Ind. J. Pharm. Edu. Res., 2024; 58(1s):s158-s166.
https://www.ijper.org

Original Article

Amelioration of Dissolution Properties of Abiraterone Acetate via Nano-Sizing Employing High-Speed Homogenization Technique: An Optimization Study

Patel Rajendra[1], Parmar Komal[2,*]

[1]Research Scholar, Department of Pharmacy, Gujarat Technological University, Ahmedabad, Gujarat, INDIA.
[2]ROFEL Shri G.M. Bilakhia College of Pharmacy, Vapi, Gujarat, INDIA.

ABSTRACT

Background: Abiraterone acetate is an anticancer molecule indicated for prostate cancer. The purpose of this study was to develop a nanosuspension of abiraterone acetate in order to improve its solubility, dissolution properties and bioavailability. **Materials and Methods:** High speed homogenization method was utilized to formulate the nanosuspension. Design of experiment (DoE) was employed for the optimization of process and formulation variables. Nanosuspension was evaluated for particle size, PDI, zeta potential, and *in vitro* drug release studies. **Results:** Preliminary studies suggested amount of stabilizer and milling time as critical variables to be taken for the optimization process. Regression analysis suggested influence of independent variables on responses. Optimized batch obtained from desirability function yielded 140.25 nm of particle size and 0.09 of PDI values. Characterization studies i.e. Differential Scanning Calorimetry and X-Ray Diffraction studies illustrated decrease in crystallinity of drug which might be thereby responsible for the dissolution enhancement of drug. The drug and formulation were found to be stable over a 6-months period in accelerated stability testing. **Conclusion:** Using high speed homogenization method, particle size of the formulation was reduced to nano-size which was further responsible for the improvement in dissolution and bioavailability of drug.

Keywords: Abiraterone acetate, Nanosuspension, Nanocrystals, Dissolution enhancement, Quality by Design.

Correspondence:
Dr. Komal Parmar
ROFEL Shri G.M. Bilakhia College of Pharmacy, Vapi, Gujarat, INDIA.
Email: komal.parmar2385@gmail.com
ORCID ID: 0000-0001-8564-163X

Received: 03-09-2022;
Revised: 30-05-2023;
Accepted: 03-11-2023.

INTRODUCTION

One of the most difficult aspects of developing novel chemical entities and generics is overcoming its poor aqueous solubility. This unfavourable physicochemical characteristic is found in the large majority of novel drug candidates. Many studies have reported poorly water-soluble drugs, with the majority falling into the Biopharmaceutical Classification System's class II or IV.[1-3] When given orally, absorption and bioavailability are limited due to the slow rate of dissolution of these drugs.[4] Solubility and/or rate of dissolution improvement of the poorly soluble drugs has been a key component in increasing their absorption rate and extent, following their oral administration.[5,6] Among the most commonly used approaches to improve drug biopharmaceutical characteristics includes particle size reduction,[7] crystallization,[8] solid dispersion,[9] complexation,[10] other lipid-based drug delivery such as self-emulsifying drug delivery systems[11] and nanoparticles.[12] Wet milling methods have also been effectively used for the development of nanosized drug delivery systems, as they do not require the use of organic solvents or severe environmental conditions, and they can be scaled up simply.[13] The dissolution profile and saturation solubility of hydrophobic compounds are both increased in nanosuspensions generated after drug nanosizing. Nanosizing increases the surface area of the particles which thereby improves the solubility and dissolution properties of drug particles. Nanosuspensions are colloidal drug delivery systems that contain surface-active compounds or polymeric stabilisers.[14,15] Retaining particle size distribution of pharmaceuticals in liquid form during long-term storage is difficult due to instability.[16] Consequently, solidification of nanosuspensions to nanocrystals appear to be a potent formulation tool for ameliorating the solubilization, dissolution and bioavailability properties of drug.[17,18] The physical and chemical stability of nanosuspensions can be improved by converting them to solid products.[19] Solidification of nanosuspensions can be achieved by granulation, spray drying, and freeze-drying techniques.[20-22]

In the United States and Europe, prostate cancer is the second highest cause of cancer death in males.[23] Abiraterone acetate is

DOI: 10.5530/ijper.58.1s.15

the medication indicated for the treatment of prostate cancer. Abiraterone is a strong and selective irreversible inhibitor of the androgen biosynthetic enzyme CYP17A1.[24] It works by reducing androgen synthesis in tumour tissues such as the testicles, adrenals, and prostate, resulting in a slower course of the disease.[25] Abiraterone acetate has poor aqueous solubility. It has limited permeability and is classified under Biopharmaceutical Classification System (BCS) category IV. This led to poor oral bioavailability of less than 10%.[26] Furthermore, abiraterone has a high melting point of 227.85°C and is weakly soluble in many organic solvents.[27] Given the observed problem with abiraterone acetate, only few works of solubility and dissolution enhancement are reported.[28-30] However, the reported research approaches employs use of organic solvents in the preparation of nanoparticles of the drug. This could thereby lead the possibility of residual solvent in the final formulation which can result into toxicity.

