ijlpr 2023; doi 10.22376/ijlpr.2023.13.2.P83-P98

International Journal of Life science and Pharma Research

ISSN 2250-0480

Review Article

Quality by Design in Lipid-Based Drug Delivery Systems

Insights of Lipid-Based Drug Delivery Systems with an Emphasis on Quality by Design

Venkatesh Battula[1], Haranath Chinthaginjala[1*], Mousami Bhavasar Telkar[1], Udit Narayan Singh[1], Nagashubha Bobbarjang[2] and Bhargav Eranti[2]

[1]Associate professor & Head, Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research Ananthapuramu -515721, India.*

[1]Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research, Ananthapuramu -515721, India.

[2]RERDS-CPR, Raghavendra Institute of Pharmaceutical Education and Research, Ananthapuramu -515721, India.

Abstract: Lipid-based drug delivery systems offer several advantages and have wide solubility, permeation, and bioavailability enhancement applications. This review provides detailed information on the fabrication, application and aspects of QbD of various lipid-based vesicles. Most of the review studies focused on lipid-based vesicles without the QbD aspect. This review article covers all the lipid-based systems in escalating on the method of QbD, which enhances the bioavailability of active pharmaceutical ingredients in different formulation approaches. Among all the different available approaches towards formulation development, lipid-based drug delivery systems (LBDDS) have continually maintained the limelight on themselves. One of the reasons for the popularity of LBDDS is their ability to solve problems with poorly water-soluble drugs and their bioavailability. Several drugs' efficacy was improved by utilizing this type of delivery system. Vesosomes, Phytosomes, Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs), and Archaeosomes are novel lipid-based systems with unique applications in drug delivery. Hence, the present perspective is to review the various LBDDS approaches utilized to enhance the formulations' performance while dissecting the studies systematically to get a clear outline of various LBDD subsystems, their applications, methods of preparation, and the mechanism of drug delivery. In addition to this, the review also focuses on overcoming the lacunas of the past literature by making an attempt to identify Quality target product profile (QTPP), Critical quality attributes (CQAs) and applying them for the statistical design of experiments and continuous strategy by QbD at the same time harnessing their potential in risk assessment. Applying QbD in developing lipid-based drug delivery systems reduces the number of trials and yields a product with in-built quality as it deliberates various critical variables, process parameters, risk assessment, and control strategy in formulation development.

Keywords: Quality by design, Lipid-based drug delivery systems, Statistical design of experiments, risk assessment.

***Corresponding Author**

Haranath Chinthaginjala , Associate professor & Head, Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research Ananthapuramu -515721, India

Received On 30 August, 2022

Revised On 31 December, 2022

Accepted On 18 January, 2023

Published On 1 March, 2023

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Venkatesh Battula, Haranath Chinthaginjala, Mousami Bhavasar Telkar, Udit Narayan Singh, Nagashubha Bobbarjang and Bhargav Eranti , Insights of Lipid-Based Drug Delivery Systems with an Emphasis on Quality by Design.(2023).Int. J. Life Sci. Pharma Res.13(2), P83-P98 http://dx.doi.org/10.22376/ijlpr.2023.13.2.P83-P98

1. INTRODUCTION

Lipid-based drug delivery systems found a prominent position for enhancing solubility and bioavailability of many poorly water-soluble drug[1]. These systems can be formulated by various techniques and can be administered through various routes. These drug delivery systems reduced the toxicity of many drugs by changing the biodistribution pattern[2]. Apart from sustaining, controlling, targeting, and protecting the drugs from gastric and enzymatic degradation these lipid-based drug delivery systems are considered to be safe and efficient thereby they possess excellent applications in the delivery of various drug molecules for the treatment of various ocular[3], cancer[4], diabetic[5], pulmonary[6] and microbial diseases[7], cartilage regeneration[8], wound healing , vaccine delivery[10], and nutraceuticals[11]. Hence in this present context, a literature survey of the past ten years of publications on lipid-based drug delivery systems like Vesosomes, Phytosomes, Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs), and Archaeosomes with updated literature was highlighted & in many cases development was carried out by trial and error-based methods. We could not find the application of QbD on these systems, but few of the studies focused on the Design of Experimentation (DoE) in formulation development. Since the application of QbD on these systems might provide a route that offers several advantages while transferring a product from pilot scale to large scale[12]. DoE is considered to be the heart of QbD. Central composite (CCD), Factorial and Box Behnken designs (BBD) are the most frequently used experimental designs that help in the identification of design space and optimized formula. The development of a lipid-based drug delivery system (LBDDS) by the implementation of QbD provides numerous benefits as it includes a systematic assessment of critical variables, factors, and responses that concern the quality of the product[13]. Based on QTPP, CQAs will be defined. A further Risk assessment by the Ishikawa fishbone diagram or by risk priority number helps in the identification of significant factors and responses[14]. A design of experimentation provides contour plots, prediction profilers, polynomial equations, ANOVA, and overlay plots that assist in revealing the significance of selected factors. QbD application in optimization yields a product with patient compliance and the required benefits would be achieved at reasonable costs. Hence in the present context, we focused on these drug delivery systems' applications, fabrication methods, and various mechanisms of drug permeation & explained the QbD context in their development[15].

1.1. Elements of QbD

The following are the main element of QbD

- QTPP: Quality Target Product Profile
- CQAs: Critical Quality Attributes
- CMAs: Critical Material Attributes
- CPP: Critical Process Parameters
- Risk Assessment
- Failure mode and effects analysis (FMEA)
- Relative risk-based matrix evaluation (RRMA)
- DoEs: Design of Experiments
- Design Space
- Process Analytical Tools
- Control Strategy

1.1.1. QTPP: Quality Target Product Profile

The summary of drug product profile characteristics that affect the quality of the product is QTPP. The dosage form, dose, mode of administration, drug release behaviour, pharmacokinetic properties, shelf life, purity, sterility and container closing system are all included in the QTPP. Regulatory requirements and information make QTPP a novel pharmaceutical product from different pharmacopoeias. All pharmaceutical equivalence, bioequivalence, and patient compliance conditions must be met for a generic drug product under QTPP, similar to that of the innovator.

1.1.2. CQAs: Critical Quality Attributes

The QTPP yields CQAs. A physical, chemical, biological or microbiological property or characteristic that needs to fall within the right range, limit or distribution to guarantee the intended product quality is referred to as a CQA. Impact and severity analysis is used to evaluate CQAs from the QTPP. Changes in formulation material attributes or formulation parameters are related to impact analysis. The effectiveness and safety of the drug product are related to severity analysis.

1.1.3. CMAs: Critical Material Attributes and CPP: Critical Process Parameters

Risk analysis is used to extract CMAs and CPPs from CQAs. The CQAs are likely to vary as a result of CMAs and CPPs. Input materials' physicochemical qualities, biopharmaceutical traits and microbiological traits are regarded as CMAs and should fall within the proper specification parameters to guarantee the intended level of finished product quality. The drug product's manufacturing process is connected to the CPPs. Several techniques, like the Ishikawa diagram and process mapping, are used to identify CMAs and CPPs.

1.1.4. Risk Assessment

A risk assessment is conducted to evaluate the effect of a specific variable or crucial properties of raw materials (API and excipients) and packaging materials. The CPP of the drug product is also determined by it. Based on how they affect the quality of the completed product, each CPP's attribute is categorized as high, medium, or low-risk. To lessen the likelihood of risk, high-risk attributes are further examined. Risk assessment can be done in several ways, including failure mode and effects analysis (FMEA) and relative risk-based matrix evaluation (RRMA).

1.1.5. DoEs: Design of Experiments and Design Space

The design of experiments (DoE) is used to conduct multivariate experiments. The design space explains the interaction between the CQAs and the process inputs (material attributes and parameters). DOE is made up of mathematical models that make use of process simulation and computer-aided process design. There are many different models available. Among the designs are Factorial, Box-Behnken, Plackett-Burman, and Taguchi.

1.1.6. Control Strategy

Consistency in product development is ensured through the use of control strategies. For example, controls over input materials (API, excipients, and packaging materials), controls over adhering to predetermined product specifications, controls over CPPs, real-time release testing (RTRT), and an overall monitoring programme are all included.

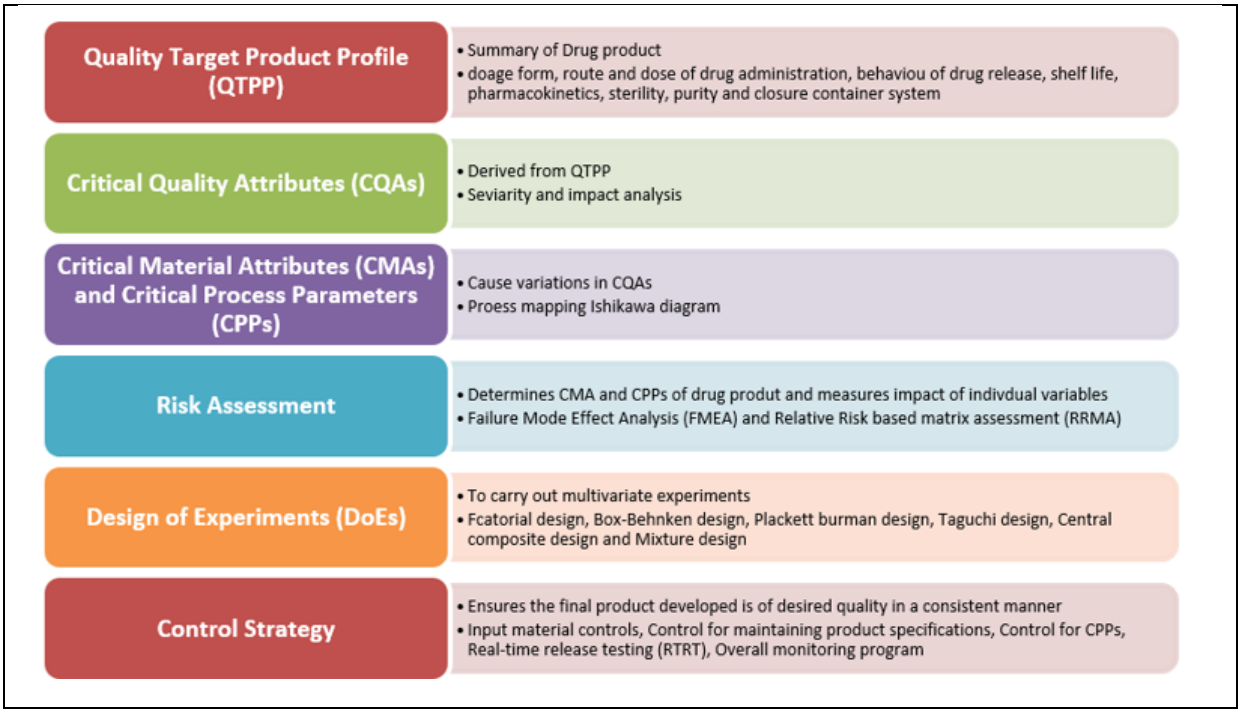

Fig 1: Elements of QbD[16]

2. LIPID-BASED DRUG DELIVERY SYSTEMS

The various lipid-based drug delivery systems' definition, applications, methods of preparation, and characterization are illustrated in Table 1.

