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

Hindustan Abdul Ahad*, Haranath Chinthaginjala, Kanama Sreekanth, Atla Sucharitha, Omer Ibrahim, Kanama Sandhya Rani, Yaduguri Ravali

Department of Industrial Pharmacy, Raghavendra Institute of Pharmaceutical Education and Research (RIPER)-Autonomous, Ananthapuramu-515001, AP, India.

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.

eIJPPR 2020; 10(3):37-42

HOW TO CITE THIS ARTICLE: Hindustan Abdul Ahad*, Haranath Chinthaginjala, Kanama Sreekanth, Atla Sucharitha, Omer Ibrahim, Kanama Sandhya Rani, Yaduguri Ravali (2020). "A Quick Guide of Optimizing Approaches on Nano suspensions Using Design of Experiments", International Journal of Pharmaceutical and Phytopharmacological Research, 10(3), pp.37-42.

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]. Nano-particle 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.

Corresponding author: Dr. Hindustan Abdul Ahad M. Pharm. Ph.D., FAGE
Address: Professor & Head, Dept. of Industrial Pharmacy, Raghavendra Institute of Pharmaceutical Education and Research (RIPER), Ananthapuramu-515003, Andhra Pradesh, India.
E-mail: ✉ abdulhindustan @ gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 11 February 2020; **Revised:** 24 May 2020; **Accepted:** 27 May2020

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	2^3 and 3^3 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	3^2 FFD	Polycaprolactone, and Poloxamer	PS, ZP, and EE	Canchi et al., 2017 [17]
Ibuprofen	2^2 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	3^2 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	3^2 FFD	Encapsulation efficiency (EE)	PS	Parekh et al., 2017 [22]
Glycyrrhizin	3^2 FFD	PS, EE, stability, and chemical interactions	Minimum PS, and maximum EE	Rani et al., 2017 [23]
Curcumin	2^3 FFD	Single Emulsion Solvent evaporation	PS, ZP, and EE	AKl 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	3^2 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	3^3 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	3^2 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	3^3 BBD	Hydroxypropyl Methylcellulose, and Polyvinylpyrolidon	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	3^2 FFD	Eubragit, and Pluronic	EE, ZP and PS	Chellampillai et al., 2011 [37]
Sucrose ester-oleanolic acid(SEOA)	o/w emulsion and organic solvent evaporation methods	Nano sizer, and HPLC	PS and PDI	Li et al., 2011 [38]
Simvastatin	2^3 FFD	PS, and in vitro dissolution study	PS, rate of dissolution, multiple linear regression analysis	Pandya et al., 2011 [39]
Olmesartan medoxomil	media milling technique	PS, ZP, saturation solubility, and dissolution rate	PS	Thakkar et al., 2011 [40]
Itraconazole	3^2 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	$2^{(5-1)}$ Factorial FD	Multiple Linear Regression analysis, and ANOVA	PS, and ZP	Verma et al., 2009 [43]
Lacidipine	3^3 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.

ACKNOWLEDGMENTS

We thank Dr. Y. Padmanabha Reddy, principal, RIPER, Ananthapuramu, for his support and Encouragement.

Conflicts of Interests

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

REFERENCES

[1] Manojkanna K, Chandana C S. Nanoparticles in endodontics – A review. J. Adv. Pharm. Edu. Res. 2017; 7(2): 58-60.
[2] Sharaf I A., El-Halwagy M E A, Alnahdi H S. Prophylactic effect of omega-3 fatty acid on gold nanoparticles toxicity in rat's brain. Pharmacophores. 2018; 9(1): 56-68.
[3] Almutairi F M. Biopolymer Nanoparticles: A Review of Prospects for Application as Carrier for Therapeutics and Diagnostics. Int. J. Pharm. Res. Allied Sci. 2019; 8(1): 25-35.
[4] Vishnuvardhan K, Kavitha B, Nimmanapalli Y. Synthesis of silver nanoparticles using

Aeschynomene indica L. aqueous leaf extract and evaluation of its Antibacterial activity. J. Biochem. Technol. 2020;11(1):1-13.

[5] Shrivastava B, Gopaiah K V, Rao G S. Lipid-Polymer Based Nanoparticles as a New Generation Therapeutic Delivery Platform for Ulcerative Colitis in Vitro/In Vivo Evaluation. Pharmacophores. 2019; 10(4): 15-27.

[6] Shekhawat PB, Pokharkar VB. Understanding peroral absorption: regulatory aspects and contemporary approaches to tackling solubility and permeability hurdles. Acta Pharmaceutica Sinica B. 2017 May 1;7(3):260-80.

[7] Ahad HA, Haranath C, Rahul Raghav D, Gowthami M, Naga Jyothi V, Sravanthi P. Overview on Recent Optimization Techniques in Gastro Retentive Microcapsules by Factorial Design. International Journal of Pharma Sciences and Research, 2019; 10(9): 247-254.

