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Review Article

## Experimental Design: Approaches and Applications in Development of Pharmaceutical Drug Delivery System

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### Abstract

Conventionally, all the delivery systems have been prepared by methodology of trial and error concept by manipulating one variable at a Time, but attainment of optimal formulation is not achievable. The systematic approach Design of Experiments (DoE) enables researchers to provide appropriate outline to develop a best optimized delivery system. Optimization techniques using DoE helps to provide effective and economical analytical tools to find the perfect solution for a particular problem. In screening designs, there is large number of screening factors in minimum number of experiments and beneficial to minimize the variables in a desired size therefore further experimentation may be performed easily by using these variables. Experimental designs and optimization techniques are the tools which are systematically used to categorize various types of problems that may influence development of pharmaceutical delivery system. Use of experimental design is the best approach to the screening and optimization of experimental factors. In the present review article we have focused on application of practically applicable experimental designs and optimization techniques for the development of quality and efficacious of pharmaceutical formulations such as, nanoparticles, Phytosomes, microspheres, liposomes, micells, films, nanostructured lipid carriers and tablets and which type of factors to be considered while optimization are also discussed.

**Keywords:** Experimental design, Optimization, Applications, Drug delivery, Phytosomes, Nano delivery System.

### INTRODUCTION:

The development of an effective delivery system involves rational combinations of various polymers and additives. The conventional approach of optimizing a formulation or process generally entails study of the influence of one variable at a time while keeping others as constant. Using this approach the attainment of the true optimum formulations or process is always unconvinced and the technique is highly tedious, time consuming as it leads to carry out unnecessary runs and formulation batches.<sup>1</sup>

The formulation of dosage form is tedious and expensive, therefore to minimize this problem there is need to develop and optimize the formulation to get the robust and efficacious pharmaceutical product. Experimental design is a method to optimize the formulation by performing minimum number of experiment for getting proper information which is necessary to perform the experiment. The screening experiments are beneficial to minimize the variables in a desired size therefore further experiment may be performed easily by using these variables which are useful to understand the whole procedure of experiment.<sup>2</sup>

### EXPERIMENTAL DESIGN:

Experimental design is a design in which some factors can be evaluated at several numbers of levels in a definite number

of experiments. Experimental design can be classified into Screening designs and Response surface designs.<sup>3-5</sup> In screening designs, there is screening of large number of factors in small number of experiments hence numbers of experiment may be reduced. This design is used to find out the most influencing factors which are evaluated only at two levels. Response surface design is the design which is used to optimize the levels in an experiment. The factors are optimized at minimum three levels after that the final result originates from the response surfaces which is developed in the design. Mixture design is also a response surface design that is used in mixture related factors in a given experiment. When the mixture of all factors in experiments is to be optimized then this type of design is used. For example: In chromatography, organic modifiers in a mobile phase, or the various excipients used in preparation of tablet or any other formulations in pharmaceutical industry. In this type of factors, which designs are used is totally depend on number and type of factors based on their purpose and also depend on analyst.

Experimental designs are useful in various pharmaceutical as well as other fields of sciences. The application of experimental design includes optimization of separation methods, process optimization to yield maximum product, optimization of formulation and pharmaceutical products, or processes. In our area of interest, the first application of

experimental design in separation science i.e., to separate and identify the valuable product in given components by developing analytical assay and their selection of techniques that means validation and optimization of the method.<sup>6-8</sup>

The most important application of experimental design which is mainly focus in this paper is the optimization of pharmaceutical formulations, products, or manufacturing process. In manufacturing process, the manufacturing of

formulations is performed by batch processing unit. Experimental designs are broadly classified into two types such as Factorial design and Response Surface design as shown in figure 1. A factorial design is a screening design which consists of full factorial design, Plackett -Burman design and Fractional factorial design. For the optimization, response surface design was used which is Central composite design and Box- Behnken design.

