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***Review article***

# *Transdermal Drug Delivery System: An Insight into Recent Advancements*

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ABSTRACT

*Around the turn of the 20th century, Sir Ronald Fisher popularized the idea of using statistical analysis. Integrating quality into the product is the goal of introducing the design method. The primary means of guaranteeing the quality of the finished product is the application of the Quality by Design (QbD) methodology in the transdermal/topical formulation. The proper application of various design approaches is carried out at the industrial scale because the optimization procedures are necessary for precise research in these disciplines. The fundamentals of QbD design are demonstrated in this review along with how they relate to the various nano-based transdermal and topical formulations.*

***Keywords:*** *Transdermal Drug Delivery System; Nanoparticles; Quality by Design; Design of Experiment; Niosomes; Liposomes; Nanoemulsions.*

## *Introduction*

Although transdermal drug administration has greatly improved medical procedures, it has not yet reached its full potential as a key substitute for oral medication delivery and hypodermic injection. Oral medicine delivery is attractively replaced by transdermal administration due to its non-invasive nature and self-application convenience. Topical formulations have been devised to address local ailments, and throughout human history, chemicals have been applied to the skin for therapeutic purposes. By using this technique, medications can be protected from the substantial first-pass effect of the liver, which can cause them to metabolize too soon [1]. Extended drug release is possible with transdermal delivery, which may improve patient compliance at a relatively cheaper cost.

The merits of transdermal medicine delivery are well documented by a plethora of research studies and scholarly reviews. These include avoiding the first-pass effect, giving smaller doses, possibly minimizing side effects, keeping plasma levels steady, and enhancing patient adherence. Because the stratum corneum acts as a barrier, improving skin penetration is essential to the development of transdermal drug delivery systems (TDDS).

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) adopted Quality-by-Design (QbD) in 2008 after the United States Food and Drug Administration (USFDA) implemented a risk-based approach to drug engineering in 2000 to assure the quality and safety of new drugs [2]. Design of Experiment (DoE) [3] and Quality-by-Design (QbD) [4] are two alternative techniques that try to incorporate quality and safety into the drug development process from the beginning, as opposed to standard methods that just concentrate on product quality testing. Though QbD is sometimes viewed as a new paradigm in the pharmaceutical sector, it is actually a development of manufacturing industry experience.

Juran popularized the QbD concept in the late 1990s after introducing it in the 1970s [5]. Juran's initial work

did not particularly address medications or medical devices, despite the fact that contributions in this field frequently make use of graphical, scoring, and statistical methods like Ishikawa and Pareto diagrams, Failure Mode Effect Analysis, Design of Experiments, and Statistical Process Control.

### *Design of Experiment (DOE) Utilized for Nano Carriers in Transdermal and Topical Applications*

Since the pharmaceutical sector places a strong focus on quality and processes, it was expected that the new paradigms would be quickly embraced [6]. Remarkably, regulatory agencies (FDA, EMA) advocated Quality by Design (QbD) at the start of the new millennium, realizing that quality ought to be ingrained in products from the outset rather than being tested into them retroactively [7]. Pharmaceutical development can be addressed using a variety of mathematical modeling tools, particularly when used in the context of quality-based drug development. These methods enable the selection of the best formulation with the least amount of time and effort by offering insights into the interactions between various formulation components at different levels [3].

Many topical and transdermal formulations have been created and statistically improved using various optimization techniques. These formulations have been well documented in the literature, utilizing several QbD techniques like Taguchi design (TD), Central Composite design (CCD), Box-Behnken design (BBD), and Plackett-Burman design (PBD). In order to see how changes in independent variables affected dependent variables, optimization was necessary. This method was selected due to its effectiveness, as it necessitates fewer runs and permits the consideration of multiple variables at different stages of optimization. Following statistical analysis, the information gathered for every response in every run was fitted into a variety of regression models.

Using a variety of formulation design techniques, numerous nano transdermal/topical formulations such as vesicles, colloidal particles, and nanoparticles have been thoroughly improved and documented in the literature. The improved applicability of these delivery systems in promoting both local and systemic medication absorption through the skin has been acknowledged. This chapter summarizes the main QbD techniques used in transdermal/topical drug delivery systems in an effort to give a thorough overview of QbD-based transdermal delivery systems (Table 1) [1].