2.1. The disadvantage of lipid-based drug delivery

Lipid-based drug delivery systems have certain limitations. Some of them are

- **Poor stability of API:** In some formulations, there is evidence of API instability; research into the variables that support API stability is currently in progress.
- Lipid-based drug delivery systems may cause pathological changes by accumulating lipids in the spleen and liver.
- **Clearance of API**
- **Incompatibility with Excipients:** The bioavailability, stability, chemical, and physical aspects of the medication or dosage may be impacted by these compatibility problems and interactions.
- **Post-dosing uncontrolled drug precipitation:** Because of the embolization, the patients may experience catastrophic side effects such as multiple organ failure, death, or even normal therapeutic failure.
- Drug bursting by eroding mechanism
- The enhanced permeability and retention effect (EPR) may differ dramatically from one human patient to the next.
- **Insufficient drug loading:** Another significant flaw in the lipid-based drug delivery system's design could result in unsatisfactory therapeutic outcomes.

Table 1: Lipid based drug delivery systems

Definition	Applications	General method of preparation	Characterization
Vesosomes			
Vesosomes are multi-compartmented structures with distinct inner sections that are segregated from the outside -membrane they also described as nested vesicles or vesicles-in-Vesicles.	• Condensed DNA and proteins can be easily encapsulated as vesosomes. • Site-specific Delivery of drug • Delivery of Anti-inflammatory drugs • In treating cancer.	• Lipid dissolved in the suitable solvent mixture • dried thin film of lipid using a rotary evaporator • Lipid hydration by adding 5 ml of saline phosphate buffer containing a drug to be encapsulated. • Multi lamellar vesicles (MLVs) can be obtained (vesosomes)	• Solubility studies • Partition coefficient • Size distribution • Morphology • Drug content • Scanning electron microscopy • X-Ray diffraction • Dissolution • Entrapment efficiency
Phytosomes			
It is a novel DDS that combines the hydrophilic bioactive botanical components of herbs/herbal extracts with phospholipids.	• As are anti-oxidant • Anti-neoplastic • Gene therapy	• Phosphatidylcholine and cholesterol • Dissolved in a suitable solvent • Organic solvent removed by rotary evaporator • Thin film hydrated with extract	• Physical size • Membrane permeability • % entrapped solute • Chemical composition

		● Sonicated for 20 min on an ice bath to get phytosomes	● Quality and purity of starting material ● Visualization
Solid Lipid Nanoparticles (SLNs)			
SLNs are a new type of submicron-sized lipid emulsion in which a solid lipid replaces the liquid lipid (oil).	● In the preparation of sunscreens ● Anti-tubercular drugs delivery ● In cancer therapy	● Melt the lipid & dissolve or disperse the drug in the lipid ● Dispersing of the drug-loaded lipid in a hot aqueous surfactant mixture. ● Premixed using a stirrer to form a coarse pre-emulsion ● High-pressurere homogenization at a temperature above the lipid melting point to get solid lipid nanoparticles.	● Measurement of particle size ● Zeta Potential ● Molecular weight ● Surface element analysis ● Density ● Molecular analysis ● Crystallinity, Lipid modification
Nanostructured Lipid Carriers (NLCs)			
These are the second generation of Solid Lipid Nanoparticles (SLNs). NLCs are the mixture of solid lipid and liquid lipid in addition to the surfactant in aqueous phase.	● As an Anti-hyperlipidemic ● As an anti-hypertensive ● As an NSAIDS ● As an Anti-fungal therapy	● Solid lipid + liquid lipid + drug melt at 80º c ● Surfactant dissolve in water and heat at 80º c ● Dissolve both mixtures ● Subject to homogenization/sonication	● Morphology (size and shape) ● Zeta Potential Analysis ● Degree of Crystallinity and Lipid Modification ● Determination of Viscosity ● Drug Content and Entrapment Efficiency ● *In-vitro* drug release study
Archaeosomes			
The term Arhaeosomes made from two words Archaea, Liposomes in which liposomes containing one otherwise more ether lipids exclusively from Archaeobacteria domain.	● Cancer vaccines with self-adjuvanting drug delivery ● Chagas disease vaccination adjuvant ● Gene delivery techniques that are new protein and peptide carriers for oral administration ● Antigen delivery techniques that are new ● Enhanced Paclitaxel delivery to breast cancer patients	● The soybean phosphatidylcholine (SPC), sodium cholate (NaChol) and polar lipids from Halorubrum tebenquichense preparation by lipid hydration method. ● Then sonication/homogenization to get Archaeosomes.	● Vesicle size (VS) ● Zeta potential ● Thickness ● *In-vitro* drug permeation ● Cytotoxic assay ● Transfection efficiency

2.2. *Vesosomes*

Vesosomes are multi-compartmented structures with distinct inner sections that are segregated from the outside - membrane they also described as nested vesicles or vesicles-in-Vesicles.

- Condensed DNA and proteins can be easily encapsulated as vesosomes.
- Site-specific delivery of drug
- Delivery of Anti-inflammatory drugs
- In treating cancer.
- Lipids dissolved in the suitable solvent mixture
- the dried thin film of lipid using a rotary evaporator
- Lipid hydration by adding 5 ml of saline phosphate buffer containing a drug to be encapsulated.
- Multi lamellar vesicles (MLVs) can be obtained (vesosomes)
- Solubility studies
- Partition coefficient
- Size distribution
- Morphology
- Drug content
- Scanning electron microscopy
- X-Ray diffraction
- Dissolution
- Entrapment efficiency

2.3. *Phytosomes*

It is a novel DDS that combines the hydrophilic bioactive botanical components of herbs/herbal extracts with phospholipids.

- As are antioxidant
- Anti-neoplastic
- Gene therapy
- Phosphatidylcholine and cholesterol
- Dissolved in a suitable solvent
- Organic solvent removed by rotary evaporator

- Thin film hydrated with extract
- Sonicated for 20 min on an ice bath to get phytosomes
- Physical size
- Membrane permeability
- % entrapped solute
- Chemical composition
- Quality and purity of starting material
- Visualization

2.4. Solid Lipid Nanoparticles (SLNs)

SLNs are a new type of submicron-sized lipid emulsion in which a solid lipid replaces the liquid lipid (oil).

- In the preparation of sunscreens
- Anti-tubercular drugs delivery
- In cancer therapy
- Melt the lipid & dissolve or disperse the drug in the lipid
- Dispersing of the drug-loaded lipid in a hot aqueous surfactant mixture.
- Premixed using a stirrer to form a coarse pre-emulsion
- High-pressure homogenization at a temperature above the lipid melting point to get solid lipid nanoparticles.
- Measurement of particle size
- Zeta Potential
- Molecular weight
- Surface element analysis
- Density
- Molecular analysis
- Crystallinity, Lipid modification

2.5. Nanostructured Lipid Carriers (NLCs)

These are the second generation of Solid Lipid Nanoparticles (SLNs). NLCs are a mixture of solid lipids and liquid lipids in addition to the surfactant in the aqueous phase.

- As an Anti-hyperlipidemic
- As an anti-hypertensive
- As an NSAIDS
- As an Anti-fungal therapy
- Solid lipid + liquid lipid + drug melt at 80^0 c
- Surfactants dissolve in water and heat at 80^0 c
- Dissolve both mixtures
- Subject to homogenization/sonication
- Morphology (size and shape)
- Zeta Potential Analysis
- Degree of Crystallinity and Lipid Modification
- Determination of Viscosity
- Drug Content and Entrapment Efficiency
- *In-vitro* drug release study

2.6. Archaeosomes

The term Arhaeosomes is made from two words Archaea, Liposomes, in which liposomes contain one other more either lipids exclusively from the Archaeobacteria domain.

- Cancer vaccines with self-adjuvant drug delivery
- Chagas disease vaccination adjuvant
- Gene delivery techniques that are new protein and peptide carriers for oral administration
- Antigen delivery techniques that are new
- Enhanced Paclitaxel delivery to breast cancer patients
- The soybean phosphatidylcholine (SPC), sodium cholate (NaChol) and polar lipids from Halorubrum tebenquichense preparation by lipid hydration method.
- Then sonication/homogenization to get Archaeosomes.
- Vesicle size (VS)
- Zeta potential
- Thickness
- *In-vitro* drug permeation
- Cytotoxic assay
- Transfection efficiency

Table 1 reveals the definition, applications, preparation methods, and characterization of many lipid-based drug delivery systems and additional information that some authors failed to disclose. Most review articles focus on a single, lipid-based drug delivery technique and include all necessary information. The study concludes that a significant component of controlling the emergence of lipid-based drug delivery is enhancing the solubility and bioavailability of many drugs that are not highly water-soluble.