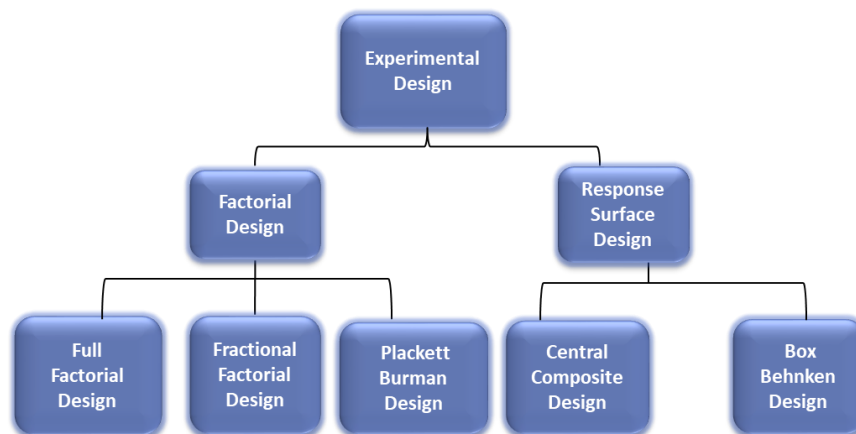


Figure 1: Classification of Experimental design

Depending on the factors to be used in experimental design, full factorial designs are of two types such as full two level factorial designs and full three level factorial designs. A two level full factorial design is a common type of screening design for the identification of significant parameters. Full factorial design is denoted by  $2^k$  where  $k$  is the number of factors that are studied in two levels i.e. high (+1) and low (-1). In this design, the number of experiment increases as the number of factors increased.<sup>9</sup>

#### APPLICATION OF EXPERIMENTAL DESIGN:

The use of experimental design is the best approach to the screening and optimization of experimental factors. Simple experimental design can provide better information in very few experiments within minimum time period. Experimental design is very important tool in process development, analytical method development & purification, biological process as well as in delivery system as mentioned in figure 2.

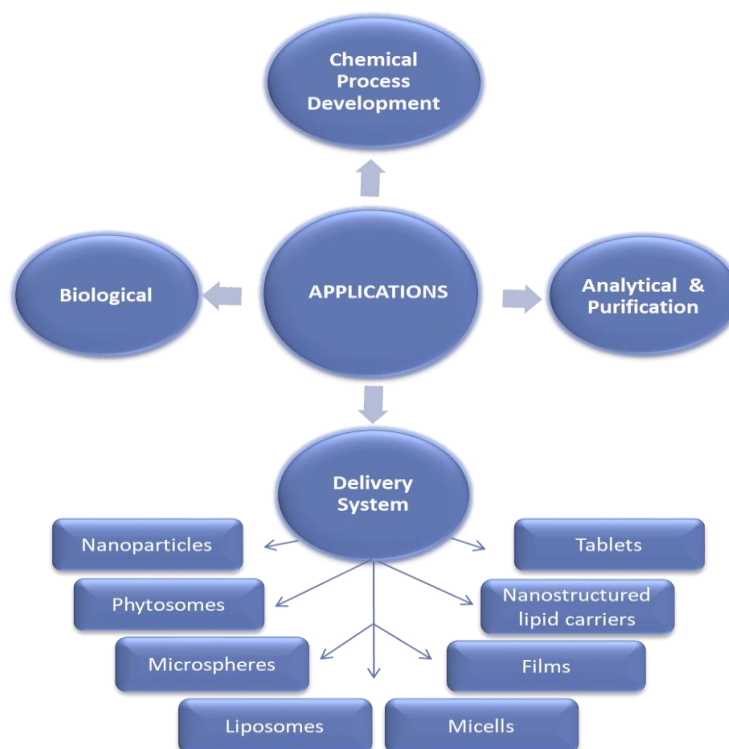


Figure 2.: Applications of Experimental Design

### 1. Chemical process development -

Experimental design is a key factor in the optimization of reactions protocol for the successful drug manufacturing process. With the help of experimental design, a strong and defendable system can find out in a short time period with affordable price. The use of experimental design is beneficial in comparison to traditional methods. In case of automatic system, the use of experimental design is advantageous to give the reliable result in a very short time.<sup>10</sup>

### 2. Analytical and purification applications -

Experimental designs are also useful in analytical and purification process with the help of chromatographic techniques. Recently Cole et al. has showed the use of this protocol in the optimization of high- throughput semi preparative LC method for the purification of compounds which results from library synthesis. <sup>11</sup>A recent application of experimental design has been the optimization of fusion protein purification with the help of metal affinity chromatography.<sup>12</sup>

### 3. Biological applications -

By optimizing pharmaceutical products or formulations, or process, screening design such as full factorial design, fractional factorial design, and Plackett-Burman designs are used.<sup>13-15</sup> Response surface design such as central composite and Box- Behnken designs are also applied to optimize the biological process and pharmaceutical products.<sup>16-19</sup>

A further new application of this approach is beneficial in PAT - related research. Designs such as full factorial was used in homogenization process of pharmaceutical suspension of freeze drying process, powder blending process, and of a fluid bed granulation process.<sup>20, 21</sup>

### 4. Drug Delivery System:

Experimental designs are also applicable in the development of various pharmaceutical formulations such as, nanoparticles, phytosomes, microspheres, liposomes, micelles, films, nanostructured lipid carriers and tablets as mentioned in table 1.