[8] Deaton A, Cartwright N. Understanding and misunderstanding randomized controlled trials. Social Science & Medicine. 2018 Aug 1; 210:2-1.

[9] Hindustan AA, Anusha GB, Haranath C, Priyanka M, Akhil K, Rahul RD. Equator Assessment of Nanoparticles Using the Design-Expert Software, International Journal of Pharmaceutical Sciences and Nanotechnology, 2020; 13 (1): 4766-4772.

[10] Mazurek S, Szostak R. Quantitative determination of diclofenac sodium in solid dosage forms by FT-Raman spectroscopy. Journal of pharmaceutical and biomedical analysis. 2008 Nov 4;48(3):814-21.

[11] Dash RN, Mohammed H, Humaira T, Ramesh D. Design, optimization and evaluation of glipizide solid self-nano emulsifying drug delivery for enhanced solubility and dissolution. Saudi Pharmaceutical Journal. 2015 Oct 1;23(5):528-40.

[12] Govindaraju R, Karki R, Chandrashekarappa J, Santhanam M, Shankar AK, Joshi HK, Divakar G. Enhanced Water Dispersibility of Curcumin Encapsulated in Alginate-polysorbate 80 Nano-Particles and Bioavailability in Healthy Human Volunteers. Pharmaceutical nanotechnology. 2019 Feb 1;7(1):39-56.

[13] Jahangir MA, Khan R, Sarim Imam S. Formulation of sitagliptin-loaded oral polymeric nano scaffold: process parameters evaluation and enhanced anti-diabetic performance. Artificial cells, nanomedicine, and biotechnology. 2018 Oct 31;46(sup1):66-78.

[14] Oktay AN, Karakucuk A, Ilbasmis-Tamer S, Celebi N. Dermal flurbiprofen nanosuspensions: Optimization with the design of experiment approach and in vitro evaluation. European Journal of Pharmaceutical Sciences. 2018 Sep 15; 122:254-63.

[15] Priyanka K, Sahu PL, Singh S. Optimization of processing parameters for the development of Ficus religiosa L. extract loaded solid lipid nanoparticles using central composite design and evaluation of antidiabetic efficacy. Journal of Drug Delivery Science and Technology. 2018 Feb 1; 43:94-102.

[16] Yao J, Cui B, Zhao X, Wang Y, Zeng Z, Sun C, Yang D, Liu G, Gao J, Cui H. Preparation, characterization, and evaluation of azoxystrobin nanosuspension produced by wet media milling. Applied Nanoscience. 2018 Mar 1;8(3):297-307.

[17] Canchi A, Khosa A, Singhvi G, Banerjee S, Dubey SK. Design and characterization of polymeric nanoparticles of pioglitazone hydrochloride and study the effect of formulation variables using QbD approach. Current Nanomaterials. 2017 Dec 1;2(3):162-8.

[18] Fernandes AR, Ferreira NR, Fangueiro JF, Santos AC, Veiga FJ, Cabral C, Silva AM, Souto EB. Ibuprofen nanocrystals developed by 22 factorial design experiment: A new approach for poorly water-soluble drugs. Saudi pharmaceutical journal. 2017 Dec 1;25(8):1117-24.

[19] Gera S, Talluri S, Rangaraj N, Sampathi S. Formulation and evaluation of naringenin nanosuspensions for bioavailability enhancement. AAPS PharmSciTech. 2017 Nov 1;18(8):3151-62.

[20] Kassem MA, ElMeshad AN, Fares AR. Enhanced solubility and dissolution rate of lacidipine nanosuspension: formulation via antisolvent sonoprecipitation technique and optimization using Box–Behnken design. AAPS PharmSciTech. 2017 May 1;18(4):983-96.

[21] Liu CZ, Chang JH, Zhang L, Xue HF, Liu XG, Liu P, Fu Q. Preparation and evaluation of diosgenin nanocrystals to improve oral bioavailability. AAPS PharmSciTech. 2017 Aug 1;18(6):2067-76.

[22] Parekh KK, Paun JS, Soniwala MM. Formulation and evaluation of nanosuspension to improve solubility and dissolution of diacerein. International Journal of Pharmaceutical Sciences and Research. 2017 Apr 1;8(4):1643.

[23] Rani R, Dahiya S, Dhingra D, Dilbaghi N, Kim KH, Kumar S. Evaluation of anti-diabetic activity of glycyrrhizin-loaded nanoparticles in nicotinamide-streptozotocin-induced diabetic rats. European Journal of Pharmaceutical Sciences. 2017 Aug 30; 106:220-30.

[24] Akl MA, Kartal-Hodzic A, Oksanen T, Ismael HR, Afouna MM, Yliperttula M, Samy AM, Viitala T. Factorial design formulation optimization and in vitro characterization of curcumin-loaded PLGA nanoparticles for colon delivery. Journal of Drug

Delivery Science and Technology. 2016 Apr 1; 32:10-20.

