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Quality by Design Approach for Development of Lyophilized Dry Emulsion Tablets (LDET)

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KEYWORDS

Lyophilization, Quality by Design, Critical Quality Attributes, Critical Material Attributes, Critical Process Parameters, Formulation variables.

ABSTRACT:

Lyophilized dry emulsion tablets (LDETs) are one of the most promising approaches to enhance the bioavailability of poorly water-soluble drugs. Rapid disintegration of these tablets when brought in contact with saliva provides additional benefits such as reduced side effects & first-pass metabolism. To achieve successful production of these complex dosage forms, different material attributes of both the drugs as well as excipients are screened. Along with this, several processing parameters of the manufacturing operations are optimized to consistently produce the final drug product with desired qualities. These operations were strictly monitored & controlled to achieve safe, efficacious, acceptable, drug products in accordance with regulatory standards. It is possible to render the Lyophilization process of dry emulsion to have fewer issues with the freezing process, water-to-ice transition, and polymorphic changes in API when subjected to freeze-drying, duration of secondary drying, by improvising the manufacturing process & critical formulation variables during a key stage of lyophilization.

The main goal of this review is to put forth the foundation for applying the QbD system principles to the design & development of LDETs. This involves executing a preliminary & systematic risk assessment of critical material attributes & process parameters in association with CQAs for both the in-process and finished product. Furthermore, examples of freeze-dried emulsion tablets are used to discuss & support the applicability of the QbD methodology based on its intended use.

1. Introduction

Drugs belonging to BCS Class 2 are characterized by poor oral bioavailability which can be attributed to insufficient aqueous solubility & extensive first-pass metabolism. To overcome these challenges, researchers have employed some of the different techniques which include micronization [1]; complexation with cyclodextrins [2]; nanoparticles [3]. Likewise, the emulsion is also one of the well-established dosage forms which have demonstrated its ability to enhance the absorption of widely used water-insoluble drugs like Amphotericin-B [4] and Penicillin-G [5]. Improved drug concentration-time profiles, enhanced elimination half-life & decline in plasma clearance rendered emulsions pharmacokinetically preferable [6]. Regardless of all the benefits, this system is still prone to degradation & microbial growth owing to its intrinsic thermodynamic instability and the presence of water [7]. The emergence of solid-state emulsions in the form of LDET presents an alternative to deal with this issue since it enables its storage in the dried form. Spray drying [8], Solvent evaporation [9] , and freeze-drying or lyophilization are some of the formulation techniques employed in the preparation of dry emulsion. Formulation of Lyophilized dry emulsion tablets (LDET) is one of the best approaches to counteract the limitations of class 2 drugs since it is intrinsically designed to serve dual advantages of both emulsions and freeze-dried dosage forms. Incorporation of drugs into the oil phase within the dry emulsion system improved its chemical stability while the formation of porous and readily soluble dry product at the end of the freeze-drying process facilitates rapid disintegration of the tablets [10]. Enhanced stability & shelf life are the added benefits offered by these freeze-dried products devoid of water. Recent studies suggested that LDET also enabled the uniform absorption of the drug without the need of consuming fatty meals and swallowing with water [11]. However, freeze-drying of dry emulsion systems at a large manufacturing scale is accompanied by several challenges influenced by process

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design and physicochemical characteristics of the excipients.

Conventional quality control methodologies utilized in developing pharmaceutical dosage forms emphasize quality checks of the finished product conducted in the laboratory. As opposed to this, QbD works towards ensuring the desired attributes of the final drug product during the process design & manufacturing process itself. QbD approach is utilized to maintain the consistency of desired product quality and eliminate the hurdles of manufacturing operations through product and process design. Due to its use in healthcare settings, pharmaceutical, surgical & biological products must conform to strict a regulatory requirement which leads to a long period for review & approval process. The pharmaceutical industry needs to work with regulatory professionals to come up with an action plan that would enable the research to flourish in the field of medicine while still upholding the integrity of the healthcare agencies. This has become less challenging with the support of regulatory agencies like the US FDA, as pharmaceutical QbD has evolved with the issuance of new ICH guidelines, ICH Q8 (R2) (Pharmaceutical development), ICH Q9 (Quality Risk Management) and ICH Q10 (Pharmaceutical Quality System). FDA's issuance of recent guidance which is less stringent than the CMC post-approval changes possessing minimal risk is a testimonial of an improved communication with the regulatory bodies [12].