### NANOPARTICLES:

Sharma Shaveta et al optimized and developed solid lipid nanoparticle (SLN) as carrier of pioglitazone for amplification of oral efficacy. In this study, the formulation was optimized by using three factors such as lipid, surfactant and homogenization speed. The results showed that optimized formulation had higher therapeutic effectiveness after encapsulating into SLN formulation. <sup>22</sup>JifuHao et al., applied Central composite design to optimize a novel baicalin loaded SLNs prepared with the coacervation technique. The researcher selected lipid and drug: lipid ratio as independent variables for the optimization and concluded that, incorporation of baicalin into SLN carrier system could improve the bioavailability.<sup>23</sup> Fengzhen Wang et al, used Box- Behnken design to optimized and developed methazolamide SLN (MTZ-SLNs) eye drops by defining the relationship between design factors and experimental results. The amount of glycerol monostearate (GMS), phospholipid, and surfactant were considered as the independent variables. The acute eye irritation study found MTZ-SLNs to be non-irritation and also concluded that, it is feasible to prepare MTZ into topical eye drops taking SLNs as a carrier.<sup>24</sup> Tanmoy Das et al., used full factorial design to develop and optimized Solid Lipid Nanoparticles based alendronate in situ gel as an implantable drug delivery system for the treatment of osteoporosis. The percentage of polymers, PF-127 & PF-68, was used as independent variables (A and B)

respectively as independent variables. From the results, they were concluded that alendronate - solid lipid nanoparticle based in- situ gel for the treatment of osteoporosis could be suitable drug delivery system over conventional dosage.<sup>25</sup>

### PHYTOSOMES:

Pooja Jain et al., applied quality by design to optimize and developed the phytosomal gel of Aloe-Vera extract for improved topical delivery by fixing the amount of Aloe-Vera extract and ethanol and by varying the concentration of lecithin and rotational speed. On the basis of in-vitro release the researchers found that the phytosomal formulation had better therapeutic potential as compared to conventional.<sup>26</sup> Sushila Rathee and Anjoo Kamboj used Box- Behnken design to optimized and developed anti-diabetic phytosomes. In this study, the prepared phytosomes formulations were optimized using three variables: Lipid (1: 3), temperature (60°C) and time (2.5h). From the results, the researchers concluded that the polyhedral phytosomes preparation can provide a convenient and safe alternative to the conventional dosage form.<sup>27</sup> Darshan R. Telange et al., applied full factorial design to formulate and characterized apigenin-phospholipid phytosome (APLC) for improved solubility, in vivo bioavailability, and antioxidant potential. The formulations were developed by fixing the amount of drug: phospholipids ratio and temperature on the extent of apigenin incorporation (% yield). The optimized formulation showed improvement in solubility, oral bioavailability, and pharmacological properties.<sup>28</sup> Mohammad H. Shariare et al., used DoE to Optimize and developed Epigallocatechin3-Gallate (EGCG) nano -phytosome. They found that the addition rate, stirring temperature and phospholipid concentration were the most critical parameters affecting both average particle size and drug loading on phytosome. <sup>29</sup>

### MICROSPHERES:

N. Mennini et al., applied Quality by design approach for developing chitosan-Calcium alginate microspheres for colon delivery of celecoxib-hydroxypropyl- $\beta$ -cyclodextrin-PVP complex. Experimental design was used to investigate the combined effect of percentage of ca-alginate, CaCl<sub>2</sub>, chitosan and time of cross-linking. They demonstrated that the prepared formulation of colon-targeted CXB microspheres suitably adaptable to obtain the desired drug release profile.<sup>30</sup> Aashima Hooda et al., used experimental design to optimized and evaluate the gastroretentive ranitidine HCl microspheres. They studied the effect of drug polymer ratio, concentration of sodium tripolyphosphate and stirring speed on the formulation and concluded that, the statistical tools like design expert are helpful in understanding the interactions between different independent variables and for rapid formulation development.<sup>31</sup>