**Table 1:** QbD used different topical formulation.

| S. No | Formulation | Drug | QbD Design |
|---|---|---|---|
| 1 | NLCs | Lappacontine, Ranaconitine | Uniform design |
| 2 | Transfersomes | Raloxifene HCl | Box-Behnken design |
| 3 | Glycerosomes | Paeoniflorin | Uniform design |
| 4 | Polymeric mixed micelles | Terconazole | $2^3$ full factorial design |
| 5 | Nanoethosomes | Vardenafil | Box–Behnken design |
| 6 | Nanoemulsion | Ceramide IIIB | Central composite design |
| 7 | Nanoemulsion | Chalcone | Full factorial |
| 9 | Pronioomes | Pioglitazone | Box–Behnken design |
| 10 | NlCs | Nimesulide | Box–Behnken design |
| 11 | Nanoethosome | Tramadol | Box–Behnken design |

| | | | |
|---|---|---|---|
| 12 | Niosomes | Lacidipine | Box–Behnken design |
| 13 | Ethosomes | Tropisetron HCl | Full factorial design |
| 14 | Liposomes | Alprazolam | Central composite design |
| 15 | Niosomes | Sumatriptan Succinate | Taguchi design |
| 16 | Microemulasion | Agomelatine | Mixture design |
| 17 | Nanolipid vesicular | Phosphatidylcholine | Two level factorial design |
| 18 | Transfersomes | Buspirone hydrochloride | Full factorial design |
| 19 | NLCs | Aceclofenac | Box–Behnken design |
| 20 | NLCs | Silymarin | Full factorial design |

**Niosomes**

Over the past three decades, niosomes which can include cholesterol or other lipids have garnered significant attention as vesicular drug delivery vehicles. They are made up of phospholipids and nonionic surfactants. Their unique qualities, which improve the solubility and bioavailability of poorly soluble medications, are the reason for this attention [8]. As demonstrated in the instance of diacerein, niosomes show great promise as carriers for medications with restricted solubility [9]

Using formulation design is one way to fully utilize the potential of niosomes. In order to create and optimize diacerein niosomes using the film hydration approach, Aziz et al. [10] used a central composite design. A three-level, three-factor design was employed in the study to produce an ideal niosomal formulation with the required properties. The impacts of the formulation variables on entrapment efficiency % (Y1), particle size (Y2), polydispersity index (Y3), and zeta potential (Y4) were examined. These variables included the quantity of salt in the hydration medium (X1), the amount of lipid (X2), and the number of surfactant components (X3). According to Aziz et al. (2018b), the improved formulation showed a low particle size of 436.65 nm, a high entrapment effectiveness of 95.63%, a polydispersity index of 0.47, and a zeta potential of -38.80 mV.

In a similar vein, research teams have looked into applying different design strategies to enhance niosomal formulations for transdermal medication delivery. For example, Zidan et al. [11] optimized methotrexate (MTX) proniosome gels by using Box-Behnken's design. The study looked at how vesicle size (Y1), entrapment efficiency (EE%-Y2), and zeta potential (Y3) were affected by independent variables, such as span 40, cholesterol (Chol-X1), tween 20 (X2), and short-chain alcohols (X3). With a vesicle size of 480 nm, a high entrapment effectiveness of 55%, and a zeta potential of -25.5 mV, the optimized MTX-loaded niosomes were demonstrated.

Various design techniques have been employed in other research to optimize niosomal formulations for particular medications. In order to optimize cholesterol-rich niosomes for diacerein distribution, Jahangir et al. used a 3-factor, 3-level Box-Behnken architecture, resulting in high efficiency and regulated flux [12]. Imam et al. [13] optimized proniosomes for transdermal distribution of risperidone using a 4-factor, 3-level Quality by Design (QbD) approach. They showed notable increases in vesicle size, encapsulation efficiency, and transdermal flux.

Moreover, Soliman et al. [14] optimized lacidipine-encapsulated proniosomes for improved transdermal administration using a 23 complete factorial design. In comparison to a commercial product, their modified formulation demonstrated a low vesicle size (162.43±0.77 nm), high entrapment efficiency

(98.01±0.68%), and release efficiency (88.33±2.43%), leading to enhanced bioavailability [14].

In a different setting, Kumar and Goindi [15] used nonionic surfactant vesicles (NSVs) using Taguchi design and D-optimal design to optimize itraconazole hydrogel. In comparison to traditional creams and greasy solutions, their ex vivo investigations showed improved medication skin penetration and retention.