QbD commences with establishing QTPP (Quality Target Product Profile) & describing CQAs (Critical Quality Attributes) desired for the finished drug product. A comprehensive review of the manufacturing operation enables the identification of CMAs (Critical Material Attributes) and CPPs (Critical Process Parameters) which are optimized throughout the process with a key objective to achieve a final drug product comprising pre-determined attributes. Risk assessment studies are conducted to recognize attributes possessing higher risk potential followed by the development of a control strategy to determine the acceptable range for them. Understanding the formulation design of LDET & its manufacturing process is of utmost importance for the successful implementation of QbD. Despite being able to produce highly stable products, freeze-drying is an economically unfeasible and time-consuming process. This is accompanied by the influence of multiple parameters like freezing characteristics of the formulation, stability of API & properties of excipients on this process. Thus, signifying the necessity of optimizing it to maintain the robustness of the process and prevent the phenomenon of physical or chemical instabilities arising due to the fragility of this technique. There are several literature-reviews that reports the critical parameters and variables arising due to the incorporation of pharmaceutical excipients in the freeze-drying process of liquid formulations [13]. However, no review article detailing the step-by-step approach of QbD in the production of LDET has been published as of now.

The primary objective behind this review article is to present a discussion on the practical set-up through which a systematic approach of QbD can be implemented for the manufacturing of LDET

2. Organised strategy of QbD employed in the development of Lyophilized dry emulsion tablet

2.1. Establishment of QTPP & CQAs for the dry emulsion tablet

QTPP presents a precise review of the primary characteristics of the final product thus providing a basic framework for the drug product development. It facilitates the recognition of those attributes which could have a significant impact on the desired quality of the output material. Ideally, it defines the basic properties of the drug formulation (Dosage form, type, route of administration) and quality attributes of the drug product (moisture content, disintegration) that has to be achieved to remain patient-compliant. The significance of QTPP could be understood while conducting the multiple dosing bioequivalence studies between generic drug & reference listed enteric coated acid labile Omeprazole tablet in an acidic-conditions with gastric pH 1. The enteric coat for these formulations differed with respect to the pH at which the tablets were designed to protect API. Along with the primary conventional targets (API, dosage form, strength, route of administration), QTPP took into account the rational design of the drug product while defining the specification of the acceptable pH range (5.0 – 5.5) in which the enteric coat should resist the acid degradation thus preventing the release of active ingredients [14]. The QTPP elements for LDET can be summarized in **Table 1**.

Table 1: **QTPP elements for LDET**

QTPP element	Target	Justification
Dosage form	Lyophilized Dry Emulsion Tablet (LDET)	Dry emulsion aids in enhancing the bioavailability of lipophilic drugs while lyophilization produces less densely packed porous solid mass
Dosage type	Immediate release	Rapid disintegration on coming in contact with saliva to release active ingredients
Route of administration	Oral drug delivery	Direct absorption of active ingredients through oral mucosa

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		by circumventing the hepatic metabolism. Rapid onset of action achieved through a convenient route is added benefit
Packaging	Blister packs	Blister packs made up of PVC (Polyvinyl chloride) provide cheap oxygen and water barrier properties
Drug Product Quality criteria • Residual moisture content • Disintegration time	NMT 4% [15] NMT 5 mins.	• Lyophilization was efficient in removing water from the tablets • Substantiates prompt release of the active ingredients. For absorption to take place through the oral mucosa, disintegration time should be less than or equal to 30 seconds