3. LITERATURE REVIEW ON VARIOUS LIPID-BASED DRUG DELIVERY SYSTEMS

Automated vesosomes were formulated using a microfluidic device and a continuous flow microcentrifugation technique. The w/o droplets consisting of nanovesicles in the water phase were formulated with T-junction geometry in the microfluidic device[17]. Multicompartment systems have been manufactured by aqueous core encapsulating dendrimers of liposomes. Due to this method, the double protection of drugs within the core can be achieved. Compared to a single-compartment system, more effective & sustained drug release can be obtained by multi-functionalization. In addition, the increased permeability, specificity, and stability can be achieved by multi-compartment-based lysosome systems[18]. Diclofenac pharmacosomes were prepared by the conventional solvent evaporation technique. The solubility & dissolution of diclofenac pharmacosomes was improved/enhanced compared to free diclofenac drugs. The Diclofenac pharmacosomes can be used to get better dissolution and reduce gastrointestinal (GI) drug toxicity[19]. Pharmacosomes are advanced carrier systems for vesicular drug delivery. The drug's effect and biological activity may be altered with the enhancement in the complex and linkages. Different approaches, like PEGylation, biotinylation, etc., are the current trends in the cellular targeting of pharmacosomes. Nowadays, pharmacosomes extend innovative challenges and opportunities for enhanced novel vesicular DDS[20]. Conventional solvent evaporation technique, Supercritical fluid process, and anhydrous co-solvent lyophilization are some of the methods for the preparation of Pharmacosomes. The bioavailability of various NSAIDs, Cardiovascular drugs, proteins, anti-neoplastic drugs, and herbal or synthetic drugs was greatly enhanced by a pharmacological lipid-based delivery system[21]. Mangiferin (MF) loaded phytosomes formulated through the phospholipid complexation method. Compared to pure mangiferin, the MF phytosomes *ex vivo* study showed enhanced absorption. The levels of reduced glutathione, catalase, and superoxide dismutase have increased, and the malonyl dehydrogenase levels have decreased for the MF phytosomes compared to Silymarin. The results showed that MF antioxidant potency and hepatoprotective activity increased by formulating it as a phytosomes[22]. The rotary evaporation technique is as useful for forming the vesicular system. Compared with the plain andrographolide (AN), the AN ribosomes (ANH) showed better absorption compared with Silymarin, the standard drug. Thus, this study revealed that the ANH has better bioavailability and enhanced hepatoprotective activity compared with the plain at the same dose[23]. Archaeosomes containing the sulfated saccharide group were covalently

bound to the free sn-1 hydroxy backbone of sulfated S-lactosylarchaeol (SLA) mixed with lactosylarchaeol (LA)[24]. Sulfated S-lactosyl archaeol (SLA) is a novel adjuvant formulation. The semi-synthetic sulfated glycolipid archaeosomes constitute a novel class of adjuvants, maintain the immune stimulatory activity and potentially facilitate manufacturing and scale-upWith the mixing of plasmid DNA with H. hispanica 2TK2 lipids, the archaeosomes were prepared. The archaeal lipids were probably used as transfection agents[25,26]. Compared to a pure drug, the drug-loaded archaeosomes showed significant improvement in efficiency for delivering small molecules. They concluded that formulated archaeosomes were nontoxic to keratinocytes at elevated doses[27]. Betamethasone dipropionate-loaded Archaesomes have major drug penetration and accumulation of skin strata in the epidermis. Based on rheological studies, archaisms are the main key ingredient for the delivery of carriers for topical application[28-30]. Archeosomes are a successful carrier system helpful in drug and gene delivery to target sites. They concluded that, for the control of various diseases, novel delivery systems like archaesomes act as active carriers for targeted drug delivery [31-33].

4. LIPID-BASED DRUG DELIVERY MECHANISMS

4.1. Phytosomes

Most phytoconstituents are hydrophilic, so they cannot penetrate through the lipophilic cell membrane to show their action. However, in the case of pyrosomes, the active phytoconstituents are entrapped in lipophilic phospholipids. Thus, delivering the drug as a pyrosome can show its ultimate action as it contains both hydrophilic drugs and lipophilic phospholipids. The process of drug permeation through phytosomes is depicted in Figure 2.

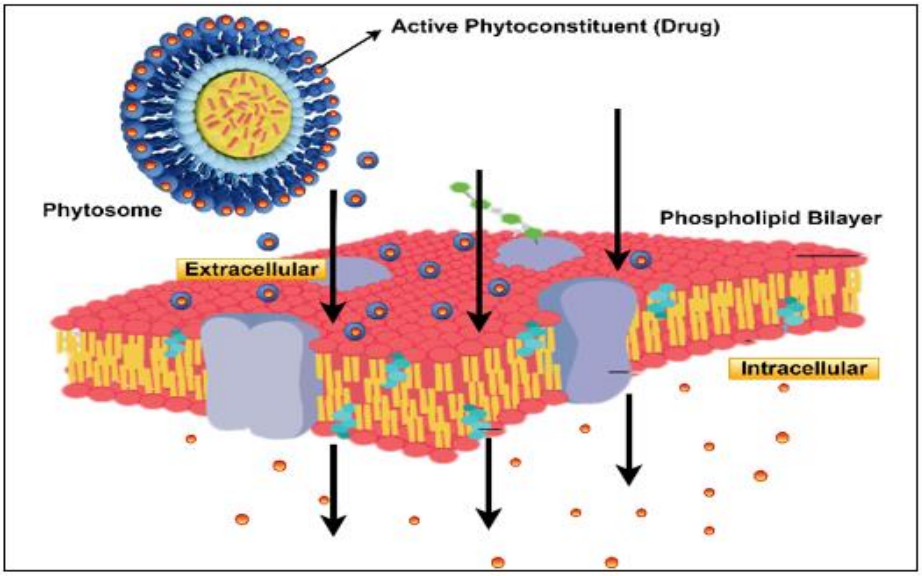

Fig 2: Mechanism of formation of Phytosomes

Phytosomes are a unique emerging technique applied to phytopharmaceuticals to enhance the bioavailability of herbal extract for medical uses. The prefix "Phyto" refers to plants, while the suffix "some" denotes "cell-like." The majority of phytoconstituents are hydrophilic. Thus they cannot operate by penetrating the lipophilic cell membrane. The active phytoconstituents in phytosomes are contained in lipophilic phospholipids. As a result, providing the drug in the form of phytosomes, which include both hydrophilic drugs and lipophilic phospholipids, can reveal the drug's full effect. In addition, phytosomes show more effective pharmacokinetic and pharmacodynamic characteristics than traditional herbal extracts. At the same time, a concentrate has been mostly on the many therapeutic uses of phytosomes and their critical function in controlling the typical difficulties associated with delivering phytoconstituents. Figure 2 illustrates how phytosomes allow drugs to pass through.

4.2. Nanostructured Lipid Carriers

As Nanostructured lipid carriers are the second generation of Solid Lipid Nanoparticles, they can overcome the drawbacks of SLNs. NLCs contain Liquid lipids along with Solid lipids as well as surfactants. NLCs can easily transport through the intestine as transportation of drugs through the intestine depends on particle size; NLCs have <500 nm particle size. The drug penetration process through nanostructured lipid carriers is depicted in Figure 3.

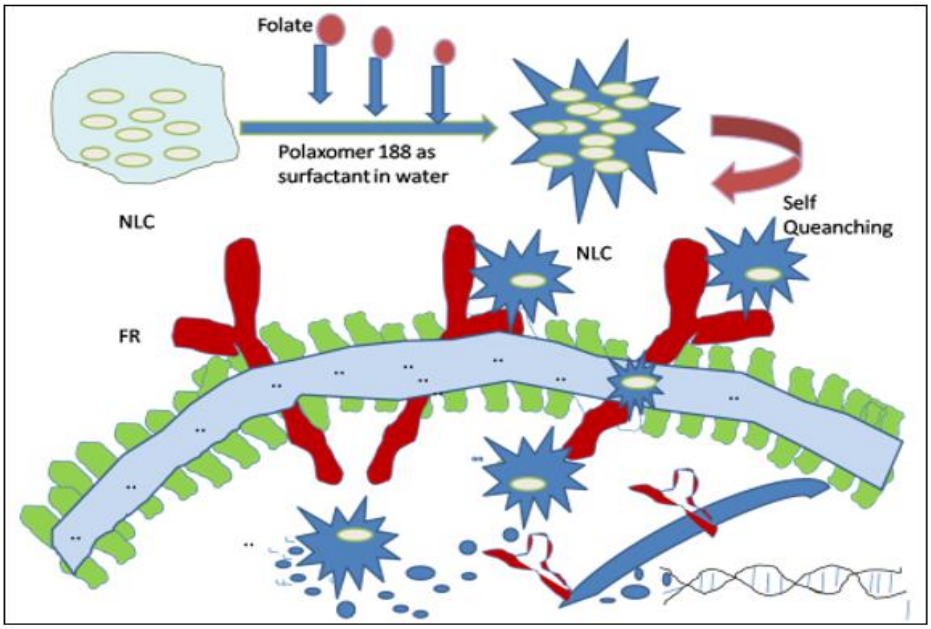

Fig 3: Mechanism of action of Nanostructured lipid carriers

As Nanostructured lipid carriers are the second generation of Solid Lipid Nanoparticles, they can overcome the drawbacks of SLNs. NLCs contain Liquid lipids along with Solid lipids as well as surfactants. NLCs have a particle size of 500 nm or less, which makes them easy to move through the intestine when drug absorption occurs. Drugs that are both hydrophilic and hydrophobic can be included in NLCs. NLCs have recently attracted the attention of researchers as a potential replacement for SLNs, polymeric nanoparticles, emulsions, microparticles, and liposomes. Figure 3 shows the drug penetration process through nanostructured lipid carriers, which may contain hydrophilic and hydrophobic medicines.

4.3. Archaeosomes

The mechanism of archaeosomes is the following key events Receptor-mediated endocytosis and acidification-dependent Ag release into the cytosol—proteasome and TAP-dependent MHC Class-I Ag processing and presentation. The drug release mechanism through archaeosomes is depicted in Figure 4.

