



# A Quick Guide of Optimizing Approaches on Nano suspensions Using Design of Experiments

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## ABSTRACT

The present work is aimed to explore the earlier optimization approaches made using design of experiments (DoE). An intensive search made by referring peer-reviewed journals on DoE made on nanosuspensions. Handsome successful attempts that were made in the optimization of Nano suspensions by DoE were brought in one platform and presented in this paper. The study concludes that and gives a desktop reference to the new researchers in finding out the earlier attempts which were made on nanosuspensions using DoE in a short span.

**Key Words:** Nano suspensions, drugs, optimization, designing, experiment, literature.

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## INTRODUCTION

Nanotechnology is a collective term referring to technological developments on the nanometer scale, usually 0.1-100 nm [1]. In recent years, there has been great excitement for creating nanoparticles [2-4]. Nanoparticle is an ultrafine unit having a magnitude that is calculated in nanometre (nm) i.e.,  $10^{-9}$  m. [5] The consequences of individual actions nanoparticles exist in nature. Due to their ultramicroscopic size, they have exceptional materialistic characters. The artificial nanoparticles have many useful applications in the field of medication, manufacturing, and ecological remediation.

Nanoparticles are many types, based on their volume, nature, and materialistic property. A few classifications also differentiate among unprocessed and inert nanoparticles; the primary group comprises of dendrimers, liposomes, and polymeric nanoparticles, whereas the secondary contains fullerenes, quantum dots, and gold nanoparticles [6]. Nanoparticles classified based on their carbon-based, ceramic, semiconducting and polymeric nature. Also, nanoparticles can be classified as hard

particles (e.g., titanium dioxide, silica particles, and fullerenes) and soft particles (e.g., liposomes, vesicles, and Nanodroplets). Nanoparticles are classified characteristically depends on the applications, such as in diagnosis or therapy or may be related to how which they were produced.

## Optimization

Optimization is the procedure of finding the most proper value for a task within a given area. This procedure is frequently used in computer science and physics, regularly called energy optimization [7]. For a function  $f(x)$  is called the objective assignment, that has a domain of actual information of set A, the utmost best possible result occurs over set A and the least good possible result occurs within set A.

The three general ways of optimizing a function are:

1. Finding the absolute extremities of the function.
2. Expending the first imitative test. Or
3. Consuming the second copied test.

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### Design of experiment (DOE)

The design of experiments (DOE) is a branch of functional information [8]. It deals with the development, conducting, analyzing, and interpreting the unnatural test to calculate the factors that organize the value of a limitation or group of limitations. DOE is potent in information gathering and it is an investigation tool that can be used in the selection of investigational situations. It allows several input issues to be handled, defining their result on a wanted output (response). By influence several inputs at equal time, DOE can recognize significant interactions if missed when testing through one factor at a time. DOE investigates all probable combinations (full factorial) or only a quota of probable combination (fractional factorial) can be examined. An intentionally designed and perform test can give a huge compact of information regarding the consequence of feedback undependable suitable to one or more factors. Several tests hold definite factors unvarying with changing the levels of an additional variable. The information about "one factor at a time" (OFAT) is incompetent when compared with varying factor levels at the same time. The designed test with present arithmetical approaches originated from the work of R. A. Fisher in the early part of the 20th century. Fisher verified how taking the time too seriously considers the plan and implementation of an experiment helped to avoid repeatedly arriving problems in analysis. Key concepts in creating a planned test consist of jamming, randomization, and duplication.

- **Blocking**

Once randomizing a factor is either impractical or too expensive, blocking lets you limit randomization, by

performing all the trials with one set of the factor and remaining with other.

- **Randomization**

The order in which trials are performed in a randomized order which eradicates the effects of unidentified or unrestrained variables.

- **Replication**

Duplication of a whole experimental treatment, including the setup.

### Quality by design (QbD)

It is a methodical advance to progress that begins with predefined objectives and highlights product, process empathetic and process control, with the information of science and quality risk management. QbD is developed to improve the guarantee of safe, effective drug supply to the patient and also promise to a significant advance in manufacturing feature performance [9].

- **Advantages of QbD**

- Better considering the process.
- Less batch failure.
- More efficient and effective control of change.
- Return on investment/cost savings.

The independent and dependent variables used in various dosage forms [10] were represented in table 1. Nano suspensions so far optimized by factorial design was illustrated in table 2.

**Table 1. Independent and dependent variables adopted in dosage forms**

Dosage form	Independent variables	Dependent variables
Tablets	Atomization air pressure, inlet temperature and spray rate	Weight gain and tablet surface roughness
Suspensions	Stirring speed, amount of initiator and suspending agent concentration	Polymeric particle formation
Ointments	Temperature, time, mixing rate, and cooling rate	Assay, content uniformity, API particle size (PS).
Creams	Stearic acid and sunflower	Viscosity and Spreadability

**Table 2. Drugs tried in preparing Nano suspensions using factorial designs**

Drug used	Design employed	Independent variables	Dependent variables	Reference
Glipizide	CCD	Captex, solutol, and imwitor	PS	Dash et al., 2019 [11]
Turmeric	Ionotropic gelation technique	FTIR and DSC	EE, PS, and ZP	Govindaraju et al., 2019 [12]
Sitagliptin	CCD	Eudragit RL100 concentration, tween 80 concentration, and sonication time	PS, drug loading and, drug release (DR)	Jahangir et al., 2018 [13]