Furthermore, Abdelbary et al. [16] optimized methotrexate (MTX) niosomes for psoriasis management using a Box-Behnken design and Design-Expert(®) software. With its spherical morphology, 1375.00 nm particle size, and high encapsulation effectiveness of 78.66%, the ideal formulation produced improved in vivo skin deposition and bioavailability.

Using a 2(3) full factorial design, various non-ionic surfactants were tested for their impact on CAR proniosomal gels in a study by Mohanty et al. [17]. The findings demonstrated how formulation factors affect niosome-forming capacity and skin penetration, suggesting that proniosomal gels especially those containing Span 60 might be a viable substitute for transdermal CAR delivery.

**Liposomes**

Liposomes are minuscule vesicles that can have a diameter of 50 nm to several hundred nm. They are made up of phospholipid bilayers enclosing aqueous spaces. Liposomes are classified as unilamellar lipid vesicles (ULV) and multilamellar lipid vesicles (MLV) based primarily on their composition, which can include phospholipids with or without cholesterol additions [18].

Hashemi et al. [19] used a four-factor, five-level central composite design (CCD) to optimize alprazolam-loaded nanoliposomes. Variables including the solvent/nonsolvent volume ratio (0.2–0.5), the phospholipid concentration (mg/mL), the alprazolam concentration (mg/mL), and the cholesterol content (2.5–10%, w/w) were the main focus of the investigation. Nanoliposomes with an entrapment effectiveness of 93.08% and a vesicle size of 121.63 nm were produced using the optimized mixture.

Madecassoside (MA) liposomes were optimized by Li et al. [20] using response surface methods, yielding an ideal formulation with a mean size of 151 nm and an encapsulation effectiveness of 70.14%.

Tsai et al. [21] used a two-factor, three-level factorial design to optimize elastic liposomes loaded with Naringenin. When compared to other treatment groups, this strategy showed considerable increases (7.3 to 1.9-fold) in the skin deposition of naringenin, taking into account varying levels of Tween 80 and cholesterol.

Response surface methodology with multivariate spline interpolation (RSM-S) was utilized by Duangjit et al. [22] to optimize liposomal formulations that included penetration enhancers (PE). The investigation evaluated a number of variables, including drug content, entrapment efficiency, vesicle size, size distribution, zeta potential, elasticity, and release rate. The findings showed that the penetration enhancer's content, drug content, and elasticity all had an impact on the reactions.

Shi et al. [23] designed and optimized the gel formulation of paeonol-loaded transdermal liposomes using a 3-factor, 3-level Box-Behnken design. The molar ratio of drug to lipid, the concentration of polymers, and the DC-Chol concentration were the main independent variables under investigation. The formulation showed how the 3D contour plots and the resultant polynomial equation helped forecast the values of the dependent variable.

Using a factorial design technique, Padamwar and Pokharkar [24] successfully improved liposomes for topical distribution of Vitamin E acetate encapsulated liposomes. The investigation took into account various phospholipid (PL) and cholesterol (CH) levels and found that lipid concentration and lipid:drug ratio affected vesicle size and drug deposition in rat skin. The factorial study demonstrated the potential of liposomal preparations for cutaneous delivery by successfully identifying important factors influencing drug deposition.

**Lipid nano particles**

Lipid-based nanoparticles, including Lipid Drug Conjugates (LDC), Nanostructured Lipid Carriers (NLC), and Solid Lipid Nanoparticles (SLN), have garnered significant attention in modern research because of their proven benefits in drug loading, encapsulation, and release. With advantages like increased drug load, reduced expulsion, and modulation of the drug release profile through variations in the lipid matrix, these lipid nanoparticles demonstrate the ability to improve the solubility and bioavailability of poorly water-soluble and/or lipophilic drugs [25]. Whereas

Nanostructured Lipid Carriers (NLC) are made of an oil and solid lipid mixture, Solid Lipid Nanoparticles (SLN) are made of a single solid lipid.

Kaur et al. [26] used supramolecular nano-engineered lipidic carriers (SNLCs) and the solvent-evaporation approach to manufacture a DIF-phospholipid complex (DIF-PL complex). Face Centered Cubic Design (FCCD) was used to optimize this formulation following variable screening using L8 Taguchi orthogonal array design. With an average particle size of 188.1 nm, a degree of entrapment of 86.77±3.33%, a permeation flux of 5.47±0.48 μg/cm$^2$/h, and skin retention of 17.72±0.68 μg/cm$^2$, the improved SNLC formulation showed good properties.