The next step in implementing QbD begins with the identification of Critical Quality Attributes (CQAs). Some of the fundamental quality attributes for the drug product comprise identity, assay, degradation products, residual solvents, drug release or dissolution, moisture content, microbial limits & physical attributes like colour, shape, size, strength, and friability, depending upon the type of dosage forms. CQAs are defined as physical, chemical, biological, or microbiological characteristics of the finished drug product that should fall within the acceptable range for the product quality to remain intact. The criticality of an attribute can be determined based on the intensity of the harm it could cause to the patient if the product fails to comply with the specification set for that attribute. CQAs are influenced by both, physicochemical characteristics of the input materials (drugs, excipients, or in-process materials) as well as manufacturing operations parameters. Provided that it represents the final attributes of the end product, constant monitoring throughout the formulation development ensures consistency in the clinical performance of the product & robustness of the process. The CQAs predefined for the LDET are represented in **Table 2**.

Table 2: **Predefined CQAs for LDETs**

Critical quality attributes	**Justification**
Drug content	Process development should be optimised to retain the consistency in the drug content of LDETs since it influences the safety & efficacy of the drug product
Crystallinity	The crystallinity of the active ingredient in LDET should be significantly less as compared to pure drugs to enable its faster dissolution from the tablet. This can be evidenced in the case of the optimised orally disintegrating tablet (ODT) of Nimesulide which exhibited remarkably small endotherm as compared to the one observed for the corresponding physical mixture in the DSC thermogram. This decline in crystallinity promotes drug release and dissolution [16]
Friability	According to the compendial standards, the friability test should display a weight loss of less than 1% thus ensuring the durability and ease of handling of LDETs [17]
In-vitro disintegration and dissolution	With an intent to achieve the main objective of LDETs of rapid disintegration & to prevent the efficacy of drug products from being challenged, it is essential for the drug to be released in the stipulated period

2.2. Application of CMAs & CPPs to optimize the process of developing lyophilized dry emulsion tablets

The establishment of QTPP& CQAs is succeeded by the product design & understanding which involves detailed study of physical, chemical, and biological characteristics of both drugs and excipients. This will enable the earlier detection of safety concerns that may arise from their potential incompatibilities. However, these details can also be utilised to maximize the benefits of the formulation design by combating toxicity and improvising the bioavailability of the drug product with the aid of

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excipients. Optimization studies are conducted to determine the concentration for each of the excipients to obtain drug products with desired quality attributes. The basic process for the formulation of LDETs as outlined in the study conducted by Corveleyn et al. [18] commenced with dispersing emulsifier and migloyl18 in the aqueous phase. This resultant blend of the aqueous and organic phases was subjected to stirring by a Silverson mixer. The emulsion then formed and was degassed through Stephan vacuum pump. The PVC blisters with predefined diameter and depth were filled with emulsion and placed on the shelves of the freeze dryer. Matrix-forming agents, cryoprotectants, emulsifier binding agents, and surfactants are some of the key excipients utilised for LDETs formulation as listed in **Table 3**.

Table 3: Excipients used in the formulation of LDETs

Excipient category	**Examples**	**Role of excipients**	**References**
Matrix former	Sodium alginate, Gelatine, Maltodextrin	Gelatine facilitates the formation of highly-distinct network through interchain H-bonds. Sodium alginate is instrumental in formulating defect-free LDETs	[19]
Surfactants	Syn108, Syn84	Stabilize the prepared oil in water emulsions. Obstructs the fusion of lipid droplets formed from LDETs upon exposure to an aqueous medium of gastric fluid	[20]
Cryoprotectants	Mannitol, Sorbitol, Maltose, Glucose, Sucrose	Protects the emulsion from physical or chemical damage during freezing & drying steps by minimizing the stress occurring in the lipid bilayer	[21]
Emulsifier binding agents	Methocel® E5 & Methocel® E15 (Hydroxy Propyl Methyl Cellulose) and Methocel® A15 (Methyl cellulose)	Aids in the stabilization of oil in water emulsion. Act as a tablet binder.	[22]
Oil phase	Grades of Miglyol (Miglyol 18 & Miglyol 812)	Miglyol are medium chain triglycerides used as an oil phase in formulating LDETs	[23]