The goal of this study was to look into the formulation possibilities for abiraterone acetate nanosuspension employing high speed homogenization technique without involving organic solvents in the preparation process; for dissolution enhancement of the drug. The study was designed to observe the influence of process and formulation variables on mean particle size. Design of Experiment (DoE) was employed to optimize the formulation on statistical note. Furthermore, optimized formulation was lyophilized to nanocrystals, which was then characterized for SEM, XRD, and DSC studies. *In vitro* release studies were carried out. Accelerated stability studies for period of 6 months was conducted on the optimized nanocrystals of abiraterone acetate.

MATERIALS AND METHODS

Materials

Abiraterone acetate was a gift sample from Cadila Health care Ltd., Wagle Ind. Estate, Thane, India. Pluronic F68, Pluronic F127 and Soluplus were obtained from BASF Ltd., Mumbai, India. Polyvinyl Pyrolidone-PVP K30, PVP K90 and Polyvinyl Alcohol (PVA) were purchased from JRS Pharma, Mumbai, India. Polyethylene glycol-PEG 4000 and PEG-6000 were obtained from Thomas Baker, Mumbai, India. Tween 80 was purchased from Rajesh Chemicals, Vapi, India. Double distilled water was used throughout the experiment. All the ingredients obtained and used in the present investigation were of analytical grade.

Methods

Saturation solubility studies

Equilibrium solubility studies of drug was carried out using an environmental shaker. Briefly, 10 mg of drug was added in 25 mL of buffer media; 0.25% SLS+56.5 mM Monobasic Sodium Phosphate and the dispersion was shaken in the shaker at 25°C for 48 hr. Further, dispersion was filtered using 0.2 µ Whatman filter paper and analyzed spectrophotometrically at 267.20 nm for drug concentration. Analysis was carried out in triplicate and average result was noted.

Preparation of nanosuspension

Abiraterone acetate nanosuspension was prepared using a high-speed homogenizer (D-500; High Speed Homogeniser, Wiggens, Germany). Briefly, 100 mg of drug was added in 50 mL of water in presence of hydrophilic stabilizer and 0.1% w/v Tween-80 as wetting agent. The dispersion was homogenized at specific speed and for specific period of time. Formulated nanosuspension was stored at refrigerated condition until further use.

Screening of process and formulation variables

Various process and formulation variables were assessed for their influence on the performance of the nanosuspension. Process variables includes homogenization speed and homogenization time, while formulation variables included type and amount of hydrophilic stabilizer. Initially, stabilizer was scrutinized by preparing nanosuspension employing various hydrophilic stabilizers such as PVP K30, PVP K 90, PVA, PEG-4000, PEG-6000, Soluplus, Pluronic F68 and Pluronic F127 at concentration of 1% w/v. Further, scrutinized stabilizer was screened at various concentration such as 0.5, 1.0, 1.5, 2.0 and 2.5% w/v. Homogenization speed and time was kept constant to 15000 rpm and 30 min, respectively. Then, homogenization speed was assessed at various levels such as 12500, 15000 and 17500 rpm. Lastly, homogenization time was evaluated for 10, 20, 30 and 40 min. All the prepared batches were subjected for particle size analysis.

Application of Design of Experiments

On the basis of scrutinization trials, amount of stabilizer (X_1) and homogenization time (X_2) were selected as independent variables. Rotatable central composite design (3^2) was employed for the optimization of abiraterone acetate nanosuspension using Design Expert Version 13. Particle size (Y_1) and Polydispersity Index (PDI) (Y_2) were selected as dependent variables. The responses were evaluated using a statistical model that included interactive and polynomial elements.

$$Y=b_0+aX_1+bX_2+abX_1X_2+a^2X_1^2+b^2X_2^2 \text{ eq 1}$$

When Y is the dependent variable, b_0 is the nine-run arithmetic mean response, and bi is the factor X_1 calculated coefficient. The main effects of X_1 and X_2 shows the influence of increase or decrease of either of the factors on the responses. Further, the interaction effect i.e., X_1X_2 shows the change in response in relation to combined effect of independent variables. Optimized formulation was prepared from overlay plot employing the desirability function. Optimized batch was lyophilized and then obtained solid nanocrystals were subjected to characterization

studies such as SEM, XRD, and DSC, followed by 6 months accelerated stability study.