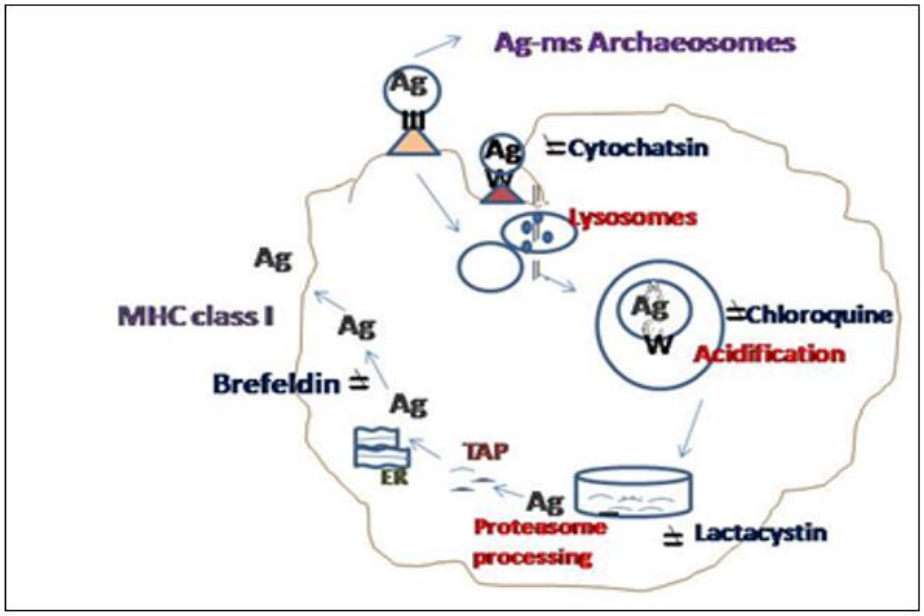

Fig 4: Mechanism of action of micro archaeosomes

Archaeosomes are a unique subclass of liposomes. Liposomes produced with one or more ether lipids from the archaea make up archaeosomes. Lipids of the Achaean type have core structures that are either archaeol (diether) or caldarchaeol (tetraether). Archaeosomes are particularly well-suited for drug delivery and encapsulation applications because of their capacity to entrap both hydrophilic and hydrophobic compounds. The following important occurrences are part of the archaeosome mechanism: Ag release into the cytosol relies on acidification and is receptor-mediated endocytosis. Processing and presentation of MHC Class-I Ag are dependent on proteasomes and TAP. Figure 4 shows the drug release mechanism via archaeosomes.

4.4. Solid lipid nanoparticles

As solid lipid nanoparticles consist of surfactants, they can easily bind the receptors by hydrogen bonding. The lipids

incorporated in SLNs are responsible for drug transportation into the lipophilic cell membrane. By endocytosis, the SLNs enter the cell. The drug release occurs in the respective organs. The release of the drug through solid lipid nanoparticles is depicted in Fig figure 5.

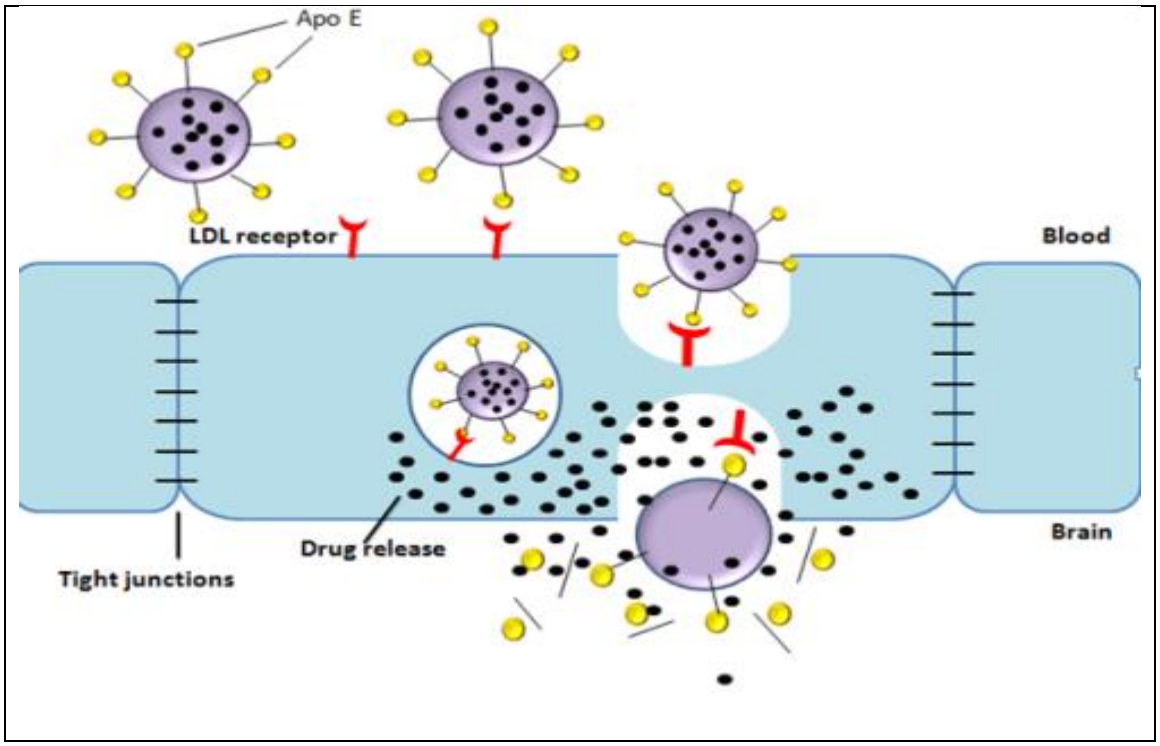

Fig 5: Mechanism of micro solid lipid nanoparticles

Nanotechnology is widely used for medication delivery methods using various passive and active administration methods. Nanoparticles are defined as 10-1000 nm colloidal particle systems. The first generation of lipid nanoparticles, known as solid lipid nanoparticles (SLNs), contains the active ingredient, solid lipids (SL), surfactants, and water. Although SLNs have many benefits, they also have significant disadvantages, including a lower drug loading capacity (DL), irregular gelation affinity, polymorphic transition, and drug leakage. Solid lipid nanoparticles can easily connect to receptors by hydrogen bonding because they contain surfactants. The movement of the drug into the lipophilic cell membrane is accomplished by the lipids included in SLNs. The SLNs get inside the cell through endocytosis. In the appropriate organs, the drug is released. Figure 5 shows how solid lipid nanoparticles deliver the medication.

5. QUALITY BY DESIGN APPLICATION TO LIPID-BASED DRUG DELIVERY SYSTEMS

Joseph M. Juran, an American quality expert, first introduced the QbD concept. Based on Juran's concept, pharmaceutical QbD mainly involves envisioning and planning quality products based on predefined objectives. For preserving quality, the concept of QbD has recently gained a lot of attraction in the pharmaceutical industry. It acts as a link between industry and drug regulatory agencies, allowing them to work together to develop pharmaceutical products in a more scientific, risk-based, holistic, and proactive manner. QbD is a systematic approach to development that starts with established goals and highlights product and process understanding and control, all while adhering to good science and quality risk management. Hence based on the data, i.e. materials, preparation, the equipment, we attempted to identify QTTP (Table 2), major quality attributes (Table 3) that affect the formulation, risk assessment, and DoE that have a critical role in the development.

Table 2: Setting up of QTTP

Attribute	QTPP	Justification
Type of Drug Delivery	Lipid-based systems	Better solubility, dissolution, diffusion, permeation, and BA thereby superior therapeutic efficacy
Dosage form type	Archaeosomes, Colloidosomes, Herbosomes, Pharmacosomes, Transferosomes, and Vesosomes	Bigger and improved BA by the strong bond formation of drug with lipids
Route of administration	Oral	Better patient compliance, easy acceptance
Target delivery	To the required sites based on the type of dosage form, disease, and its need for targeting	Site targeting enhances efficacy and overcome resistance
Packing	Capsules, Suspensions, Emulsions	To maintain Shelf life
Impurities/degradation products	At acceptable limits	Ensures safety of the product indication the stability

Drug release	Prolonged drug release	Developing this type of formulation, a single dose DR for the required period
Pharmacokinetic parameters	Better C_{max}, Tmax and AUC	Improved bioavailability
Stability	At least for 24 months under particular conditions	To maintain therapeutic efficacy

This (Table 2) includes information on the material, the preparation, the equipment, risk assessment, and DoE, all of which are important in establishing QTTP's primary quality features. With the use of QTTP, this table mostly provides attribute correlations. In this review, we take into account several study-related characteristics while concentrating on the quality target product profile of particular lipid-based drug delivery. Additionally, explaining each attribute used to choose the QTTP. Setting up QTTP Aids in learning how different lipid-based drug delivery systems are prepared and developed.

Table 3: Identification of CMAs, CPPs, and responses (CQAs)

S.No	CMAs	CPPs	Responses
		Archaeosomes	
1	Phosphatidylcholine 90, Cholesterol (CHOL) their concentrations and ratio	Thin-film hydration time, RPM, temperature (Rotary Vacuum evaporator), Sonication time, amplitude, cycles, Vacuum application, Purification by gel chromatography	Vesicle size (VS) ZP Thickness *In-vitro* drug permeation
2	Soya phosphatidylcholine, CHOL (6:1 w/w)[34] .	Thin-film hydration time, RPM, temperature (Rotary Vacuum evaporator), Sonication time (45 min with bath type Sonicator 80 w, 40 kHz Extrusion (15 times, Thermo barrel extruder), Freeze-thaw cycles (-70°C to 40°C), Separation of the free drug from nanovesicles by Sephadex G-75 mini-column centrifugation	VS Morphology ZP
3	Archaeal polar lipids, their concentrations and ratio[35] .	Thin-film hydration by Rotary vacuum evaporator (time, temperature, RPM), Freeze-thaw - 37°C, 10 cycles, Extrusion (0.45 µm polycarbonate filter – 21 times using lipo extrusion apparatus, Separation by centrifugation at 30.000 g for 5 min, Non entrapped drug separation by assaying at 474nm spectrophotometrically	VS ZP Drug loading (%) % EE Morphology *In vitro* DR
4	1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine (POPC): CHOL Concentrations and ratios (Archael lipid: CHOL – 0-50%)[36]	Rotary vacuum evaporator (time, temperature, RPM), Vortexing – time, cycles Freeze-thaw cycles – 3, Extrusion by polycarbonate filter, mini extruder, Nonencapsulated Calcein removal by Sephadex G-50 column (monitoring with Quanta master spectrofluorometer)	Sedimentation assay Tryptophan fluorescence Calcein release Transmission Electron Microscopy (TEM) Electro formation and imaging of giant unilamellar vesicles
5	Halobacterium salinarum, Lactosylarchaeol (LL): sulfated Lactosylarchaeol (SL) their concentration and ratio[24] .	Hydration time, temperature Bath sonication, Non entrapped drug removal by centrifugation (200,000 x gmax, 120 min, 2 washes), Extrusion by SDS polyacrylamide gel electrophoresis	VS ZP
6	Sulfated glycolipids, LL SL their concentration and ratio [0-100: 90-1037] .	Hydration time, temperature Sonication, Non entrapped drug removal by centrifugation (200,000 x gmax, 30 min, 2 washes), Extrusion by SDS polyacrylamide gel electrophoresis	ZP Assay
7	Archael polar lipids concentration and the ratio[26].	Hydration by Rotary vacuum evaporator, Vortexing and extrusion by Agarose gel electrophoresis, polycarbonate filter (100 nm)	VS ZP TEM ß-galactosidase activity assay Agarose gel electrophoresis study