While studying the multiple formulations of LDETs reported in the literature, it was observed that emulsifier binding agents replaced the surfactants & binders as they served the dual purpose of stabilization of emulsion and tablet binders. During the freeze-drying step, water is segregated from other components of the formulation due to its conversion into the ice form. This may cause highly concentrated droplets of lipid bilayer to irreversibly fuse ultimately leading to the destabilization of the system. The incorporation of cryoprotectants obviates this process as it occupies the space between polar head groups of the lipid bilayer thus forcing the hydrocarbon chains to space out from each other which results in decreased van der Waals attraction between non-polar chains. This causes the temperature of the phase transition to decline [24]. According to the other protective method described in Sussichet et al [25], Hydroxyl groups of the cryoprotectants associates with the water molecules while free alcoholic groups present on the surface of the system enhances the viscosity of the solution which limits the ice-crystallization and mechanical stress. Critical Material Attributes (CMAs) are physical, chemical, biological, or microbiological characteristic of the input raw materials that should fall within the acceptable range for that attribute to ensure the desired quality of both drugs and excipients remain intact. The type, concentration as well as the grade of the excipients influences the characteristics of the final drug product to a significant extent [26]. Therefore, it is essential to select the appropriate excipients or raw materials with the most optimal quality that will aid in the development of LDETs with the intended CQAs. The criticality of these material attributes is established through a screening process which is conducted along with formulation optimisation studies. This process of associating CMAs to CQAs is fundamental to the successful implementation of QbD

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with an intent to ensure commercial production of LDETs with desired QTPP. While formulating LDET, it was discovered that hydrophilicity of the excipients, most predominantly surfactants and emulsifier tablet binding agents influenced the disintegration time, friability as well as the porosity of LDETs to a remarkable extent [27]. Apart from the physicochemical characteristics of the excipients, incompatibility within the excipients also influences the CQAs of the final drug product. Chemical ionic interaction between 'G' residues of anionic alginate polymer & cationic divalent Ca^{2+} ions of ATV-Ca salt form of the drug led to the formation of a rigid gel-like structure that resisted the penetration of water into the tablets. Subsequent increase in the disintegration time accompanied by a decline in the percentage of drug dissolved at a specific time interval was observed in the presence of sodium alginate as a matrix former [28]. The CMAs impacting CQAs are enlisted in **Table 4**.

Table 4: Influence of the possible CMAs on the CQAs of LDET

CQAs	CMAs impacting CQAs	Description
In-vitro disintegration time and dissolution	HLB value & type of surfactant	Hydrophilicity of Synperonic surfactants has significantly influenced the disintegration of LDETs. Significantly enhanced the disintegration of LDET. Poly ethylene glycol poly propylene glycol block-co-polymer exhibiting relatively high HLB values could have accelerated the hydration of tablets further leading to its increased dissolution[29]
	Concentration & type of the cellulosic binder	Increase in the concentration of the cellulosic binder significantly enhanced the disintegration time of the tablets. This could be ascribed to the increased binding ability at higher binder concentrations. However, this effect was more predominant when relatively less hydrophilic cellulosic binder was used. Resultant LDETs formulated with cellulosic binders possessing relatively high hydrophilicity displayed rapid disintegration. These observations complied with the results obtained for the dissolution of the drug. LDETs developed with highly hydrophilic grade cellulosic binder displayed enhanced dissolution [30].
	Dextrose Equivalents (DE) of spray-dried maltodextrins as matrix former	At elevated concentrations (10-20%), LDETs developed with corn starch maltodextrin comprising of highest DE, DE38 exhibited shorter disintegration times as opposed to those tablets formulated with DE12 & DE24 maltodextrins [31].
	Concentration of oil phase	Enhanced concentration of the medium chain tri-glyceride oil phase delayed the disintegration process of the tablets. Decline in the residual moisture content of the tablet due to the increasing concentration of the oil phase could be the probable reason behind it.
	Type of emulsifier	Xanthan gum undergoes surface

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	binding agents	swelling upon immediate contact with the saliva which accounted for its enhanced ability to delay the disintegration process of the tablets as compared to cellulosic binders [32]
Friability of tablets	Concentration of the cellulosic binders	Increase in the concentration of the cellulosic binder produced a decline in the friability of the tablets which can be attributed to its high binding capacity.