Evaluation of the prepared nanosuspension

Particle size, PDI and Zeta Potential

Nanosuspensions were evaluated for particle size, PDI and zeta potential employing Particle size analyzer (Malvern, UK). Briefly, sample was diluted 100 times with water and particle size measurement was carried out at room temperature.

In vitro drug release study

Drug release study was performed using 900 mL of 0.25%w/v SLS+56.5 mM Monobasic Sodium Phosphate Buffer as dissolution media, at speed of 50 rpm, temperature 37°C in USP II (Paddle) dissolution apparatus. Sample (5 mL) was collected at specific time period viz. 5, 10, 15, 30, 45 and 60 min. thereby, fresh media (5 mL) was added to maintain the sink condition. Sample was then filtered, diluted and analyzed spectrophotometrically at 267.2 nm for drug concentration. Study was carried out in triplicate and average result was noted.

Differential Scanning Calorimetry (DSC)

DSC analysis of abiraterone acetate and lyophilized nanocrystal of drug was carried out using Differential scanning calorimeter (Shimadzu-Model 60, India). Sample of about 5 mg was sealed in the aluminum pan and heated at rate of 5°C/min, under a nitrogen flow of 25 mL/min from temperature range of 25 to 150°C.

X-ray Diffraction studies (XRD) studies

X-ray diffraction studies was carried out to study the influence of nanosizing on crystallinity of drug. The analysis was conducted using X-ray diffractometer (Shimadzu-Model 6000, Japan). In a glass sample holder, the sample (drug/lyophilized nanocrystals) was placed and scanned from 5 to 40; at 30 mA and 40 kV.

Scanning Electron Microscopy (SEM) studies

Lyophilized nanocrystals were subjected to scanning electron microscopy analysis using Philips XL30 ESEM. Briefly, sample was dispersed in water and the dispersion was mounted on double-sided carbon tape, sputter coated with a thin layer of gold and observed for morphology.

Accelerated stability studies

Lyophilized nanocrystals were subjected for short term stability studies at accelerated conditions of 40 ± 2°C/75±5% RH for 6 months. Sample was stored in glass bottle and kept in stability chamber (Remi Instruments, India). Samples were evaluated at interval of 3 months for particle size, PDI, zeta potential and drug release analysis. Results were compared with the initial data using student *t*-test.

Table 1: Screening of process and formulation variables.

Screening parameter	Screening Levels	Particle size (nm)	PDI	Batch code
Type of stabilizer	PVPK30	348.13	0.56	N1
	PVP K90	431.25	0.31	N2
	PVA	267.91	0.67	N3
	PEG 4000	301.43	0.24	N4
	PEG 6000	519.52	0.23	N5
	Soluplus	150.32	0.12	N6
	Pluronic F68	163.84	0.14	N7
	Pluronic F127	165.48	0.16	N8
Amount of stabilizer (%w/v)	0.5	219.65	0.52	N9
	1	150.32	0.12	N10
	1.5	164.11	0.22	N11
	2	198.19	0.18	N12
	2.5	231.25	0.31	N13
Stirring speed (rpm)	12500	237.18	0.54	N14
	15000	150.32	0.12	N15
	17500	149.54	0.25	N16
Milling time (min)	10	211.56	0.23	N17
	20	208.94	0.20	N18
	30	150.32	0.12	N19
	40	150.93	0.18	N20

RESULTS

Saturation solubility study

Equilibrium solubility studies of abiraterone acetate was carried out in the dissolution media i.e., 0.25% SLS+56.5 mM Monobasic Sodium Phosphate buffer. Solubility of drug was observed to be 0.027±0.003 mg/mL.

Scrutinization of independent variables

Various nanosuspension batches were prepared for the selection of critical process and product variables for further optimization of formulation. Firstly, scrutinization of hydrophilic stabilizer was done from the pool of selected stabilizers. Particle size data of the prepared nanosuspension as shown in Table 1 suggested Soluplus as best hydrophilic stabilizer for the preparation of nanosuspension. Further investigation was carried out to check the influence of concentration change on the particle size of nanosuspension. Results from Table 1 demonstrated higher particle size at lower concentrations of stabilizer in nanosuspension. Likewise, higher particle size was observed at higher concentration of stabilizer. Later, impact of different homogenization speed was evaluated on the performance of nanosuspension in terms of particle size. From the results (Table 1), it was observed that as homogenization speed was increased, particle size was found to be decreased. However, there was no remarkable difference among the batches N15 and N16. Thus, homogenization speed of 15000 rpm was kept constant for further optimization process. Then, influence of milling time was investigated on the particle size of nanosuspension. Results (Table 1) exhibited decrease in particle size with increase in homogenization time. However, there was no remarkable difference in the particle size after 30 min of homogenization time.

