover, their cholesterol and PEG structure will mend stability, circulation and membrane ingress [118]. Two main factors affect cellular uptake of NL incorporated system including hydrophilicity and charge. The phospholipid nature of NL will aid in crossing cell

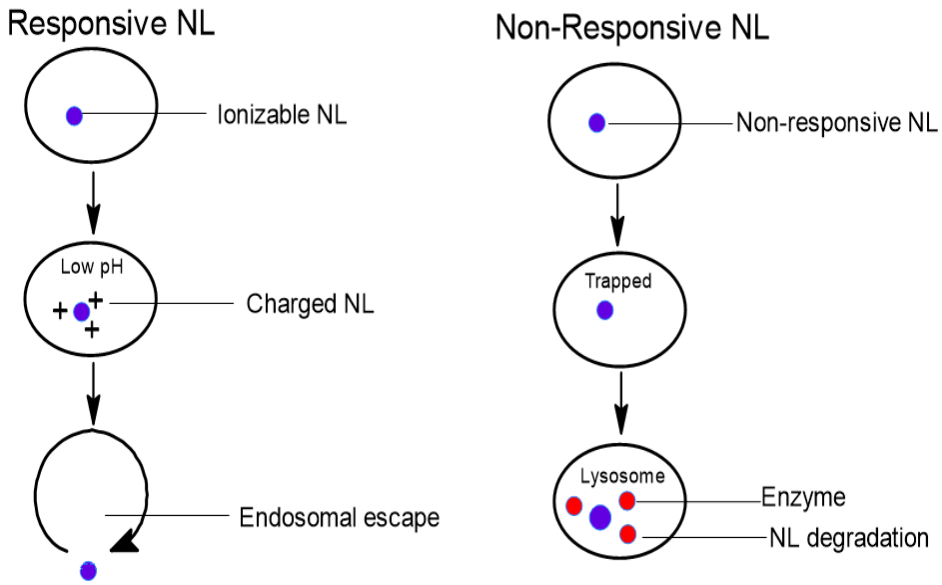

Fig. 7. Comparison between Responsive and non-responsive NL for intracellular delivery

membrane because of negative charge [119].

Inside cell, alter in chemical alignment and pH will occur which transmute the vesicle into lysosome with concomitant pH lowering and surge ionic forte that disturb NL stability [120]. Cationic NL carried materials are admirable specimens for booming nucleic acids into cells [121]. The lower pH inside cell will breakdown the linkers leading to NL analysis and fused martials release [122]. The shape of NL can boost the intracellular conveyance of genetics (like nano stars) [123]. In addition, relying on pH receptive displayed an auspicious in aiming mitochondria for definite cancers and dazed barriers struggle [124].

The mechanism which encompasses the engulfing of NL loaded RNA by cells are based on complexation of nucleic acid with cationic material [125]. Cations exploited for nucleic acid transport embrace lipids and polymers like cyclodextrin. These are receptive to the intra-cellular milieu augmenting to integrate passive / active pointing rudiments to certify endo-cytic uptake [126]. To attain RNA incorporation into mark cell, two alleyways were suggested either through using minute particles that can athwart nuclear aperture or via functionality that is used after endosomal discharge [127].

As a summery, to achieve functional delivery, NL must escape from these compartments before they acidify to achieve functional delivery. So, responsive NL (ionizable NL) that charged in low-pH environments undergo endosomal escape accompanying intracellular delivery rather than unresponsive NL which trapped and destroyed by lysosome and enzymes [128].

Future scope of LBDDS and molecular approaches

The use of lipid-based dosage forms to optimize drug absorption or delivery has attracted substantial attention from pharmaceutical scientists. The wide range of excipients to empower the expansion of an LBDDS in which drug is completely solubilised, certain iotas at their necessary unit dose do not dissolve in lipid excipients. Lipid-based nanoparticles are one of the promising candidates for drug delivery and were the longest-studied nanocarriers. Notwithstanding big efforts, yet only a few formulations are accepted for clinical use. Further, the clinical implementations of aimed nanoparticles are still to be seen. Nanotechnology application has enormous potential in therapeutic effectiveness with target of the medication to disease site. To enhance protection, effectiveness, toxicity profile reduction, dosage reduction, nano pharmaceutical administration frequency, enhanced patient compliance, lower cost, the nanotechnology plays a promising role in the production of new pharmaceutical products. However, the efficient application of nanoparticles for drug delivery depends upon the ability to move through various anatomical barriers, their continuing release of formulations and their

stability in the nanometer sized.

The absence of well-known knowledge about nanoparticles and their high cost producing techniques provide restricted implementations about them. To overcome these limitations of polymeric nanoparticles, lipids, particularly for lipophilic pharmaceuticals, have been put forward as an alternative carrier. These lipids are considered as SL and NSLC which are most attracting research in the development of new pharmaceuticals formulations around the world. The solid lipid nanoparticles are a kind of natural or synthetic colloidal for drug carriers to conventional drug carriers such as emulsions and liposomes. According to these conventional carriers, the unique nature of the NSLC like small size, big surface area, high drug loading allows better binding, adsorption, and transportation of compounds in bioavailability and solubility of the drugs.

CONCLUSION

The expectation is that nanotechnology will modernize drug delivery. The capability to incorporate drugs into nanocarriers provides a modern technology that could be used for drug targeting in drug delivery. SL and NSLC do not illustrate biotoxicity because they are prepared from physiological lipids. These unique delivery systems are particularly useful in the delivery of drugs as they can boost the drug's absorption and improve the bioavailability of both hydrophilic and lipophilic drugs. NSLC have clear advantages including physiological compatibility, fast and flexible large-scale production with high encapsulation efficiency. On the other hand, pharmaceutical and modern sciences have been searching and using various alternatives for decades to reduce the emerging diseases, toxicity, and side effects of drugs. The nanotechnology has shown controlled and site-specific delivery of drugs but has also drawn broad attention from researchers.In the future, we can foresee several proprietary dosage shapes in the form of NSLC. A computational method will provide understanding of solubility and atomic interactions for solubility process. QSAR, QSPR and MDS are the main computational instruments applied in formulation design, MDS was used to study CUR and THC interaction with different lipids to choose the optimum lipid-based formula with best solubility and loading capacity. In-silico method were applied as a promising way to estimate drug solubility in complex lipid mixtures since prediction of solubility through statistical analysis will minimize the cost and time consumed when applying experimental tests.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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