Dana Hales et al, used a QbD approach for the optimization of enoxaparin sodium loaded polymeric microspheres for colon-specific delivery. The Process parameters studied were Eudragit® FS-30D/Eudragit® RS-PO ratio, poly (vinyl alcohol) concentration and sodium chloride concentration. This study demonstrated the usefulness of QbD approach in pharmaceutical drug development.<sup>32</sup>

### LIPOSOMES:

Naghmeh Samadi et al., used Box- Behnken design to optimized and formulate vitamin K1 oxide-loaded nanoliposomes for transdermal delivery. The independent variables selected were the ratio of phospholipid to cholesterol, drug concentration a well sonication time. The researcher found that optimized nano liposomes formulation has higher drug release in a controlled manner as compared

to solution.<sup>33</sup>ArpitaBhattacharjee et al., applied Full factorial design to optimized and developed besifloxacin hydrochloride loaded liposomal gel prepared by thin film hydration method. The effect of independent factors i.e. soya lecithin to cholesterol ratio and lipid to drug ratio on characteristics of liposomes were examined. From this study concluded that, the prepared liposomal gel could be used as an effective ocular drug delivery system.<sup>34</sup>

M.L. Gonzalez-Rodriguez et al., applied fractional factorial design to study the formulation variables which influence the coating process of lidocaine liposomes. The variables which

selected for optimization were the concentration of coating solution, the dripping rate of solution on the liposome colloidal dispersion, stirring rate, time and amount of drug entrapped into liposomes.<sup>35</sup>Anil Kumar Sahu and Vishal Jain used Plackett- Burman design for the screening of process variables in the fabrication of gedunin- loaded liposomes. They selected three formulation factors for optimization such as drug concentration, lipid concentration, cholesterol/lecithin ratio and concluded that, Plackett - Burman design was a beneficial to identify the independent factors which affect the response variables and also identify the significant factor.<sup>36</sup>

Table 1: Experimental design used in various formulations

Formulations	API	Experimental Design	Factors	Reference
NANOPARTICLES	Pioglitazone	BBD	-Lipid -Surfactant -Homogenization speed	[22]
	Baicalin	CCD	-Lipid -Drug: Lipid ratio	[23]
	Methazolamide	BBD	-GMS -Phospholipid -Surfactant	[24]
	Alendronate	FFD	-% of PF-127 (Polymer) -% Of PF-68 (Polymer)	[25]
PHYTOSOMES	Aloevera extract	CCD	-Conc. of Lecithin -Speed of rotation	[26]
	Flavonoid extract	BBD	-Lipid -Temperature & Time	[27]
	Apigenin	FFD	-Drug: Phospholipid ratio -Temperature	[28]
	EGCG	FFD	-Conc. of Phospholipid -Addition rate -Stirring temperature	[29]
MICROSPHERE	Celecoxib-hydroxypropyl-b-cyclodextrin-PVP complex	QbD	-% of Calcium alginate -Calcium of chloride -Chitosan -Time of cross-linking	[30]
	Ranidine HCL	CCD	-Drug : polymer ratio -Conc. of Sodium tripolyphosphate -Stirring speed	[31]
	Enoxaparin sodium	CCD	-Eudragit® FS-30D / Eudragit® RS-PO ratio -Conc. of Poly(vinylalcohol) -Conc. of Sodium chloride	[32]
LIPOSOMES	Vit. K <sub>1</sub> Oxide	BBD	-PC/CHO ratio -Conc. of Drug -Sonication time	[33]
	Bacifloxacin HCL	FFD	-Soya lecithin/cholesterol ratio -Lipid/Drug ratio	[34]
	Lidocaine	FrFD	-Conc. of Coating Sol <sup>n</sup> -Dripping rate -Stirring rate -Time -Conc. of drug	[35]
	Gedunin	PBD	-Conc. of Drug -Conc. of Lipid -Cholesterol/lecithin ratio	[36]
	Valsartan	BBD	-Ratio of surfactant -Ratio of solid carrier	[37]