Optimization of nanosuspension by DoE

The central composite design was used to generate parameters for subsequent trial runs based on the estimated optimized set of attributes. Table 2 lists the derived parameters and their matching experimental responses. Response surface plots including contour plots and 3d surface plots were produced to show interaction effects among variables on the response (Figure 1). The effects of amount of stabilizer (X_1) and homogenization time (X_2) on particle size (Y_1) are demonstrated to be opposite, with increase in homogenization time resulting in decreased particle size. Similarly, effects of X_1 and X_2 on PDI were observed to be opposite in nature. Zeta potential of design batches was found to in range of -11.23 to -15.91 mV. It was clear from the polynomial data that all primary variables, including X_1 and X_2, have a considerable impact on particle size. Positive sign of X_1 showed increase in value of particle size with increase in amount of stabilizer, while negative value of X_2 showed decrease in particle size with increase in homogenization time. Whereas X_1 and X_2 had negative sign showing decrease in PDI with increments in amount of stabilizer and homogenization time. The results of the multiple regression analysis as tabulated in Table 3 revealed that both factors influenced both dependent variables statistically significantly ($p<0.005$). Two-way ANOVA was used to determine the quantitative role of different amounts of each variable (Table 3). The dependent variable's correlation coefficient (R^2=0.9865 (Y_1) and 0.9810 (Y_2)) suggests a satisfactory fit of the mathematical model. The findings of the statistical analysis demonstrate that the independent variable has a considerable effect on dependent variable with $p<0.01$, hence reduce model was not generated.

Desirability constraints were kept minimum for both particle size and PDI. Desirability function of 0.948 was obtained with predicted values of 137.584 nm and 0.093 for particle size and PDI respectively (Figure 1). Optimized batch was prepared employing the obtained values of independent variables (Figure 1). Experimental results of optimized batch for particle size (140.25 nm) and PDI (0.09) were found to be in concordance with theoretical values with lower % relative error of 1.74 and 3.22 respectively. Zeta potential of optimized batch was found to be -14.32 mV.

Table 2: Responses of design batches.

Batch	Amount of stabilizer (%w/v) X_1	Milling time (min) X_2	Particle size (nm) Y_1	PDI Y_2	Zeta Potential (mV)
AN1	-1.41421	0	204.57	0.27	-15.91
AN2	1	-1	201.11	0.19	-11.46
AN3	-1	1	150.32	0.12	-15.24
AN4	-1	-1	211.56	0.23	-14.59
AN5	0	1.41421	137.15	0.08	-13.76
AN6	1	1	198.19	0.18	-11.23
AN7	1.41421	0	215.93	0.24	-12.55
AN8	0	-1.41421	187.54	0.15	-14.65
AN9	0	0	152.18	0.13	-13.98

In vitro drug release study

In terms of cumulative percentage release, an optimized batch of nanosuspension was compared to a pure drug coarse suspension. *In vitro* drug release profile is shown in Figure 2. The graph suggested that drug release was remarkably increased by preparing nanosuspension of the pure drug. This could be attributed to nano-size of drug particles in nanosuspension along with a hydrophilic stabilizer assisting in amelioration of drug dissolution.[23,31] In addition, parameters like f_1 and f_2 were calculated; non similarity of *in vitro* release profile of drug nanocrystals was obtained as compared to its pure form with f_1 value higher than 15 and f_2 value lower than 50.[32]