8	Lipids[27].	Hydration, Vortexing, Fractionation by adsorption chromatography, Extrusion by Whatman membrane (400 nm)	Cytotoxic assay Transfection efficiency
	Phytosomes		
9	Mangiferin: SPC (1:1) ratio[22]	Magnetic stirrer – time, RPM Rotary vacuum evaporator – time, temperature, RPM	VS TEM Complexation efficiency Ex-vivo study
10	Andrographolide:SPC (1:1) ratio[23] .	Rotary vacuum evaporator – time, temperature, RPM Stirring time, temperature (Magnetic stirrer) Vacuum dryer, Sonication	VS Complexation efficiency Ex-vivo study
11	Drug: Phosphatidylcholine (1:3)[38]	Temperature (40°C-60°C), time (1.5-3.5 h)	EE % Yield
12	Extract: lipid.	Rotary vacuum evaporator temperature, stirring time	VS, % EE, DR
	Vesosomes		
13	Asolectin: CHOL (4:1) [17] .	The microfluidic device, Continuous flow micro centrifuge speed, The flow rate of aqueous solution (20μL/h), oil (10020μL/h) Stabilization time (lipid monolayer), Ultrasonication, Probe sonication Axis of rotation	Size distribution Uniformity
14	Types of lipids and ratios Polymeric lipids type and concentration[18] .	Heating temperature, time	EE
15	Dipalmitoyl phosphatidylcholine (DPPC): CHOL	Mini extruder, Vortexing time, preheating temperature, Filtration type, pore size Purification type, Addition of guest liposomes	Size distribution Drug loading DR
	Pharmacosomes		
16	Drug: lipid ratio	Rotary vacuum evaporator, Vacuum desiccator time	Solubility Drug content SEM, XRD Dissolution

This (Table 3) covers the identification of CMAs, CPPs, and responses (CQAs) of different lipid-based drug delivery systems for the objectives of obtaining good bioavailability and solubility, as well as the development of a new approach for the lipid phase.

5.1. Safety and Efficacy

With advances in *in vivo* and genetic engineering, the new lipid- and polymer-based drug delivery systems are successful in the clinical trials stage. However, rates of post-marketing surveillance vary in some of these drug delivery systems because EPR and other factors vary from person to person and many other factors also need to be characterized to form a system. Nevertheless, the effect works the same for everyone. The manufacturers and formulators take care to eliminate any elements that could lead to further difficulties in guaranteeing the safety of these medication delivery systems. However, more literature and research are needed to identify the factors influencing drug efficacy in patients and prevent unwanted side effects.

5.2. Ishikawa Diagram

Ishikawa diagram, also known as the fishbone diagram, herringbone diagram, cause and effect diagram, or Fishikawa, is a diagrammatic approach developed by Kaoru Ishikawa to aid the brainstorming process and detect the possible reasons accountable for a problem. In a more elaborate approach, the Ishikawa diagram breaks down the problem into successive layers to get a clear view of the superficial problems' root causes. The Ishikawa diagram is based on the 5 M's, which can be held responsible for almost every deviation from the predetermined plan. The 5 M's are – Machine, Method, Material, Man/Mindpower, and Measurement/Medium.

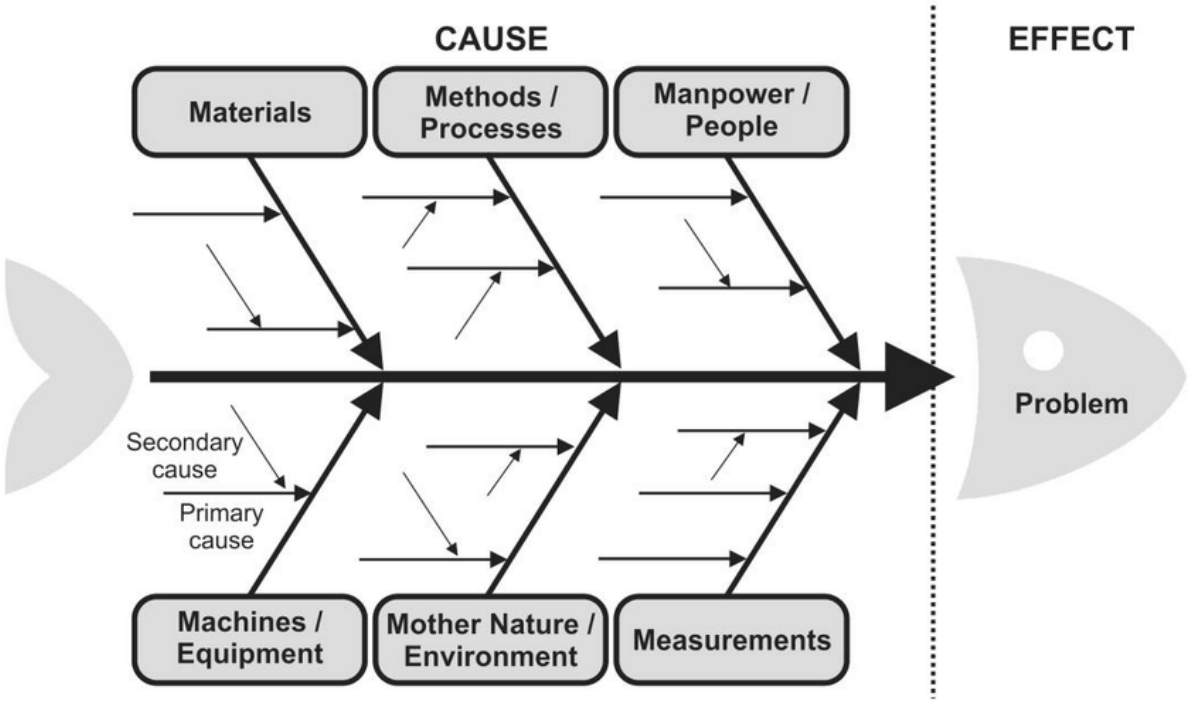

Fig 6: Ishikawa diagram

The Risk assessment associated with the formulation development can be accomplished by implementing the Ishikawa diagram approach, where the CQAs and the CMAs have divided appropriately among the 5 M's.

5.3. Risk assessment

Risk assessment helps in the identification of factors that affect responses out of several factors identified from CQAs. Ishikawa (Fishbone) diagrams and Risk priority numbers (Low, medium, high) are generally used for risk assessment. The selected factors will be used for DoE. A risk assessment is conducted to evaluate the effect of a specific variable or crucial properties of raw materials (API and excipients) and packaging materials. The CPP of the drug product is also determined by it. Based on how they affect the quality of the completed product, each CPP's attribute is categorized as high, medium, or low-risk. To lessen the likelihood of risk, high-risk attributes are further examined. Risk assessment can be done in several ways, including failure mode and effects analysis (FMEA) and relative risk-based matrix evaluation (RRMA). FMEA is a systematic, proactive strategy for assessing a process to determine where and how it might fail and to gauge the relative impact of various failures to pinpoint the areas of the process that require the greatest improvement. It is also called potential failure modes and effects analysis, failure modes, effects and criticality analysis (FMECA). It is a widely used tool for process analysis. The phrase "failure modes" refers to the possible failure modes for a certain system. Any mistakes or flaws, especially those that negatively impact the client, are considered failures, whether actual or hypothetical. The term "effects analysis" describes examining the effects of those mistakes. The importance of a failure is determined by its implications, frequency of occurrence, and detection ease. Using the highest-priority failures as a starting point, the FMEA's goal is to take steps to eliminate or reduce failures. Failure modes and effects analysis also outline the most recent actions and knowledge around failure risks to support ongoing development. To stop failures from happening, FMEA is utilized during design. It is employed for control before and throughout the process' continuing operation. When designing a product or service, FMEA should ideally start in the early conceptual stages and continue throughout the whole life of the item. There are mainly two types of FMEA: Design FMEA (DFMEA) and Process FMEA (PFMEA). Design FMEA (DFMEA) is a methodology used to examine risks connected with a new, updated, or modified product design and explores the potential for product/design malfunctions, shortened product life, and safety and regulatory concerns/effects on the consumer-generated from material Properties, Engineering Noise, Product Geometry, and How It Interacts with Other Systems and Components. Process FMEA (PFMEA) is a technique for identifying risks connected to process modifications, such as failure that affects product quality, decreased process reliability, customer discontent, and safety or environmental hazards derived from the 6Ms: Man, Method, Materials, Machinery, Measurement, Mother Earth. [39]

5.4. Design of experimentation

Design experts and JMP software are commonly used to design experimentation in optimizing formulations. Some other software such as Minitab, MODDE, and Design expert is used. The factors exhibited significance at $p<0.05$, i.e. 95% confidence interval (CI) confirmed by ANOVA (Table 4)[40]. Based on polynomial equation results by design expert software, it was concluded that extract: lipid and temperature had synergistic (positive) and rotation time with a negative effect. The enhanced EE might be because of improved drug solubility in the selected lipid phase. The normal probability plot was formed like an 'S' curve and followed a normal distribution. Random scattering was seen in the Residuals against the expected response plot and Residuals versus experimental run plots, indicating relevance and identifying the elements that influenced the responses in an experiment. Actual response values Vs expected response, as shown by a 45° line split of data points and the Box-cox plot. Cook's distance is another plot to detect significant components; all of the factors were within the red line, indicating that they were free of errors. The desirability approach can be used to

select the optimum formula from the study of contour and overlay plots. The optimized formula is then scaled up, and the applicability of the formula is evaluated within the design space region. DoE is a useful tool for lipid-based system optimization. We also attempted to explain DoE by considering the factors and their responses from Glycyrrhiza glabra pyrosomes. We applied the same to statistical DoE software, i.e. JMP (statistical Discovery SAS), to understand the optimization in different software. Prediction profilers, leverage plots, and contour plots are visualization tools that help understand the model. They are also utilized to optimize responses simultaneously by investigating the noise effect. The leverage plot shows that confidence curves cross the line, indicating a significant effect at a 95% confidence interval ($p<0.05$). % CDR actual Vs predicted showed no obvious evidence of lack of fit, and the *p*-value exhibited significance as it is less than 0.001. The model displayed an R squared value of 0.89, closer to 1 and a Root Mean Square error 3.23, indicating the decreased error. For each factor (Extract: lipid, temperature, rotation time), the line in the plot showed how vesicle size, % EE, % CDR varied when these set factors values defined by the red dashed vertical lines were changed. The profiler displayed a desirability value 0.60 (closer to 1) when the factors were set at 1:1.25 extract lipid ratio, 62.5°C temperature and 1.39 rotation time, respectively. The contour plot displayed a better % CDR (90%-94%) in the region of light and dark red indicating design space. It can be concluded that Design expert and JMP software provides almost similar design space through contour plots and in identifying significant factors by ANOVA (*p* values).