It is substantially difficult to manufacture LDETs as compared to conventional tablets. The criticality of the process parameters can be determined based on the impact it produces on CQAs. ICH Q8 (R2) guidelines for QbD define Critical Process Parameters (CPPs) as process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. It is crucial to recognize the critical formulation parameters to improve process design. which commences with the first step of freeze-drying which is freezing. The formation of ice crystals during the freezing process led to the aggregation of droplets in the emulsified systems. Hence, the possibility of change in the pH of the final formulation increased due to the crystallization of the buffer salts [33]. As reported in the findings of Ingvarrson et.al. rate of freezing influences crystal formation to a remarkable extent [34]. Slow freezing was observed to produce larger, fewer crystals while fast freezing creates smaller & numerous crystals. Subsequently the freezing cycle proceeds with the primary drying step. Through porous layers, the sublimated vapour is eliminated by diffusion or convection. Given the fact that diffusivity is associated with the pore size. Samples with small ice crystals that were formed out of high freezing rates took a long time to dry as compared to those samples containing large ice crystals that were previously subjected to low freezing rates during the primary drying stage. For the complete solidification of Lyophilized cake, the product temperature has to remain at or below the glass transition temperature as it hinders the collapse and melts break of the final product [35]. Apart from product appearance, this collapse can have a profound impact on key quality attributes such as reconstitution time, residual water, and stability. Product temperature can be controlled through shelf temperature and the chamber pressure both of which can be considered as CPPs. In most of the lyophilization methods reported so far, the final shelf temperature is set at -50°C.

Despite the primary drying, the product still contains 10-35% of the water hence it is essential to truncate the moisture content to an acceptable level of stability. After the secondary drying, the water desorption rate is limited for all freezing techniques which results in large crystals & lower specific surface area. Samples with small numerous crystals offering larger surface areas promoted the desorption of water. From the perspective of process efficiency, it is essential to optimize the size of the crystal which produces a direct impact on the length of the primary drying time as well. Improper regulation of secondary drying time culminates in a final product with higher residual moisture content. The impact of the process parameters on the physical state of excipients could be understood from the example of mannitol which displayed an amorphous state when it was exposed to the rapid freezing rate of -20°C/min [36] whereas crystalline form was seen to predominate on reducing the rate to -2°C/min [37]. Apart from the freezing rate even concentration of the mannitol has been demonstrated to produce a significant impact on the physical state of the sample. As per the analytical results published by Kim et. Al [38] during exposure to rapid drying, 10% mannitol sample formed delta polymorph while 5% mannitol sample favoured the formation of beta polymorph. Solidification time was noticed to vary linearly with the fill volume. According to Tang et al., samples having a fill depth of less than or equal to 1 cm should be maintained at the final shelf temperature for 1 hour [39]. From the perspective of patient compliance, the fill depth of LDETs can be assumed to be less than 1 cm to ease tablet swallowing. **Table 5** lists the possible manufacturing process parameters that impact the quality attributes of the final drug product.

Owing to the advantageous benefits offered by the freeze-dried product, streamlining of the Lyophilization process has been the primary focus in the pharmaceutical industry. Single-step drying [40] or continuous drying manufacturing [41] is some of the strategies employed with the intent to reduce manufacturing time & cost. As the name intends in the single-step drying process, primary & secondary drying are performed simultaneously in one step. Results obtained in the recent study demonstrated the superiority of single step freeze drying process over the traditional drying process in the following aspects;

A) Position of the vials kept on the shelf of the freeze dryer has a profound impact on the uniformity of the process, however in the single-step drying process, both the center & edge vials were subjected to drying

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simultaneously which accounted for the homogeneity in the drying rate [42].

B) Remarkable decline was observed in the primary drying time as compared to the conventional freeze drying [43].