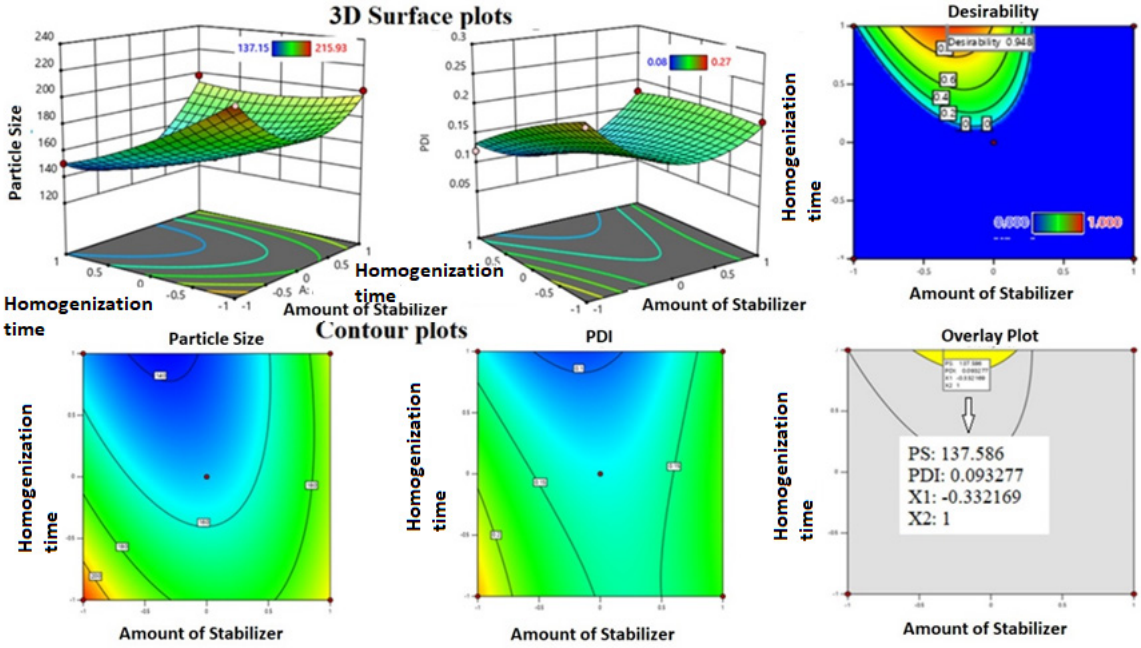

Figure 1: Graphs showing Response Surface plot: 3D Surface plots and Contour plots; Desirability function and overlay plot.

Table 3: Multiple Regression Analysis and ANOVA.

Term	Coefficient for Y_1	*P* value	Coefficient for Y_2	*p* value
X_1	6.69	0.0439	-0.0028	0.6120
X_2	-16.93	0.0034	-0.0274	0.0118
X_1X_2	14.58	0.0140	0.0250	0.0379
X_1^2	30.03	0.0028	0.0612	0.0050
X_2^2	6.08	0.1629	-0.0087	0.3661
R^2 value	0.9865		0.9810	

ANOVA					
Source of variation	Degree of Freedom	Sum of Squares	Mean Square	F Value	*p* Value
Particle size (Y_1)					
Regression	5	6954.63	1390.93	43.80	0.0053
Residual	3	95.27	31.76		
Total	8	7049.90			
PDI (Y_2)					
Regression	5	0.0306	0.0061	31.01	0.0087
Residual	3	0.0006	0.0002		
Total	8	0.0312			

Differential Scanning Calorimetry (DSC)

DSC analysis of pure drug and lyophilized nanocrystals were carried out to characterize thermal transitions of drug. Figure 3a shows melting point of pure drug at 144.52°C. DSC thermogram (Figure 3b) of lyophilized nanocrystal depicted drug peak at 143.26°C with reduced intensity.[33]

X-ray Diffraction (XRD)

Figure 4 depicts X-ray diffraction patterns of pure drug and lyophilized nanocrystals of abiraterone acetate. The Figures 4a, 4b depicted variations in the crystal structure of the drug. The X-ray patterns of the pure drug exhibited the existence of number of distinct peaks at 5.833°, 12.071°, 14.840°, 15.113°, 17.229° and 21.696°, suggesting crystalline nature of drug.[34] Nanocrystals showed similar peaks but with lower intensity suggesting decrease in crystalline nature of drug leading faster dissolution rate.[35]

Scanning Electron Microscopy (SEM)

SEM image of pure drug and lyophilized nanocrystal is shown in Figure 5. SEM images of nanosuspension formulation demonstrated a change in the look of the surface after the nanosuspension was created. Particle size of drug is reduced in nano-crystallization.

Accelerated Stability Studies

The formulation revealed no significant differences in particle size, PDI, zeta potential, or *in vitro* drug release results after completing the 6-months accelerated stability trial. There was no substantial change in nanosuspension stability, as observed values were in concordance with the initial values (Table 4).

DISCUSSION

Nanosuspension prepared using Soluplus as hydrophilic stabilizer exhibited smaller particle size as compared to other stabilizers. Further, concentration of Soluplus was varied for the preparation of nanosuspension to check the impact on particle size. Table 2 shows that lower stabilizer concentrations resulted in larger particle sizes in nanosuspension. This could be due to an insufficient amount of stabilizer being used to nano-size the medication particles. Similarly, with higher stabilizer concentrations, larger particles were detected, which could be attributable to an increase in dispersion viscosity, resulting in more friction for homogenization. The homogenization speed and homogenization time were examined to find their influence on particle size of nanosuspension. Initially speed was kept 12500 rpm followed by increment of 2500 rpm for other batches. Particle size reduction was observed with increase in the homogenization speed. However, no significant decrease in particle size was