Flurbiprofen	2 <sup>3</sup> and 3 <sup>3</sup> FFD	Plantacare 2000	PS, PDI and ZP	Oktay et al., 2018 [14]
Ficus religiosa	CCD	PS, PDI, and ZP	EE and surface morphology	Priyanka et al., 2018 [15]
Azoxystrobin	Media milling method	PS, and PDI	Increased retention volume, reduced contact angle, and enhanced wettability	Yao et al., 2018 [16]
Pioglitazone Hydrochloride	3 <sup>2</sup> FFD	Polycaprolactone, and Poloxamer	PS, ZP, and EE	Canchi et al., 2017 [17]
Ibuprofen	2 <sup>2</sup> FFD	Milling time, solvent to antisolvent ratio	PS and PDI	Fernandes et al., 2017 [18]
Naringenin	Antisolvent sonoprecipitation method	Optimization of sonication time, and drug concentration and stabilizers	Increased sonication time and concentration of stabilizer and drug	Gera et al., 2017 [19]
Lacidipine	3 <sup>2</sup> BBD	Stabilizer to drug ratio, sodium deoxycholate percentage, and sonication time	Dissolution rate, PS, size reduction and decreased crystallinity	Kassem et al., 2017 [20]
Diosgenin	Media milling method	PS and morphology	PS and PDI	Liu et al., 2017 [21]
Diacerein	3 <sup>2</sup> FFD	Encapsulation efficiency (EE)	PS	Parekh et al., 2017 [22]
Glycyrrhizin	3 <sup>2</sup> FFD	PS, EE, stability, and chemical interactions	Minimum PS, and maximum EE	Rani et al., 2017 [23]
Curcumin	2 <sup>3</sup> FFD	Single Emulsion Solvent evaporation	PS, ZP, and EE	AKI et al., 2016 [24]
Febuxostat	CCD	Polymer and surfactant concentration, bead volume, and milling time	PS, polydispersity index (PDI) and zeta potential (ZP)	Ahuja et al., 2015 [25]
Polypeptide-k	BBD	Drug ratio, tween-80 to drug ratio, inlet air temperature, and feed flow rate	Moisture content, solubility, product yield and angle of repose	Kaur et al., 2015 [26]
Nateglinide	FFD	Solvent evaporation, and freeze-drying	PS, ZP, x-ray diffraction, and EE	Lokhande et al., 2015 [27]
Naproxen	3 <sup>2</sup> FFD	Ultra-sonification	PS	Mishra et al., 2015 [28]
Embelin	Media milling techniques	Amount of stabilizers, and amount of milling agents	PS, DR	Parmar et al., 2015 [29]
Losartan Potassium	3 <sup>3</sup> BBD	Polymer concentration (Ethylcellulose), surfactant concentration (Tween 80), and the inner diameter	EE and DR	Patil et al., 2015 [30]
Repaglinide	Taguchi design	% polymer concentration, PS, and ZP	PS and PDI	Shinde et al., 2014 [31]
Betulin	anti-solvent precipitation	Ethanol, and Deionized water	PS	Zhao et al., 2014 [32]
Acyclovir	3 <sup>2</sup> FFD	Pluronic F68, and Tween 80 concentration	PS, PDI, ZP, EE	El-Feky et al., 2013 [33]

Glibenclamide	Plackett-Burman screening Design	Solvent to Anti-solvent volume ratio, amount of GLB, speed of mixing, PS, saturation solubility, and % dissolution efficiency	PS	Shah et al., 2013 [34]
Metformin Hydrochloride	3 <sup>3</sup> BBD	Hydroxypropyl Methylcellulose, and Polyvinylpyrrolidone	DR, percentage, dissolution curve shape	Lee et al., 2012 [35]
Glimepiride	Full Factorial Design	Maximum plasma concentration, and PS	ZP, PDI, entrapment efficiency	Yadav et al., 2012 [36]
Andrographolide	3 <sup>2</sup> FFD	Eubragit, and Pluronic	EE, ZP and PS	Chellampillai et al., 2011 [37]
Sucrose ester-oleanic acid(SEOA)	o/w emulsion and organic solvent evaporation methods	Nano sizer, and HPLC	PS and PDI	Li et al., 2011 [38]
Simvastatin	2 <sup>3</sup> FFD	PS, and in vitro dissolution study	PS, rate of dissolution, multiple linear regression analysis	Pandya et al., 2011 [39]
Olmestartan medoxomil	media milling technique	PS, ZP, saturation solubility, and dissolution rate	PS	Thakkar et al., 2011 [40]
Itraconazole	3 <sup>2</sup> FFD	PS, size distribution, and drug content	PS	Nakarani et al., 2010 [41]
Dihydroartemisinin	CCD	Drug concentration, and lipid concentration, and the ratio of liquid lipid to total lipid	EE	Zhang et al., 2010 [42]
Indomethacin	2 <sup>(5-1)</sup> Factorial FD	Multiple Linear Regression analysis, and ANOVA	PS, and ZP	Verma et al., 2009 [43]
Lacidipine	3 <sup>3</sup> BBD	Stabilizer to drug ratio, sodium deoxycholate percentage, and sonication time	PS, ZP, and PDI	Kassem et al., 2017 [44]

## CONCLUSION

The literature survey revealed that the design of experiments (DoE) in designing nanosuspensions plays a vital role in optimization. DoE has regularly adopted methodology in experiments and reported the most accepted precise approach in optimization as it is a safe, economical and accurate approach using DoE software. The study concludes and gives a quick reference to the researchers in surfing the past work done on nanosuspensions using DoE with a single click of a computer mouse with no time.

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## Conflicts of Interests

Authors do not have any conflicts of interest with the publication of the manuscript.

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