Garg et al. [27] prepared and characterized aceclofenac nanostructured lipid carriers (NLCs) using an approach focused on Quality by Design (QbD). To maximize critical quality characteristics (CQAs) such particle size and drug entrapment efficiency, a 33 factorial design was used. Higher drug loading, entrapment efficiency, spherical structure, and nano size were all displayed by the optimized ACE-NLCs. Research on the release of drugs in vitro revealed a Korsmeyer-Peppas model that reflected Fickian diffusion.

Pioglitazone-loaded nanostructured lipid carriers (PZNLCs) were effectively created by Alam et al. [28] via an ultrasonication technique after high-pressure homogenization. Particle size, drug loading, ex-vivo skin transport tests, and in vivo bioactivity investigations were assessed for statistically optimized (BBD) NLCs. The improved formulation showed a flux value of 47.36 μg/cm$^2$/h, a mean size of 166.05 nm, and a drug loading of 10.41%. Studies conducted in vivo demonstrated a continuous drop in blood sugar levels and a 2.17-fold increase in bioavailability.

The double emulsion solvent evaporation (DESE) technique was used by Ghasemian et al. [29] to create and enhance sildenafil-loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles (NPs). The methodology of response surface (BBD) was utilized to evaluate the correlation between design elements and experimental results. After 12 hours, the improved formulation showed a cumulative drug release of 79%, a particle size of 270 nm, an entrapment efficiency of 55%, and a drug loading of 3.9%.

Box–Behnken design optimized capsaicin-loaded nanolipoidal carriers (NLCs) were created by Wang et al. [30] in order to improve permeability and produce analgesic, anti-inflammatory effects. The potential of BBD-optimized NLCs as a carrier for the topical delivery of capsaicin was shown by in vivo therapeutic tests.

Patil et al. [31] produced Fenofibrate (FBT) solid lipid nanoparticles (SLN) continuously using the hot-melt extrusion (HME) process. The study employed the concepts of Quality by Design (QbD) to integrate high-pressure homogenization (HPH) with HME technology in order to reduce size. In comparison to the crude drug and commercially available micronized formulation, drug absorption was enhanced when process parameters were adjusted to get SLN below 200 nm.

Keshri and Pathak [32] used central composite design to successfully optimize topical econazole nitrate nanostructured lipid carriers. After the formulations were made into hydrogels, permeation tests revealed that G3 was the most effective formulation, showing zero-order permeability.

**Nanoemulsions**

Another topic of interest are the transparent and thermodynamically stable dispersions of two immiscible liquids. Box-Behnken design was utilized by Tripathi et al. [33] to create doxorubicin (Dox) loaded folate functionalized nanoemulsion (NE). The enhanced NE showed characteristics appropriate for therapeutic action against cancer of the mammary gland.

Ngan et al. [34] evaluated the process parameters for the optimization of fullerene nanoemulsions using a combined statistical design approach of Box-Behnken design and central composite rotatable design. The actual response values obtained with the recommended process settings were nearly identical to the projected values.

Using Quality by Design, Negi et al. [35] methodically improved the lidocaine and prilocaine nanoemulsions (NEs) used as local anesthetics. In comparison to the marketed cream, the improved NE carriers showed higher drug concentrations in skin layers and better penetration rates.

Huang et al. [36] used a mixing strategy to study and improve citalopram-loaded microemulsions. In comparison to the aqueous control, the improved

microemulsions showed noticeably higher drug penetration rates and shorter lag times.

This research demonstrate how well response surface methodology, Box-Behnken design, and Quality by Design [37] work to improve the characteristics and functionality of lipid-based nanoparticles and nanoemulsions for use in drug delivery applications.

**Invasomes**

Invasomes are lipid-based vesicles with remarkable penetration augmentation capabilities [38]. They are distinguished by their high membrane fluidity and can contain either one or a combination of terpenes. This unique quality is provided by the addition of ethanol and terpenes (1–5%).

Olmesartan nano-invasomes for transdermal distribution were created, refined, and assessed using the Box-Behnken design in a 2016 study by Kamran et al. [39]. With a vesicle size of 83.35±3.25 nm, an entrapment efficiency of 65.21±2.25%, and a flux of 32.78±0.703 μg/cm$^2$/h, the improved formulation showed promising results. These numbers matched the Box-Behnken design's projected values rather well. The response surfaces as determined by the Design Expert confirmed, according to the researchers, a distinct correlation between response variables and formulation parameters. It was determined that the created Olmesartan invasomes were the best transdermal carrier.