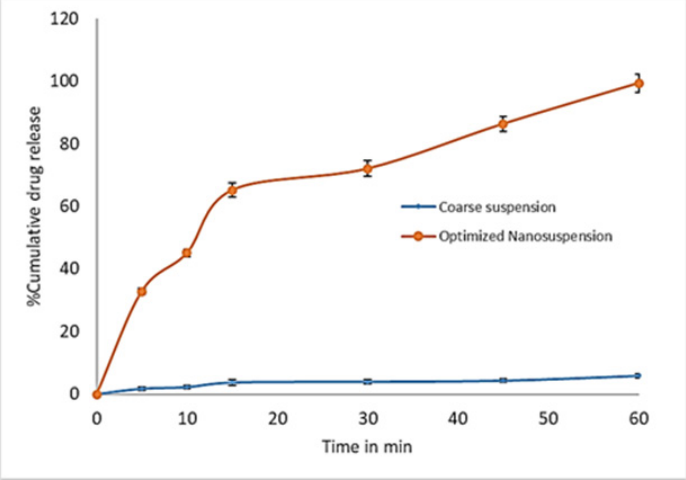

Figure 2: Dissolution profile of optimized nanosuspension and coarse suspension containing abiraterone acetate.

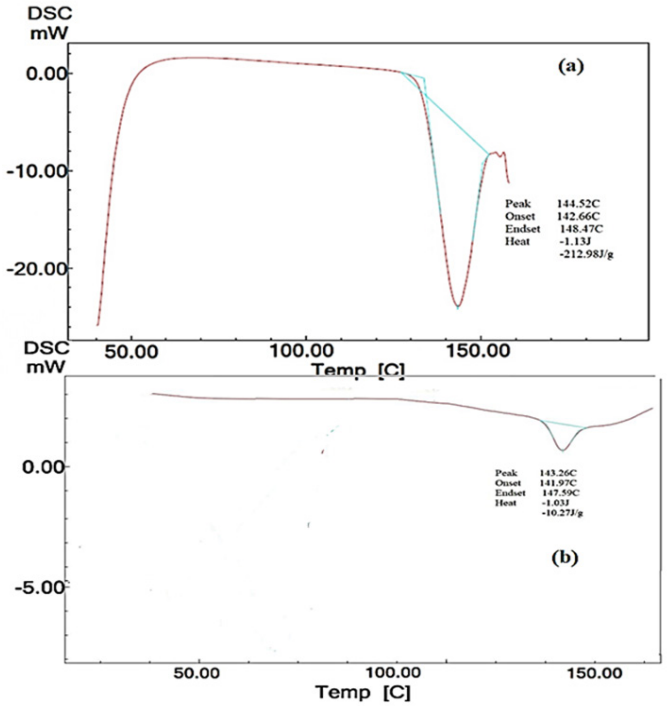

Figure 3: DSC thermograms (a) Pure drug and (b) Lyophilized nanocrystal.

Table 4: Accelerated stability studies.

Time (month)	Particle size (nm)	PDI	Zeta Potential (mV)	Drug release at 60 min (%)
0	140.25	0.09	-15.27	99.55±1.16
3	140.63	0.10	-15.11	98.27±0.91
6	140.98	0.11	-15.16	99.31±1.03

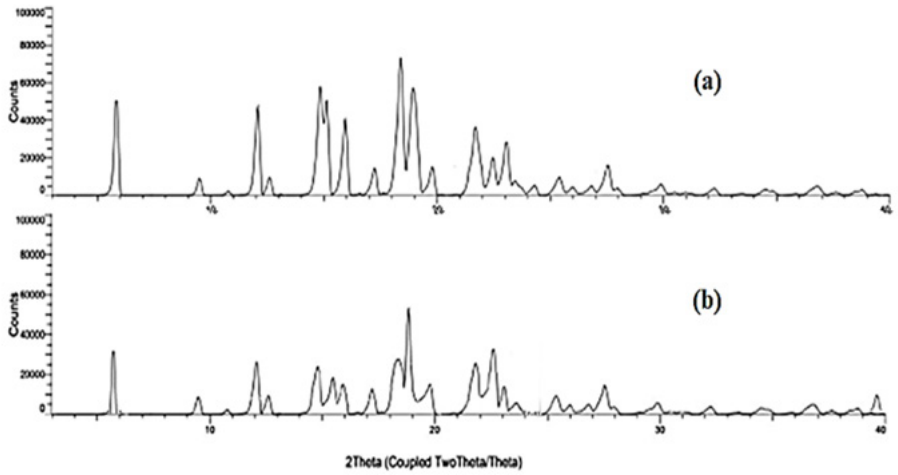

Figure 4: XRD graphs (a) pure drug and (b) lyophilized nanocrystals.