Table 4: Statistical analysis (ANOVA table)

Source	Sum of Squares	df	Mean Square	F-value	p-value Prob > F	p<0.05	R^2
Model	471.79	9	52.42	5.59	0.0167	significant	Adj R-Squared 0.904
A-Extract: lipid	68.47	1	68.47	12.28	0.0072		
B-temp	9.46	1	9.46	1.01	0.3485		Pred R-Squared 0.852
C-rotation time	120.90	1	120.90	12.90	0.0088		
AB	28.62	1	28.62	3.05	0.1240		
AC	1.82	1	1.82	0.19	0.6725		
BC	4.41	1	4.41	0.47	0.5148		Adeq precision 14.86
A^2	61.28	1	61.28	6.54	0.0377		
B^2	99.45	1	99.45	10.61	0.0139		
C^2	149.56	1	149.56	15.96	0.0052		
Residual	65.60	7	9.37				
Cor Total	605.57	16					

The entire statistical analysis of the expert's design for a lipid-based medication delivery strategy is covered in this Table 4. Rotation time was found to have a negative effect, whereas extract, lipid, and temperature had synergistic (positive) impacts, according to the findings of polynomial equations produced by design expert software. The better EE could be due to the medication's increased solubility in the selected lipid phase. The normal probability plot was normally distributed and resembled the "S" curve. In some lipid-based drug delivery systems, Adj R-Squared and Pred R-Squared are also determined for the selected lipid phase.

5.5. Control strategy

Since these are lipid drug delivery systems, key control is associated with the various lipid components used in development. These lipids influence the properties and performance of the developed product, thereby exhibiting a direct correlation with quality. The various separation techniques in the analysis (detection and quantification) of lipid components, such as liquid chromatography, gas chromatography, and electro chromatography, are essential to evaluate the stability of these lipids in the developed formulation. In order to determine the quality of these products, it is essential to evaluate VS, ZP, morphology, % EE and *in vitro* DR of the formulation. Any variation in these parameters indicates a loss of quality in the formulated products and might affect the efficacy and bioavailability.

6. DEVELOPMENT OF LIPID-BASED DRUG DELIVERY SYSTEMS (LBDDS) BY THE APPLICATION OF DOE

Due to their large size, most of the phytoconstituents exhibit poor BA. Compared to metformin, the standard drug in low doses, this M. balsamina, *C. colocynthis* (L.) and *M. dioica* phytosomes were found to afford a safe and convenient alternative delivery to the existing dosage form[41]. The thin layer ultrasonication technique was used for formulating 3', 5'-dioctanoyl-5-fluoro-2'-deoxyuridine pharmacosomes (DO-FUdR-PS). DO-FUdR-PS optimized by using CCD by considering factors like glycerol tristearate concentration, pluronic F-68 and drug to phosphatidylcholine ratio on drug loading, drug entrapment ratio and particle size. The results demonstrated that the response variables were found to be vastly dependent on formulation variables—the pharmacosomes act as an alternative method for absorbing and permeating biologically active ingredients[42]. Nanostructured Lipid Carriers (NLCs) can systematically load poorly water-soluble drugs like polyphenols with simple drug-loading methods. QbD approach[43] can attain the large-scale production of these delivery systems. NLCs containing Salicylic acid dosage forms were produced consisting of Compritol 888 ATO (solid lipid), Miglyol 812 (liquid lipid) and Cremophor RH 60 (surfactant). Based on the initial risk assessment results, PS, particle size distribution and aggregation were found to be three CQAs, ultrasonication time, the concentration of surfactant and solid lipid-liquid lipid ratio was three CMA and CPP were recognized. Therefore, the optimal formulation can be acquired when the ultrasonic time is about 20 min, the surfactant concentration is 5% and the solid lipid: liquid lipid is 7:3. Melt-emulsification and ultra-sonication technique, Ibuprofen (IBU)-loaded NLCs (IBU-NLCs) were prepared by Dynasan 114 (solid lipid), Miglyol 840 (liquid lipid) and Kolliphor HS 15 (surfactant). The Plackett-Burman design, followed by BBD, was applied for optimization.

QbD was successfully implemented in developing and optimizing IBU-loaded NLCs in ocular application[44]. The microwave-assisted method is utilized for the preparation of NLCs containing zidovudine. QbD methodology was used for the optimization of all processes. According to the study, both the optimized formulations were considered safe and suitable for oral administration[45]. NLCs loaded with Olmesartan Medoxomil (OLM) were developed with the help of hot-micro emulsion methods with enhanced biopharmaceutical attributes. The optimized formulation was assessed by design space face-centred cubic design. The results of FMEA and PCA have suggested that oleic acid, stearic acid and tween 80 are the CMAs for formulating NLCs. They successfully developed the OLM as NLCs using the QbD approach for enhanced therapeutic performance in treating hypertension. The optimal lipid nanoparticle formulations produced by the high-pressure homogenization method had nanometric PS, narrow size distribution and negative ZP. Compared to free 5-FU, optimal NLCs showed a higher anticancer effect on epidermoid carcinoma cells and less cytotoxicity towards human keratinocyte cells. Applying QbD in the formulation and development of NLCs consumed less time and saved the cost process to ensure a high-quality product[46]. Diflunisal-Phospholipid complex (DIF-PL complex) formulated by solvent evaporation method was characterized by various studies like SEM, DSC, FT-IR, PXRD etc., DIF-PL complex was included into NLCs. After screening variables by tauguchi design, the optimization was done by face-centred cubic design (FCCD). This study concludes that QbD-based formulation, optimization, characterization and preclinical investigation of DIF-PL complexes as SNLCs successfully relieved the pain associated with inflammation for the treatment of rheumatoid arthritis[47]. Ibrutinib (IBR)-NLCs produced by solvent diffusion and QbD were successfully applied. The Placket-Burman Design (PBD) and CCD were applied for characterization. The *in vivo* PK studies exhibited enhanced oral BA of formulated NLCs compared to pure drug[48]. In the proniosome delivery systems, the product degradation was determined by performing stress degradation studies using acid, base, peroxide, thermal and photolytic methods[49]. Type III self-emulsifying delivery system (Type III SEDDS) loaded with sorafenib tosylate (SFN) were formulated with enhanced biopharmaceutical performance. Thus the formulated batches were evaluated for their globular size, ZP and % of CDR. The agents PVP and HPMC were useful in enhancing the formulation stability for prolonged periods. The type III SEDDS showed nearly eight-fold increase in dissolution rates compared to pure drug, according to *in vitro* DR studies. The greater efficacy of optimized type III SEDDS was disclosed by cytotoxicity studies using Hep G2 cells. The results of studies demonstrated that Sat Type III SEDDS acts as an alternative to enhance the efficacy of drug with high dose and low aqueous solubility with increased anticancer potential[50]. SLN loaded with efavirenz (EFZ) Ibrutinib (IBR) were developed by using the Nanoprecipitation method 32 factorial design[51]. Nano-sized liposomal formulations loaded with lipophilic drugs developed to adapt QbD by lipid film hydration method. The prepared formulations were evaluated for VS, size distribution and specific surface area. The study's results confirmed the improvement in applying QbD in liposome development. Furthermore, the study demonstrated that novel design and development models could aid in optimizing and rationalizing liposomal development[52]. QbD approach was used in developing curcumin (CUR) and doxorubicin (DOX) loaded long-circulating liposomes and evaluated for their cytotoxic potential, C26 murine carcinoma cell lines. In addition, the critical quality attributes investigated, such as PS, ZP, drug loading capacity and EE. According to the *in vitro* antiproliferative test, the CUR concentration showed a greater cytotoxic effect exhibited by CUR-DOX-loaded liposomes compared to DOX-loaded liposome[s53]. The lyophilized long-circulating liposomes loaded with simvastatin (SIM) (lyo-LCL-SIM) was developed and optimized using the QbD approach. The most important formulation factor was the cholesterol content, whereas the no of extrusions through polycarbonate membranes was the process parameter. QbD demonstrated knowledge regarding the design space for lyo-LCL-SIM and risk factors. Thus, the QbD is a helpful, time-effective strategy for formulating liposomes with predictable and controlled quality[54]. Compared to free drugs, the liposomal gel containing insulin showed 16 times improvement in the rate of wound healing, a decrease in the erythema of ulcer and an absence of signs of hyperglycemia[55]. Hot emulsification and ultrasonication formulated quetiapine fumarate (QF) loaded solid lipid nanoparticles (QF-SLNs). The precirol ATO5 as a lipid, phospholipon 90G as a stabilizer, and poloxamer as a surfactant was used in formulation development. The 32 central composite design revealed the two independent variables, the concentration of lipid and stabilizer, exhibited a profound effect on the %EE response dependent variable[56]. Pomegranate Extract-SLNs (PE-SLNs) were prepared by hot homogenization and ultrasonication techniques. Compared to free drugs, the optimized PE-SLNs showed a more than the 40-fold improved effect on cell growth inhibition. Additionally, the optimized formulation expressed selective activities against cancer cells in MCF-7 breast cancer cells more than in normal cells. SLNs loaded with Carvedilol were formulated by a homogenization method followed by ultrasonication. As a result, the oral BA of CVD-SLNs increased more than two times compared to free CVD[57].