Imam et al. [40] used phospholipid, safranal, and ethanol to create transdermal risperidone invasomes. The work optimized the soft lipid vesicles using a 3-factor 3-level Box-Behnken design. The impacts on dependent variables, including vesicle size (81.28 – 153.87 nm), entrapment efficiency (70.43 – 89.74%), and flux (97.43 – 182.65 μg/cm$^2$/h), were observed. The formulation of the improved risperidone soft lipid vesicles involved the use of phospholipid (8.65 mg), ethanol (5.78% w/v), and safranal (0.85% w/v). The improved formulation exhibited higher absorption as compared to oral risperidone solution, as demonstrated by its 177% relative bioavailability.

The same research group used phospholipon 90G, b-citronellene (terpene), and ethanol to create isradipine invasomes using the Box-Behnken design in another work [41]. The produced isradipine-loaded invasomes demonstrated improved transdermal administration efficacy (22.80 ± 2.10 mg/cm$^2$/h through rat skin), a respectable entrapment efficiency (88.46%), and an increased flux. The created isradipine invasomes have the potential to be used in the treatment of hypertension, according to the researchers' findings, because of their enhanced flow and skin penetration.

**Transferosomes**

Elastic or deformable vesicles, or transfersomes, have a lipid bilayer structure with an edge activator integrated into them. Transfersomes™, created by Idea AG in Germany and named after Cevc and Blume in 1992, are composed of surfactants and phospholipids such phosphatidylcholine [42].

A Box–Behnken design was used in a recent work by Moolakkadath et al. [43] to optimize a transethosomes formulation for cutaneous distribution of fisetin. The transethosomes that resulted from the formulation of lipoid S 100, ethanol, and sodium cholate were evaluated for vesicle size, entrapment efficiency, and in vitro skin penetration. The improved formulation showed 74.21 ± 2.65 nm in size, 68.31 ± 1.48% entrapment efficiency, and 4.13 ± 0.17 mg/cm$^2$/h in flux. The formulation of these statistically adjusted transethosomes vesicles showed promise as a potent carrier for the cutaneous administration of fisetin.

Ahmed [44] evaluated the effects of different formulation and processing parameters on sildenafil (SD) transferosomes using a Plackett–Burman design. The formulation that was most desirable had a vesicle size of 610 nm and an entrapment effectiveness of 97.21%. When compared to a conventional drug suspension, the in vitro permeation of the drug-loaded transferosomes showed a permeation rate that was more than five times higher. In order to increase sildenafil permeability from the optimized transferosome formulation, the relevant factors were further tuned to produce smaller vesicle sizes.

In a study, Mahmood et al. used response surface methodology (Box-Behnken design) to develop and assess raloxifene hydrochloride-loaded transferosomes. Three levels of independent variables were evaluated in the study: sonication time, sodium deoxycholate, and phospholipon(®) 90G. The proposed formulation exhibited a transdermal flow of 6.5±1.1 μg/cm$^2$/h, an entrapment efficiency of 91.00%±4.90%, and vesicle sizes in the range of 134±9 nm. Comparing the raloxifene hydrochloride-loaded transferosomes to an ethanolic phosphate buffer saline and a normal

formulation of drug-loaded conventional liposomes, the latter showed noticeably inferior drug penetration and deposition in the skin [45].

Utilizing a modified lipid hydration approach, Badr-Eldin et al. [46] generated sildenafil citrate (SLD) loaded nano-transfersomal transdermal films and optimized them utilizing central composite design. In comparison to SLD control films, the resultant transfersomes showed improved ex vivo permeability properties and a regulated profile. They were spherical and unilamellar, with a vesicular size of 130 nm. The SLD nano-transfersomal films demonstrated prolonged absorption and improved bioavailability.

Using a $2^3$ complete factorial design, Morsi et al. [47] developed and refined timolol maleate (TiM) transfersomal gel for transdermal distribution. Particle size of 2.72 μm, entrapment efficiency of 39.96%, and release rate of 134.49 μg/cm$^2$/h were observed in the optimized transfersomal gel.