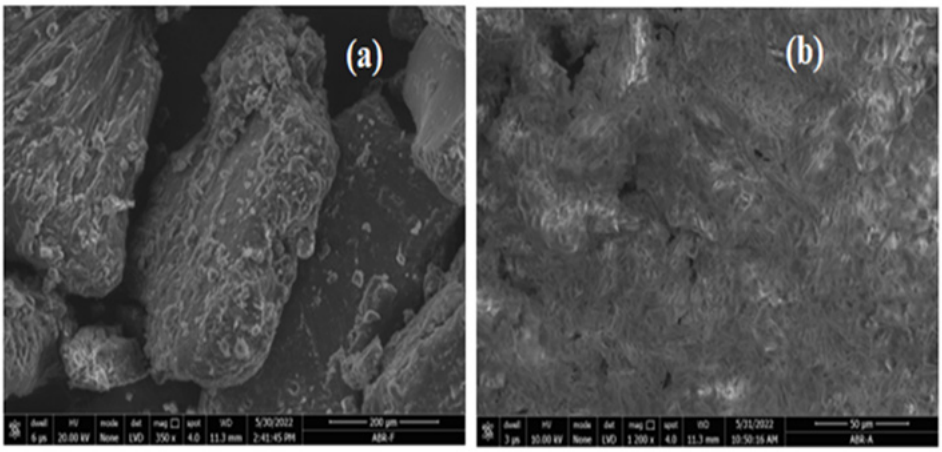

Figure 5: SEM graphs (a) pure drug and (b) lyophilized nanocrystals.

observed after 15000 rpm. Then, milling time was varied from 10, 20, 30 and 40 min. Particle size of nanosuspension was reduced with increase in homogenization time. However, no significant decrease in particle size was observed after 30 min homogenization. From the scrutinization trials, two independent variables viz. amount of stabilizer and homogenization time were selected for further optimization process. Central composite design was employed for the optimization of nanosuspension. Particle size and PDI were taken as independent variables.

Design batches showed strong influence of independent variables on responses. Zeta potential of design batches was found to in range of -11.23 to -15.91 mV. It was clear from the polynomial data that all primary variables, including X_1 and X_2, have a considerable impact on particle size. Positive sign of X_1 showed increase in value of particle size with increase in amount of stabilizer, while negative value of X_2 showed decrease in particle size with increase in homogenization time. Whereas X_1 and X_2 had negative sign showing decrease in PDI with increments in amount of stabilizer and homogenization time. The findings of the statistical analysis demonstrate that the independent variable has a considerable effect on dependent variable with $p<0.01$, hence reduce model was not generated. The desirability function was used to perform statistical optimization for dependent variables i.e., Y_1-Particle size and Y_2-PDI. A low percentage error (less than 5%) suggests that the theoretical and actual values are in concordance. It also demonstrates the mathematical model's resilience of formulation and excellent predictive power.

In vitro drug release of nanosuspension illustrated enhanced drug dissolution rate as compared to pure drug coarse suspension. This could be attributed to increase surface area due to nano-size of particles. In addition, presence of hydrophilic stabilizer also contributed dissolution enhancement of drug from prepared nanosuspension. Further the optimized nanosuspension was converted to solid form employing lyophilization technique using mannitol as cryoprotectant in ratio of 1:1. The obtained lyophilized nanocrystals were further characterized for DSC, XRD and SEM analysis. DSC thermogram indicated decreased in intensity of drug peak in the formulation. XRD graph showed

decreased in drug crystalline peaks in the formulation. This demonstrates decrease in drug crystallinity which could thereby be responsible for the dissolution enhancement of drug. SEM graphs showed amalgamation of drug in hydrophilic stabilizer which could also be responsible improvement in drug release. Lastly, accelerated stability studies were carried out for 6 months period. Particle size, PDI, Zeta Potential and Drug release analysis was done. Results indicated stability of formulation.

CONCLUSION

Abiraterone acetate nanosuspension was prepared using high speed homogenization method. Various process and formulation variables were screened for further optimization process. Central composite design was employed for optimization of formulation. The optimized nanosuspension had particle size of 140.25 nm and PDI of 0.09. Nanosized abiraterone acetate dissolves at faster rate than its coarser form. Characterization studies exhibited decrease in drug crystallinity. Accelerated stability studies concluded stability of formulation for period of 6 months.