Table 5: Impact of the CPPs on the CQAs of the final product

Manufacturing process steps	Process parameters	Justification	CQAs of the final product impacted
Freezing	-	Along with the aggregation of droplets in the emulsified systems, there is crystallisation of buffer salts	Change in the pH of the final formulation
Primary drying	Product temperature, Glass transition temperature, Collapse temperature	Product temperature should remain below the glass transition temperature, non-conformity to which can led to final product collapse or melt break	Reconstitution time, residual moisture content, stability of the final drug product
	Fill volume	No product collapse is observed with 30% fill volume as opposed to 70% fill volume [44]	
Secondary drying	Secondary drying time	Efficient removal of the residual water absorbed in the solid cake	Residual moisture content of LDETs

The stability of the LDETs obtained after manufacturing is highly influenced by the type of packaging material. Studies conducted have proved that PVDC-coated PVC films offered better barrier properties against moisture penetration as compared to PVC blister packs and closed containers. The glass transitions temperature of the maltodextrins was reduced as a result of the absorption of moisture. When it declined further below the storage temperature of the formulation, the amorphous substance transitioned from a glassy state into a rubbery state which ultimately culminated in the loss of the rigidity of the tablet matrix. This eventually resulted in decreased hardness and porosity of the tablet [45].

3. Risk Assessment

Following the determination of CQAs, CMAs & CPPs, functional relationships are established that connect material attributes (CMAs) and process parameters (CPPs) to the product CQAs by employing risk assessment techniques that are crucial for qualitative risk analysis [46]. The ICH Q9 quality risk management guideline effectively describes how a constructive utilization of risk assessment & management tools comprises a vital part of QbD. Using this technique, it is feasible to determine the high risked process parameters that could potentially impact one or more CQAs and would require close attention to details during the developmental stage. The first step of the risk assessment (RA) commences with elucidating the specific operational parameter or variable which might go wrong during the execution of that manufacturing step following the description of the probable causes that will directly impact the desired qualities of the final drug products. This involves analysing the physicochemical properties of all the excipients & drug products used in the formulation of LDETs as well as studying the overall operational parameters of the Lyophilization process. The identified risks are then subsequently evaluated for the negative outcomes they could have in terms of both quality as well as quantity. After the risk evaluation, the decision to determine whether the risk should be reduced or accepted is highly influenced by its ability to affect the clinical performance of the drug product. Reduction of the risk can be performed in either way by minimizing the severity & probability of its occurrence or enhancing its detectability. This can be comprehended from the example of a streamlined single-step Lyophilization process that yielded a final product with collapsed appearance. The risk of product shrinkage is acceptable as long as it does not exhibit a crucial impact on the desired qualities of the final drug product considering the precedence it offers over the conventional two-step freeze-drying process [47].

The use of different types of risk assessment tools varied depending upon the stage of product development. Risk triage & risk relationship matrices are two very basic

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qualitative tools employed during the initial stage of product development. These tools are beneficial as an immediate means to arrive at some strategies which would enable easy detection of risks requiring deep analysis. Typical risk triage as shown in **Table 6** takes into account the impact or severity as well as the probability of the risk to establish an overall level of risk. Failure mode & effect analysis (FMEA) and the Ishikawa fish-bone diagram [48] are the potential tools reported to be utilised for the prior assessment of failures in the later stages of the product development process when adequate information regarding manufacturing operations and formulation components of the final product is compiled. FMEA analysis involves recognizing process parameter components depending on the drug delivery system & dosage form. For every process component determined, the mode of failure and the effect were elucidated. A scale of 1-5 is allotted for the variables signifying the probability of event occurrence; severity & detectability of that process parameter. The relative risk for each of the process variables was estimated through risk priority number (RPN) calculated by a given formula. Process variables with RPN>40 were considered to be high risk, those with RPN>20-40 were found to be medium risk & those with RPN 20 were deemed to be low risk [49].