MICELLS			-Total mass of solid carrier	
	Lopinavir Vit.E TPGS	CCD	-TPGS: Drug ratio -Rotational speed	[38]
	Paclitaxel	BBD	-Effect of pressure -ScCO <sub>2</sub> release rate -Vol <sup>m</sup> ratio of water against ScCO <sub>2</sub>	[39]
FILMS	Tenoxicam	FFD	-Conc. of Chitosan -Conc. of PVP	[40]
	Asiaticoside	BBD	-PVA conc. -PEG conc. -Freeze thaw cycle days	[41]
	Zolmitriptan	FFD	-PEG 400 -Sucralose	[42]
	Tolterodine	BBD	-Carbopol 980 -Hydroxypropyl cellulose -HPMC -Tween 80	[43]
NANO STRUCTURED LIPID CARRIERS	Methotrexate	BBD	-Amount of lipid -Surfactant -Drug	[44]
	Lurasidone HCL	BBD	-Conc. of lipid -Surfactant -Sonication time	[45]
	Sulforaphane	BBD	-Lipid conc. -Surfactant conc. -Sonication time	[46]
	Telmisartan	BBD	-Lipid conc. -Surfactant conc. -Sonication time	[47]
TABLETS	Indapamide hemihydrate	CCD	-Binder Conc. -Matrix Conc. -Grade of indapamide	[48]
	Valsartan	CCD	-Conc. of pH modifier -Conc. of Solubility	[49]
	Domperidone	FFD	-Polymer Conc. -Drug Conc.	[50]

(BBD- Box – Behnken design, CCD- Central composite design, FFD- Full factorial design, QbD- Quality by design, FrFD- Fractional factorial design)

## MICELLS:

Yoon Tae Goo et al., applied Box- Behnken design to optimize solid self-Dispersing micelles (S-SDM) for enhancing the dissolution and oral bioavailability of valsartan. Experiment was performed by using three independent variables such as the ratio of surfactants, ratio of solid carriers, and total mass of solid carriers. In this study they concluded that, optimized S-SDM could be a selectable candidate for developing water insoluble drugs in reduced quantity.<sup>37</sup> Hitendra Mahajan and Payal Patil used central composite design to optimized Lopinavir Vitamin E TPGS micelle. In this study, they selected two parameters such as TPGS: drug ratio and rotational speed as independent variables. The study concluded that micelles have a wide scope for the development of such formulations can overcome challenges of current highly active anti- retroviral therapy (HAART).<sup>38</sup> Zhen Jiao et al., applied Box-Behnken design to prepared and optimized Drug loaded micelles through supercritical carbon dioxide evaporation method. In this study, authors selected three factors such as the effects of pressure, ScCO<sub>2</sub> (super critical carbon-dioxide) release rate and the volume ratio of water against ScCO<sub>2</sub>. The study revealed that, the optimized

micelles formulation showed a narrow size distribution, regularly spherical shape, and also the sustained release of paclitaxel from the micelles.<sup>39</sup>

## FILMS:

Lubna Y. Ashri et al., used factorial design to optimize and evaluate Buccal Mucoadhesive tenoxicam (TNX) local delivery system using two independent factors i.e. Chitosan and PVP concentrations. This study revealed that, the optimized TNX mucoadhesive buccal film could be suitable for oral therapy and could be a means to overcome the side effects of orally delivered drug.<sup>40</sup> Afnan Sh. Ahmed et al., prepared and optimize PVA-PEG physically cross-linked hydrogel film as a wound dressing. The independent variables used in this study were PVA concentration (%), PEG concentration (%), and freeze-thaw cycles (days, 1 cycle=1 day). From this study it was concluded that, the optimized batch of PVA/PEG hydrogel had a high capacity to absorb fluid and was elastic and safe therefore, it possesses an immense potential as a wound dressing material.<sup>41</sup>

Vipul D. Prajapati et al., applied factorial design to developed and optimize Pullulan based oral thin film formulation of

zolmitriptan by selecting independent variables such as PEG 400 (X1) and sucralose (X2). From this study it was concluded that, pullulan can be successfully utilized at lab-scale for the formulation of oral thin film of zolmitriptan using PEG 400 and sucralose as best compatible plasticizer and sweetener, respectively.<sup>42</sup>Ximing Liu et al., used Box - Behnken design to developed and optimize transparent film forming hydrogels and their consequence on stratum corneum. Carbopol 980, hydroxypropylcellulose, hydroxypropyl methyl cellulose (HPMC) and Tween 80 were used as independent variables. From this study, authors concluded that optimization of tolterodine hydrogels preparation is simple and effective with the help of ternary phase diagram and response surface methodology.<sup>43</sup>