7. CONCLUSION

Quality by design is an important computer-assisted tool used in the pharmaceutical industry for developing various formulations. Identifying QTTP, CQAs, and risk assessment, with an emphasis on statistical DoE, has been explained in developing various lipid-based drug delivery systems. Application of QbD ensures inbuilt quality while designing, and the product will be delivered with the intended performance. Prior knowledge and a thorough literature survey are required to apply various tools of QbD during its implementation. This reduces variability in product and faults by enhanced development. Computer-enabled (Design expert and JMP software) contour plots, diagnostic plots, ANOVA, Prediction profilers, and leverage plots assisted in optimizing the formulation. Design space created during the QbD process enables regulatory flexibility during submissions to FDA and SUPAC. The attempt made by the authors paves the way for understanding the importance of lipid-based drug delivery methods, applications & characterizations, and QbD application knowledge in various lipid-based delivery systems for formulation development. It would also provide knowledge on those parameters that should be considered for the transformation of the developed products to large scale easily, i.e., industrial application, thereby satisfying criteria of patentability.

8. FUTURE PROSPECTIVE

But in spite of the benefits of the Lipid-based drug delivery

system, many of the products developed by this technology were not transferred to a large scale, only there was the existence of a few marketed products. Moreover, as most of the formulation and optimization of these systems were carried out by trial-and-error Formulation by Design (FbD) based methods, it adds cost to the development. Hence the adoption of Quality by Design (QbD) in the development can easily transfer the product from Research and development (R&D) scale to the pilot scale and from the pilot scale to the large scale, which would satisfy the criteria of patentability as it provides the industrial application.

9. ABBREVIATIONS

BA – Bioavailability, BBD - Box Behnken Design, CCD – Central Composite Design, CMA - Critical Material Attributes, Conc – Concentration, CPP - Critical Process Parameters, CQA - Critical Quality Attributes, DDS - Drug Delivery System, df – degrees of freedom, DoE - Design of Experiments, DR - Drug Release, EE - Encapsulation Efficiency, FbD – Formulation by Design, GI - Gastrointestinal, LBDDS - Lipid-Based Drug Delivery System, PDI - Poly Dispersity Index, PS - Particle size, QbD - Quality by Design, QTPP - Quality Target Product Profile, VS - Vesicle Size, ZP - Zeta Potential

10. AUTHORS CONTRIBUTION STATEMENT

Dr Haranath conceptualized the work and improvised the manuscript. Mr Venkatesh collected the information related to the QbD aspects. Ms Mousami and Mr Udit gathered the data regarding lipid-based drug delivery systems. Mr Bhargav and Mrs Naga Shubha collected the data on lipid-based drug delivery mechanisms and prepared the draft. All authors were equally involved in drafting the manuscript.

11. CONFLICT OF INTEREST

Conflict of interest declared none.

12. REFERENCES

1. Kalepu S, Manthina M, Padavala V. Oral lipid-based drug delivery systems – an overview. Acta Pharm Sin B. 2013;3(6):361-72[6]:361-72. doi: 10.1016/j.apsb.2013.10.001.
2. Lavik EB, Kuppermann BD, Humayun MS. Chapter 38. Drug delivery. In: Ryan SJ, Sadda SR, Hinton DR, Schachat AP, Sadda SR, Wilkinson CP, et al., editors. Retina. 5th ed. London: W B Saunders; 2013. p. 734-45.
3. Nayak K, Choudhari MV, Bagul S, Chavan TA, Misra M. Chapter 24. Ocular drug delivery systems. In: Chappel E, editor. Drug delivery devices and therapeutic systems. Academic Press; 2021. p. 515-66.
4. Senapati S, Mahanta AK, Kumar S, Maiti P. Controlled drug delivery vehicles for cancer treatment and their performance. Signal Transduct Target Ther. 2018;3:7[1]:7. doi: 10.1038/s41392-017-0004-3, PMID 29560283.
5. Ng LC, Gupta M. Transdermal drug delivery systems in diabetes management: a review. Asian J Pharm Sci. 2020[1]:13-25;15(1):13-25. doi: 10.1016/j.ajps.2019.04.006, PMID 32175015.
6. CHAPTER AM. Pulmonary drug delivery. In: Kulkarni VS, editor. Handbook of non-invasive drug delivery systems. Vol. 9. Boston: William Andrew Publishing; 2010. p. 209-46.
7. Shende P, Basarkar V. Recent trends and advances in microbe-based drug delivery systems. Daru. 2019[2]:799-809;27(2):799-809. doi: 10.1007/s40199-019-00291-2, PMID 31376116.
8. Naghizadeh Z, Karkhaneh A, Nokhbatolfoghahaei H, Farzad-Mohajeri S, Rezai-Rad M, Dehghan MM, et al. Cartilage regeneration with dual-drug-releasing injectable hydrogel/microparticle system: in vitro and in vivo study. J Cell Physiol. 2021[3]:2194-204;236(3):2194-204. doi: 10.1002/jcp.30006, PMID 32776540.
9. Kim HS, Sun X, Lee JH, Kim HW, Fu X, Leong KW. Advanced drug delivery systems and artificial skin grafts for skin wound healing. Adv Drug Deliv Rev. 2019;146:209-39. doi: 10.1016/j.addr.2018.12.014, PMID 30605737.
10. Abd El Hadi SR, Zien El-Deen EE, Bahaa MM, Sadakah AA, Yassin HA. COVID-19: vaccine delivery system, drug repurposing and application of molecular modeling approach. Drug Des Devel Ther. 2021;15:3313-30. doi: 10.2147/DDDT.S320320, PMID 34366663.
11. Mukherjee S, Hettiarachchy N, Verghese M. Nutraceutical delivery system. In: Pal K, Banerjee I, Sarkar P, Bit A, Kim D, Anis A, et al., editors. Food, medical, and environmental applications of polysaccharides. Vol. 5. Elsevier; 2021. p. 135-59.
12. Zhang L, Mao S. Application of quality by design in the current drug development. Asian J Pharm Sci. 2017[1]:1-8;12(1):1-8. doi: 10.1016/j.ajps.2016.07.006, PMID 32104308.
13. Chinthaginjala H, Ahad HA, Bhargav E, Pradeepkumar B. Central composite design aided formulation development and optimization of Clarythromycin extended-release tablets. Indian J Pharm Educ Res. 2021[2]:395-406;55(2):395-406. doi: 10.5530/ijper.55.2.77.
14. Beg S, Sandhu PS, Batra RS, Khurana RK, Singh B. QbD-based systematic development of novel optimized solid self-nanoemulsifying drug delivery systems (SNEDDS) of lovastatin with enhanced biopharmaceutical performance. Drug Deliv. 2015;22(6):765-84. doi: 10.3109/10717544.2014.900154. PMID 24673611.
15. Mishra V, Thakur S, Patil A, Shukla A. Quality by design (QbD) approaches in current pharmaceutical set-up. Expert Opin Drug Deliv. 2018;15(8):737-58. doi: 10.1080/17425247.2018.1504768, PMID 30044646.
16. Rahman M, Panda SS, Beg S. Pharmaceutical QbD-Omnipresence in the product development lifecycle. Eur Pharm Rev. 2017:1-10.
17. Waghule T, Dabholkar N, Gorantla S, Rapalli VK, Saha RN, Singhvi G. Quality by design (QbD) in the formulation and optimization of liquid crystalline nanoparticles (LCNPs): a risk based industrial approach. Biomed Pharmacother. 2021;141:111940. doi: 10.1016/j.biopha.2021.111940. PMID 34328089. Jang H, Hu PC, Jung S, Kim WY, Kim SM, Malmstadt N et al.. Automated formation of multicomponent-encapuslating vesosomes using continuous flow microcentrifugation. Biotechnol J. 2013;8(11):1341-6. doi: 10.1002/biot.201200388. PMID 23894035.
18. Paleos CM, Tsiourvas D, Sideratou Z, Pantos A. Formation of artificial multicompartment vesosome and dendrosome as prospected drug and gene delivery