Table 6: Qualitative Risk Assessment

Potential Failure	**Risk**	**Impact rating**	**Probability rating**	**Overall risk rating**
Secondary drying time is too short	Stability of LDETs is challenged if residual moisture content exceeds 4%	High	Low	Moderate
Very less amount of sucrose added	Decline in the hardness of tablets	Moderate	Low	Low
Too high concentrations of Carbopol 974PNF added	Tablets with poor mechanical properties are formed	Low	Low	Low
Increasing the mannitol concentration beyond 50%	Deformation of the tablet which compromises the product's appearance	Low	Low	Low
Increasing the concentration of surfactant PF-127	Disintegration of tablet delayed beyond 3 minutes	High	Low	Moderate
Temperature of primary drying is very short	The emulsion sample will melt	High	High	High
Increasing the concentration of cryoprotectant beyond 5-20%	Destabilization of the dispersion formed subsequent to the reconstitution of LDETs	High	Low	Moderate

Once the potential failure & risks pertaining to CMAs and CPPs are determined, the subsequent step will be to perform a Design of Experiment (DoE) to mitigate the identified risks. Through the implementation of DoE, a design space is created during drug product development by analysing as well as improvising CMAs & CPPs. Within the design space, CMAs & CPPs can be modified without the requirement for regulatory approval. The selection of a design with adequate resolution & sufficient number of experimental runs, combined with the necessary information and understanding of input products & process characteristics, are prerequisites for demonstrating a proper & valid design space [50]. In DoE, factors influencing CQAs are established by taking into account previously acquired information about the product/process through pertinent literature and their preliminary experimental data. To determine how factors affect reactions, it is crucial to choose the elements at their finest levels. To arrive at a well-defined design space, it is recommended to adopt screening models such as fractional factorial or Placket Burman design to establish potential factors. This is well explained in a study conducted by Iman et. al that evaluated the impact of material attributes and formulation variables of the cellulosic binders and matrix formers on the final LDETs using full factorial design with an intent to specify an

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acceptable concentration range for each excipient thus enabling the output dry emulsion tablets to exhibit better clinical performance [51]. These factors are then optimized using Box Behnken or Central Composite design. According to ICH Q8 (R2), design space is a three-dimensional combination and interaction of input variables and process parameters that have been demonstrated to assure quality.

4. Control strategy

The knowledge acquired throughout the entire formulation & the process development of LDETs enabled the establishment of a control strategy. The inferences drawn from the risk assessment studies, process understanding & design space considerations comprise the key element of this strategy. The main objective behind the control strategy is to ensure that the process performs as desired & retains its quality. Process analytical technology (PAT) that strengthens innovation and enhances process efficiency in the manufacturing operation & quality assurance of the drug product is an effective tool that anticipates proper execution of analytical techniques like Raman spectroscopy, near-infrared (NIR) spectroscopy & terahertz pulsed spectroscopy in co-operation with multivariate analysis (MVA) which ultimately provides Real-time release testing (RTRT). As defined by ICH Q8 (R2), RTRT is, 'the ability to evaluate and ensure the quality of in-process or final drug products based on process data which typically includes a valid combination of 'measured material attribute' & 'process control'. The FDA has recognized PAT which is based on a framework that designs, analyses, and controls manufacturing through conducting quality control testing on the samples of in-process materials or raw materials withdrawn throughout the manufacturing process in a timely manner, intending to ensure final drug product quality. Through PAT, quality is not tested on the final drug product, it is built into the system. PAT framework lists down multiple rules for the continuous upgradation of manufacturing operations & develops risk reduction strategies. Depending upon the type of manufacturing process, a suitable combination of some or all of these tools is employed.

For lyophilization, the process analyser tool of PAT enables the continuous monitoring of all the physical & chemical properties of the sample facilitate the understanding and knowledge of the process. This can be understood with the application of NIR spectroscopy to analyse & monitor the drying phase. Even though Raman spectroscopy is also a widely reported process analyser PAT tool, NIR spectroscopy is preferred due to the strong absorption signals of ice and water displayed in the spectra. These PAT tools are instrumental in detecting water-to-ice conversion, product crystallisation, annealing step, the kinetics of polymorphic transitions, and solid-state characterizations of intermediate & end products. An explanation for this could be found in the studies conducted by De Beer et al. wherein the reversely correlated nature of ice & water was predicted from the variations observed in its absorption bands [52]. During crystallization in the freeze-drying stage, Mannitol hemihydrate was present in its metastable form, the formation of which should be prevented. This hydrate water after release can probably be taken up by amorphous freeze-dried API, thus producing a significant influence on the stability of the formulation. Cao et al. demonstrated the application of NIR spectra for the qualitative as well as quantitative detection of mannitol hemihydrate & surface water in the freeze-dried sample. Surface water displayed peaks at 7002 & 5249 cm^{-1} while bound water exhibited peaks at 6825 & 5136 cm^{-1}[53]. Thermocouples and resistance temperature detectors are traditionally employed to maintain the product temperature below the acceptable limit [54]. This explains the utility of PAT tools to detect the stability threat concerning the final drug product at the preliminary stage.