### NANOSTRUCTURED LIPID CARRIER:

Mara Ferreira et al., applied Box- Behnken design to optimize nanostructured lipid carriers which are loaded with methotrexate. They selected three parameters such as amount of liquid lipid, amount of surfactant and amount of methotrexate as independent variables. Researchers revealed that, the optimized formulation of methotrexate was appropriate for systemic and topical administration.<sup>44</sup>ImranaJazuli et al., used to optimize nanostructured lipid carriers of Lurasidone Hydrochloride for brain targeting and to study the in-vitro, in-vivo protocol. In this study, they had selected three parameters such as lipid concentration, surfactant, and sonication times for the optimization. The results showed that, the intranasal route can be suitable for the delivery of drug directly to the brain and also increased the efficacy of drug in brain.<sup>45</sup>

Kriti Soni et al., applied Box-Behnken design to optimize and developed nanostructured lipid carriers loaded with sulforaphane for improved oral efficacy against cancer. In this study, researcher selected three variables for the optimization: lipid concentration, surfactant concentration and sonication time. The results revealed that, nanostructured lipid carriers loaded with sulforaphane could be an important strategy for the management of cancer by oral delivery.<sup>46</sup>

Chhitij Thapa et al., used Box-Behnken design to formulate and optimize nano structured lipid carriers of telmisartan to increase its oral bioavailability by selecting three independent variables i.e. total lipid concentration, surfactant concentration, and sonication time. From the results, it was concluded that, the bioavailability of nanostructured lipid carriers loaded with telmisartan was increased as compared to the marketed formulation.<sup>47</sup>

### TABLETS:

Packa Antovska et al., used Central Composite Face Design (CCD) to developed and optimize novel controlled-release matrix tablet formulation for indapamide hemihydrate. From the results, it was concluded that concentration of the chosen high-viscosity polymer, such as hydroxyl-ethylcellulose, play an important role in the dissolution profile of indapamide.<sup>48</sup>

Mehtap Saydam & Sevgi Takka applied central composite design to developed and evaluate pH-independent controlled release matrix tablet of valsartan and its in-vitro study. Researchers were selected two variables: the concentration of pH modifier sodium citrate and the concentration of solubility enhancer. From the results, it was observed that, for 12 hours of controlled release, HPMC E4M was found to be most suitable hydrophilic matrix polymer.<sup>49</sup>

Hemlata G. Patil et al., used factorial design for the formulation and development of oro disperse and sustained release tablet loaded with domperidone. They selected two

independent variables i.e. polymer concentration and drug concentration for the optimization. The optimized formulation showed disintegration time of 21 seconds and matrix controlled drug release for 9 h.<sup>50</sup>

### OTHERS:

Kamlesh Wadher et al., prepared nine emulgel formulations of *Pongamia pinnata* according to a 3<sup>2</sup> factorial design employing the qualitative factors and levels. Two independent variables were evaluated as amount of Carbapol and amount of Emulsified agent; Viscosity and spreadability were selected as the dependent variables. From the observed results it was concluded that there is increase in the drug release in optimized formulation with respect to time.<sup>51</sup>

Abhishek Sharma et al., used Box-Behnken design to Developed and optimized nanoemulsion based gel for enhanced transdermal delivery of nitrendipine. They were selected oil, surfactant and co-surfactant as independent variables for the optimization. This study revealed that, the prepared nanoemulsion gel could be used as a carrier for transdermal delivery of nitrendipine.<sup>52</sup>

Trivedi S et al., prepared Thymoquinone loaded polymer-lipid hybrid vesicles to enhance the permeation and anti-cancer potency. The formulations were prepared by ethanol injection technique using 3<sup>2</sup> factorial designs. The results concluded that the optimized nano carrier loaded formulation could be considered as a promising formulation for delivery of drug with enhanced treatment of cancer with reduced toxicity.<sup>53</sup>

Yanping Deng et al., applied Central composite design to prepared and optimized Fat-soluble Vitamins lipid injectable emulsion. In this study, the percentage of emulsifier (X1), homogenization pressure (X2) and homogenization recirculation (X3) were selected as independent variables. From this study, they were concluded that by using Quality by design approach, lipid injectable emulsion for fat soluble vitamins was successfully prepared.<sup>54</sup>

### CONCLUSION:

Experimental design is a method used to optimize the formulation to getting effective pharmaceutical product. Experimental design can accurately analyze the all factors which are to be considered while performing the experimentation. This method is economical and less tedious than traditional methods used for optimization. In future, experimental design plays an important role for developing various pharmaceutical formulations. In this review article, we describe the type of experimental design and emphasize on the applications of experimental design in drug delivery system and factors to be considered while performing particular formulation such as phytosomes, liposomes, microspheres etc.

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