In the development of sodium stibogluconate (SSG) nano-deformable liposomes (NDLs) for topical medication delivery against cutaneous leishmaniasis (CL) by Dar et al. [48]. The formulation's physicochemical parameters included vesicle size (195.1 nm), polydispersity index (0.158), zeta potential (−32.8 mV), and entrapment efficiency (35.26%), all of which were improved using the Box–Behnken statistical design. While in vivo data indicated greater anti-leishmanial effectiveness, the ex vivo skin permeation investigation showed higher skin retention in deeper layers, accomplished without traditional permeation enhancers.

**Ethosomes**

Soft vesicles called ethersomes are intended to be non-invasively delivered carriers that aid in the penetration of drugs into the deep layers of the skin and/or the bloodstream. These pliable vesicles, which are primarily composed of phospholipids, contain a significant amount of ethanol and water, and are designed to transfer active substances as efficiently as possible.

Colchicine-loaded transethosomal gels were created via the cold method and statistically optimized using three sets of twenty-four factorial design trials, according to a 2018 study by Abdulbaqi et al [49]. The improved gels showed aspherical irregular shape, excellent entrapment efficiency, and nanometric size. Colchicine-loaded transethosomal gels markedly improved the drug's skin penetration properties when compared to non-ethosomal gel.

Using a 41.21 full factorial design, Aziz et al. [50] studied Diacerein (DCN) elastosomes, novel edge activator (EA)-based vesicular nanocarriers. When compared to DCN-loaded bilosomes and drug suspension, the ideal elastosomes (E1) showed great entrapment efficiency, nanometric particle size, and improved skin penetration potential. Different EAs were used in varying doses.

An ideal ethosomal formulation of glimepiride for transdermal films was developed by Ahmed et al. [51] The optimization of four formulation parameters revealed that the alcohol content had a substantial impact on the size, flexibility, and entrapment efficiency of the vesicles. When put into transdermal films, the resultant ethosomal formulation demonstrated better ex-vivo penetration than transdermal films containing only the medication.

Mishra et al. created and refined ethosomes using varying phospholipid, ethanol, ropinirole HCl, and water concentrations. Using 3(2) complete factorial designs, the study showed that the independent variables selected had a substantial impact on both in-vitro drug release and entrapment efficiency. In the improved formulation, 4% w/v lecithin and 30% w/v ethanol were present [52].

Terpenes and ethanol are added to invasomes, which are lipid-based vesicles with high membrane fluidity that aid in penetration. Olmesartan nano-invasomes for transdermal distribution were developed, refined, and assessed by Kamran et al. [39] utilizing the Box-Behnken design. The improved formulation demonstrated positive attributes, such as flow, vesicle size, and entrapment efficiency, indicating its potential as an enhanced transdermal carrier.

Imam et al. [53] used a 3-factor 3-level Box-Behnken design to create transdermal risperidone invasomes. The entrapment efficiency, flux, and vesicle size of the optimized soft lipid vesicles were all improved. The same study team also created isradipine invasomes using the Box-Behnken architecture, which showed enhanced flow, entrapment efficiency, and efficacy for transdermal distribution.

These investigations demonstrate the potential of ethosomes and invasomes as efficient transdermal drug

delivery vehicles, including benefits like increased bioavailability and penetration.

**Lipid based vesicular carrier**

Drug delivery with nano vesicular carriers has demonstrated a good response in terms of improving drug bioavailability and penetration. These carriers have a number of benefits, such as the capacity to accommodate both hydrophilic and lipophilic pharmaceuticals, the ability to encapsulate drugs with a variety of solubility profiles, and the possibility of producing the drug using natural materials [54]. Numerous vesicular carriers have been well documented in the literature, including liposomes, niosomes, Transfersomes® (Idea AG, Germany), and invasomes. Because of the initial generation of vesicular systems' success especially that of liposome carriers they are now often used in modern drug delivery applications [55-59].

## *Conclusion*

By increasing solubility and bioavailability, numerous QbD design-based nanoformulations have demonstrated significant promise in the efficient delivery of numerous local and systemic medications. The QbD technique is now widely recognized in both industry and academics. Because of its many benefits, the QbD technique has demonstrated broad utility in the optimization of many nano formulations. It is a method that shows promise for addressing various delivery system restrictions. These methods have emerged as tactics to resurrect the process of developing an optimal formulation through interactions among the various independent variables at various levels. The QbD technique has come a long way, but there are still certain obstacles to overcome. Therefore, transdermal/topical nano formulations based on QbD provide researchers with an opportunity to expand their research and development efforts in order to address the shortcomings of the conventional optimization approach.

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## *Conflict of Interest*

None declared.

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