LDETs offer an excellent opportunity of enhancing the bioavailability of poorly aqueous soluble drugs. This advantage is coupled with the ability of the porous matrix of the tablet formed through the Lyophilization process to disintegrate rapidly. This formulation design has proved to be successful in enhancing the absorption and reducing the toxicity of lipophilic drugs. These benefits superseded the highly complex & expensive Lyophilization process.

5. Literature review

The objective of this review article was to elaborate on the systematic approach of Quality by design phenomenon adopted in the formulation development of Lyophilized dry emulsion tablet. This dosage form has successfully enhanced the bioavailability of poorly aqueous soluble drugs. LDET formulation was reported to enhance the anti-hyperlipidaemic activity of the Atorvastatin drug [55]. This can be evidenced by the increased dissolution rate & rapid disintegration observed for the ATV-LDET as compared to plain atorvastatin drug. Freeze-dried emulsion tablets are robust dosage forms that have successfully elevated the absorption of Griseofulvin subsequent to oral administration [56]. For the currently available immediate-release tablet formulation, patients need to consume the medicine in the fed state. As a result, remarkable inter-subject variability was observed in drug absorption. Rapid disintegration of porous LDET in the saliva accounted for the elimination of the need to consume tablets with food. Thus, promoting the uniform & effective absorption of the drug. In one more cited paper, the effect of several formulation variables was studied on the clinical efficacy of LDETs. Multiple combinations of emulsifier & tablet binders were evaluated to achieve the most optimum tablet. Successful

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characterization of the LDETs was conducted through droplet size analysis & Turbidimetric analysis during reconstitution. The reconstituted emulsion was subjected to quality control testing based on droplet size reconstitution. Mannitol was observed to be most effective as compared to erythritol and lactose. It was observed that HLB value and type of surfactant exhibited profound effects on the disintegration & dissolution of LDETs [20].

6. Conclusion:

Following the systematic approach of QbD, QTPP for the final drug product was defined. Subsequently, CQAs were established. Then a detailed analysis of the excipients to be utilised in the formulation of LDETs was done to detect several material attributes that could produce a significant impact on QTPP. The HLB value, types, and concentration of the surfactants, binders, matrix formers, and oil phase are some of the critical formulation variables that influence the disintegration time of emulsion tablets. Once the formulation variables and material attributes were identified, a thorough analysis of the freeze-drying process was carried out to detect those process parameters that could have a remarkable effect on the final drug product. Glass transition temperature of the excipients, product temperature, shelf temperature as well as the duration of secondary drying are some of the process parameters studied till today. An assessment of the possible risk factors was carried out. As a part of the control strategy, PAT tools such as NIR and Raman spectroscopy was employed to detect the onset & endpoint of the crystallization process of water, possible structural or polymorphic changes occurring in the active principles as well as excipients during various phases of the freeze-drying process thus preventing the potential failures by ensuring the critical process aspects of the manufacturing operation complies.

Step-by-step implementation of QbD strategy while developing LDETs is beneficial as it would assist to manage the material attributes & critical aspects of the manufacturing operation with an intent to maintain the uniformity of the process. A full factorial design of the experiment was performed to study the impact of the multiple variables of the excipients. The results obtained enabled the creation of design space that aimed to improve the product lifecycle & achieve a robust formulation. This would assist in dealing with some critical challenges involved in the formulation as well as manufacturing of LDET successfully.

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