carriers. J Control Release. 2013[1]:141-52;170(1):141-52. doi: 10.1016/j.jconrel.2013.05.011, PMID 23707326.
19. Semalty A, Semalty M, Singh D, Rawat MS. Development and physicochemical evaluation of pharmacosomes of diclofenac. Acta Pharm (Zagreb Croatia). 2009;59(3):335-44. doi: 10.2478/v10007-009-0023-x, PMID 19819829.
20. Pandita A, Sharma P. Pharmacosomes: an emerging novel vesicular drug delivery system for poorly soluble synthetic and herbal drugs. ISRN Pharm. 2013;2013:348186. doi: 10.1155/2013/348186, PMID 24106615.
21. Kapoor B, Gupta R, Singh SK, Gulati M, Singh S. Prodrugs, phospholipids and vesicular delivery - an effective triumvirate of pharmacosomes. Adv Colloid Interface Sci. 2018;253:35-65. doi: 10.1016/j.cis.2018.01.003, PMID 29454464.
22. Jain PK, Kharya M, Gajbhiye A. Pharmacological evaluation of mangiferin herbosomes for antioxidant and hepatoprotection potential against ethanol induced hepatic damage. Drug Dev Ind Pharm. 2013[11]:1840-50;39(11):1840-50. doi: 10.3109/03639045.2012.738685, PMID 23167243.
23. Jain PK, Khurana N, Pounikar Y, Gajbhiye A, Kharya MD. Enhancement of absorption and hepatoprotective potential through soya-phosphatidylcholine-andrographolide vesicular system. J Liposome Res. 2013[2]:110-8;23(2):110-8. doi: 10.3109/08982104.2012.753456, PMID 23506220.
24. Akache B, Stark FC, Iqbal U, Chen W, Jia Y, Krishnan L, et al. Safety and biodistribution of sulfated archaeal glycolipid archaeosomes as vaccine adjuvants. Hum Vaccin Immunother. 2018[7]:1746-59;14(7):1746-59. doi: 10.1080/21645515.2017.1423154, PMID 29336668.
25. Akache B, Stark FC, Iqbal U, Chen W, Jia Y, Krishnan L, et al. Safety and biodistribution of sulfated archaeal glycolipid archaeosomes as vaccine adjuvants. Hum Vaccin Immunother. 2018[7]:1746-59;14(7):1746-59. doi: 10.1080/21645515.2017.1423154, PMID 29336668.
26. Attar A, Ogan A, Yucel S, Turan K. The potential of archaeosomes as carriers of pDNA into mammalian cells. Artif Cells Nanomed Biotechnol. 2016[2]:710-6;44(2):710-6. doi: 10.3109/21691401.2014.982800, PMID 25650647.
27. Zavec AB, Ota A, Zupancic T, Komel R, Ulrih NP, Liovic M. Archaeosomes can efficiently deliver different types of cargo into epithelial cells grown in vitro. J Biotechnol. 2014;192(A) Pt A:130-5:130-5. doi: 10.1016/j.jbiotec.2014.09.015, PMID 25270023.
28. Bhise K, Kashaw SK, Sau S, Iyer AK. Nanostructured lipid carriers employing polyphenols as promising anticancer agents: quality by design (QbD) approach. Int J Pharm. 2017 Jun 30[1-2]:506-515;526(1-2):506-15. doi: 10.1016/j.ijpharm.2017.04.078, PMID 28502895.
29. Cunha S, Costa CP, Moreira JN, Sousa Lobo JM, Silva AC. Using the quality by design (QbD) approach to optimize formulations of lipid nanoparticles and nanoemulsions: a review. Nanomedicine. 2020;28:102206. doi: 10.1016/j.nano.2020.102206, PMID 32334097.
30. Shah P, Goodyear B, Haq A, Puri V, Michniak-Kohn B. Evaluations of quality by design (QbD) elements impact for developing niosomes as a promising topical drug delivery platform. Pharmaceutics. 2020;12(3). doi: 10.3390/pharmaceutics12030246, PMID 32182792.
31. Kaur G, Garg T, Rath G, Goyal AK. Archaeosomes: an excellent carrier for drug and cell delivery. Drug Deliv. 2016[7]:2497-512;23(7):2497-512. doi: 10.3109/10717544.2015.1019653, PMID 25777339.
32. Dobó DG, Németh Z, Sipos B, Cseh M, Pallagi E, Berkesi D et al. Pharmaceutical development and design of thermosensitive liposomes based on the QbD approach. Molecules. 2022;27(5). doi: 10.3390/molecules27051536, PMID 35268637.
33. Scioli-Montoto S, Sbaraglini ML, Cisneros JS, Chain CY, Ferretti V, León IE et al. Novel phenobarbital-loaded nanostructured lipid carriers for epilepsy treatment: from QbD to in vivo evaluation. Front Chem. 2022;10:908386. doi: 10.3389/fchem.2022.908386, PMID 36059881.
34. Higa LH, Arnal L, Vermeulen M, Perez AP, Schilrreff P, Mundiña-Weilenmann C, et al. Ultradeformable archaeosomes for needle free nanovaccination with Leishmania braziliensis antigens. PLOS ONE. 2016[3]:[e0150185 p.];11(3):e0150185. doi: 10.1371/journal.pone.0150185, PMID 26934726.
35. Attar A, Bakir C, Yuce-Dursun B, Demir S, Cakmakci E, Danis O, et al. Preparation, characterization, and in vitro evaluation of isoniazid and rifampicin-loaded archaeosomes. Chem Biol Drug Des. 2018[1]:153-61;91(1):153-61. doi: 10.1111/cbdd.13066, PMID 28667670.
36. Rezelj S, Kozorog M, Švigelj T, Ulrih NP, Žnidaršič N, Podobnik M, et al. Cholesterol enriched archaeosomes as a molecular system for studying interactions of cholesterol-dependent cytolysins with membranes. J Membr Biol. 2018[3]:491-505;251(3):491-505. doi: 10.1007/s00232-018-0018-y, PMID 29476261.
37. McCluskie MJ, Deschatelets L, Krishnan L. Sulfated archaeal glycolipid archaeosomes as a safe and effective vaccine adjuvant for induction of cell-mediated immunity. Hum Vaccin Immunother. 2017[12]:2772-9;13(12):2772-9. doi: 10.1080/21645515.2017.1316912, PMID 28537465.
38. Rathee S, Kamboj A. Optimization and development of antidiabetic phytosomes by the Box-Behnken design. J Liposome Res. 2018[2]:161-72;28(2):161-72. doi: 10.1080/08982104.2017.1311913, PMID 28337938.
39. Fahmy R, Kona R, Dandu R, Xie W, Claycamp G, Hoag SW. Quality by design I: Application of failure mode effect analysis (FMEA) and Plackett–Burman design of experiments in the identification of "main factors" in the formulation and process design space for roller-compacted ciprofloxacin hydrochloride immediate-release tablets. AAPS PharmSciTech. 2012 Dec[4]:1243–1254;13(4):1243-54. doi: 10.1208/s12249-012-9844-x, PMID 22993122.
40. Zhang X, Zong W, Cheng W, Han X. Codelivery of doxorubicin and sodium tanshinone IIA sulfonate using multicompartmentalized vesosomes to enhance synergism and prevent doxorubicin-induced cardiomyocyte apoptosis. J Mater Chem B. 2018;6(32):5243-7[32]:5243-7. doi: 10.1039/c8tb01136b, PMID 32254761.
41. Zhang ZR, Wang JX, Lu J. [Optimization of the preparation of 3′,5′-dioctanoyl-5-fluoro-2′-deoxyuridine pharmacosomes using central composite design]. Yao Xue Xue Bao. 2001[6]:456-61;36(6):456-61. PMID 12585133.
42. Bhise K, Kashaw SK, Sau S, Iyer AK. Nanostructured lipid carriers employing polyphenols as promising

anticancer agents: quality by design (QbD) approach. Int J Pharm. 2017[1-2]:506-15;526(1-2):506-15. doi: 10.1016/j.ijpharm.2017.04.078, PMID 28502895.
43. Kovács A, Berkó S, Csányi E, Csóka I. Development of nanostructured lipid carriers containing salicyclic acid for dermal use based on the Quality by Design method. Eur J Pharm Sci. 2017;99:246-57. doi: 10.1016/j.ejps.2016.12.020, PMID 28012940.
44. Cavalcanti SMT, Nunes C, Costa Lima SA, Soares-Sobrinho JL, Reis S. Optimization of nanostructured lipid carriers for zidovudine delivery using a microwave-assisted production method. Eur J Pharm Sci. 2018;122:22-30. doi: 10.1016/j.ejps.2018.06.017, PMID 29933076.
45. Amasya G, Aksu B, Badilli U, Onay-Besikci A, Tarimci N. QbD guided early pharmaceutical development study: production of lipid nanoparticles by high pressure homogenization for skin cancer treatment. Int J Pharm. 2019;563:110-21. doi: 10.1016/j.ijpharm.2019.03.056, PMID 30935913.
46. Kaur A, Bhoop BS, Chhibber S, Sharma G, Gondil VS, Katare OP. Supramolecular nano-engineered lipidic carriers based on diflunisal-phospholipid complex for transdermal delivery: QbD based optimization, characterization and preclinical investigations for management of rheumatoid arthritis. Int J Pharm. 2017[1]:206-24;533(1):206-24. doi: 10.1016/j.ijpharm.2017.09.041, PMID 28943207.
47. Rangaraj N, Pailla SR, Shah S, Prajapati S, Sampathi S. QbD aided development of ibrutinib-loaded nanostructured lipid carriers aimed for lymphatic targeting: evaluation using chylomicron flow blocking approach. Drug Deliv Transl Res. 2020[5]:1476-94;10(5):1476-94. doi: 10.1007/s13346-020-00803-7, PMID 32519202.
48. Yadav NK, Raghuvanshi A, Sharma G, Beg S, Katare OP, Nanda S. QbD-based development and validation of a stability-indicating HPLC method for estimating ketoprofen in bulk drug and proniosomal vesicular system. J Chromatogr Sci. 2016[3]:377-89;54(3):377-89. doi: 10.1093/chromsci/bmv151, PMID 26514627.
49. Sharma T, Jain A, Kaur R, Saini S, Katare OP, Singh B. Supersaturated LFCS type III self-emulsifying delivery systems of sorafenib tosylate with improved biopharmaceutical performance: QbD-enabled development and evaluation. Drug Deliv Transl Res. 2020[4]:839-61;10(4):839-61. doi: 10.1007/s13346-020-00772-x, PMID 32415654.
50. Raina H, Kaur S, Jindal AB. Development of efavirenz loaded solid lipid nanoparticles: risk assessment, quality-by-design (QbD) based optimisation and physicochemical characterisation. J Drug Deliv Sci Technol. 2017;39:180-91. doi: 10.1016/j.jddst.2017.02.013.
51. Pallagi E, Jójárt-Laczkovich O, Németh Z, Szabó-Révész P, Csóka I. Application of the QbD-based approach in the early development of liposomes for nasal administration. Int J Pharm. 2019;562:11-22. doi: 10.1016/j.ijpharm.2019.03.021, PMID 30877028.
52. Tefas LR, Sylvester B, Tomuta I, Sesarman A, Licarete E, Banciu M, et al. Development of antiproliferative long-circulating liposomes co-encapsulating doxorubicin and curcumin, through the use of a quality-by-design approach. Drug Des Devel Ther. 2017;11:1605-21. doi: 10.2147/DDDT.S129008, PMID 28579758.
53. Porfire A, Muntean DM, Rus L, Sylvester B, Tomuță I. A quality by design approach for the development of lyophilized liposomes with simvastatin. Saudi Pharm J. 2017[7]:981-92;25(7):981-92. doi: 10.1016/j.jsps.2017.01.007, PMID 29158704.
54. Dawoud MHS, Yassin GE, Ghorab DM, Morsi NM. Insulin mucoadhesive liposomal gel for wound healing: a formulation with sustained release and extended stability using quality by design approach. AAPS PharmSciTech. 2019[4]:158;20(4):158. doi: 10.1208/s12249-019-1363-6, PMID 30963353.
55. Agarwal S, Murthy RSR, Harikumar SL, Garg R. Quality by Design Approach for Development and Characterisation of Solid Lipid Nanoparticles of Quetiapine Fumarate. Curr Comput Aided Drug Des. 2020[1]:73-91;16(1):73-91. doi: 10.2174/1573409915666190722122827, PMID 31429691.
56. Badawi NM, Teaima MH, El-Say KM, Attia DA, El-Nabarawi MA, Elmazar MM. Pomegranate extract-loaded solid lipid nanoparticles: design, optimization, and in vitro cytotoxicity study. Int J Nanomedicine. 2018;13:1313-26. doi: 10.2147/IJN.S154033, PMID 29563789.
57. El-Say KM, Hosny KM. Optimization of carvedilol solid lipid nanoparticles: an approach to control the release and enhance the oral bioavailability on rabbits. PLOS ONE. 2018[8]:e0203405;13(8):e0203405. doi: 10.1371/journal.pone.0203405, PMID 30161251.