[25] Ahuja BK, Jena SK, Paidi SK, Bagri S, Suresh S. Formulation, optimization and in vitro–in vivo evaluation of febuxostat nanosuspension. International journal of pharmaceutics. 2015 Jan 30;478(2):540-52.

[26] Kaur P, Singh SK, Garg V, Gulati M, Vaidya Y. Optimization of spray drying process for formulation of solid dispersion containing polypeptide-k powder through quality by design approach. Powder Technology. 2015 Nov 1; 284:1-11.

[27] Lokhande A, Mishra S, Kulkarni R, Naik J. Development and evaluation of nateglinide loaded polycaprolactone nanoparticles. Micro and Nanosystems. 2015 Feb 1;7(1):43-8.

[28] Mishra B, Sahoo J, Dixit PK. Formulation and process optimization of naproxen nanosuspensions stabilized by hydroxypropyl methylcellulose. Carbohydrate polymers. 2015 Aug 20; 127:300-8.

[29] Parmar K, Patel J, Sheth N. Formulation and optimization of Embelin nanosuspensions using central composite design for dissolution enhancement. Journal of Drug Delivery Science and Technology. 2015 Oct 1; 29:1-7.

[30] Patil P, Khairnar G, Naik J. Preparation and statistical optimization of losartan potassium loaded nanoparticles using Box Behnken factorial design: Microreactor precipitation. Chemical Engineering Research and Design. 2015 Dec 1; 104:98-109.

[31] Pathak Y, Thassu D, editors. Drug delivery nanoparticle formulation and characterization. CRC Press; 2016 Apr 19.

[32] Zhao X, Wang W, Zu Y, Zhang Y, Li Y, Sun W, Shan C, Ge Y. Preparation and characterization of betulin nanoparticles for oral hypoglycemic drugs by antisolvent precipitation. Drug delivery. 2014 Sep 1;21(6):467-79.

[33] El-Feky GS, Zayed GA, Farrag AR. Optimization of an ocular nanosuspension formulation for acyclovir using factorial design. Int J Pharm Pharm Sci. 2013; 5:213-9.

[34] Shah SR, Parikh RH, Chavda JR, Sheth NR. Application of Plackett–Burman screening design for preparing glibenclamide nanoparticles for dissolution enhancement. Powder technology. 2013 Feb 1; 235:405-11.

[35] Lee YL, Kim MS, Park MY, Han K. Quality by design: understanding the formulation variables and optimization of metformin hydrochloride 750 mg sustained-release tablet by Box–Behnken design. Journal of Pharmaceutical Investigation. 2012 Aug 1;42(4):213-20.

[36] Yadav SK, Mishra S, Mishra B. Eudragit-based nanosuspension of poorly water-soluble drug: formulation and in vitro–in vivo evaluation. AAPS pharmscitech. 2012 Dec 1;13(4):1031-44.

[37] Chellampillai B, Pawar AP. Improved bioavailability of orally administered andrographolide from pH-sensitive nanoparticles. European journal of drug metabolism and pharmacokinetics. 2011 Jan 1;35(3-4):123-9.

[38] Li W, Das S, Ng KY, Heng PW. Formulation, biological and pharmacokinetic studies of sucrose ester-stabilized nanosuspensions of oleanolic acid. Pharmaceutical research. 2011 Aug 1;28(8):2020-33.

[39] Pandya VM, Patel JK, Patel DJ. Formulation, optimization, and characterization of simvastatin nanosuspension prepared by nanoprecipitation technique. Der Pharmacia Lettre. 2011;3(2):129-40.

[40] Thakkar HP, Patel BV, Thakkar SP. Development and characterization of nanosuspensions of olmesartan medoxomil for bioavailability enhancement. Journal of Pharmacy and Bioallied Sciences. 2011 Jul;3(3):426.

[41] Nakarani M, Misra AK, Patel JK, Vaghani SS. Itraconazole nanosuspension for oral delivery: Formulation, characterization and in vitro comparison with marketed formulation. Daru: journal of Faculty of Pharmacy, Tehran University of Medical Sciences. 2010;18(2):84.

[42] Zhang X, Liu J, Qiao H, Liu H, Ni J, Zhang W, Shi Y. Formulation optimization of dihydroartemisinin nanostructured lipid carrier using response surface methodology. Powder technology. 2010 Jan 10;197(1-2):120-8.

[43] Verma S, Lan Y, Gokhale R, Burgess DJ. Quality by design approach to understand the process of nanosuspension preparation. International journal of pharmaceutics. 2009 Jul 30;377(1-2):185-98.

[44] Kassem MA, ElMeshad AN, Fares AR. Enhanced solubility and dissolution rate of lacidipine nanosuspension: formulation via antisolvent sonoprecipitation technique and optimization using Box–Behnken design. AAPS PharmSciTech. 2017 May 1;18(4):983-96.