ACKNOWLEDGEMENT

Authors are thankful to the management for providing the requisite facilities to complete this research work. Authors acknowledge Cadila Health Care Ltd., Wagle Ind. Estate, Thane, India for providing gift sample of abiraterone acetate.

CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

ABBREVIATIONS

DoE: Design of Experiments; **DSC:** Differential Scanning Calorimetry; **XRD:** X-ray Diffraction; **PDI:** Polydispersity index; **BCS:** Biopharmaceutical Classification System; **SEM:** Scanning Electron Microscopy; **PVP:** Polyvinyl pyrrolidone; **PVA:** Polyvinyl alcohol; **PEG:** Polyethylene glycol; **Rpm:** Rotation per minute.

REFERENCES

1. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. Int J Pharm. 2011;420(1):1-10. doi: 10.1016/j.ijpharm.2011.08.032, PMID 21884771.
2. Papich MG, Martinez MN. Applying Biopharmaceutical Classification System (BCS) criteria to predict oral absorption of drugs in dogs: challenges and pitfalls. AAPS J. 2015;17(4):948-64. doi: 10.1208/s12248-015-9743-7, PMID 25916691.
3. Boyd BJ, Bergström CAS, Vinarov Z, Kuentz M, Brouwers J, Augustijns P, *et al.* Successful oral delivery of poorly water-soluble drugs both depends on the intraluminal behavior of drugs and of appropriate advanced drug delivery systems. Eur J Pharm Sci. 2019;137:104967. doi: 10.1016/j.ejps.2019.104967, PMID 31252052.
4. Paul A. Drug absorption and bioavailability. In: Raj G, Raveendran R, editors. editors Introduction to basics of pharmacology and toxicology. Singapore: Springer; 2019.
5. Jain S, Patel N, Lin S. Solubility and dissolution enhancement strategies: current understanding and recent trends. Drug Dev Ind Pharm. 2015;41(6):875-87. doi: 10.3109/03639045.2014.971027, PMID 25342479.
6. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012; 2012:195727. doi: 10.5402/2012/195727, PMID 22830056.
7. Dizaj SM, Vazifehasl Zh, Salatin S, Adibkia Kh, Javadzadeh Y. Nanosizing of drugs: effect on dissolution rate. Res Pharm Sci. 2015;10(2):95-108. PMID 26487886.
8. Samie A, Desiraju GR, Banik M. M. Salts and cocrystals of the antidiabetic drugs gliclazide, tolbutamide, and glipizide: solubility enhancements through drug–conformer interactions. Cryst Growth Des. 2017;17(5):2406-17. doi: 10.1021/acs.cgd.6b01804.
9. Alshehri S, Imam SS, Hussain A, Altamimi MA, Alruwaili NK, Alotaibi F, *et al.* Potential of solid dispersions to enhance solubility, bioavailability, and therapeutic efficacy of poorly water-soluble drugs: newer formulation techniques, current marketed scenario and patents. Drug Deliv. 2020;27(1):1625-43. doi: 10.1080/10717544.2020.1846638, PMID 33207947.
10. Semalty A. Cyclodextrin and phospholipid complexation in solubility and dissolution enhancement: A critical and meta-analysis. Expert Opin Drug Deliv. 2014;11(8):1255-72. doi: 10.1517/17425247.2014.916271, PMID 24909802.
11. Patel H, Pandey N, Patel B, Ranch K, Bodiwala K, Vyas B. Enhancement of *in vivo* hypoglycemic effect of gliclazide by developing self microemulsifying pellet dosage form. Future J Pharm Sci. 2020;6(1):17. doi: 10.1186/s43094-020-00034-0.
12. Muzafar W, Kanwal T, Rehman K, Perveen S, Jabri T, Qamar F, *et al.* Green synthesis of iron oxide nanoparticles using *Melia azedarach* flowers extract and evaluation of their antimicrobial and antioxidant activities. J Mol Struct. 2022; 1269:133824. doi: 10.1016/j.molstruc.2022.133824.
13. Borkhataria C, Patel D, Bhagora S, Patel N, Patel K, Manek R. Study of homogenization on media milling time in preparation of irbesartan nanosuspension and optimization using design of experiments (DoE). Futur J Pharm Sci. 2020;6(1):87. doi: 10.1186/s43094-020-00105-2.
14. Jacob S, Nair AB, Shah J. Emerging role of nanosuspensions in drug delivery systems. Biomater Res. 2020;24:3. doi: 10.1186/s40824-020-0184-8, PMID 31969986.
15. Sattar A, Chen D, Jiang L, Pan Y, Tao Y, Huang L, *et al.* Preparation, characterization and pharmacokinetics of cyadox nanosuspension. Sci Rep. 2017;7(1):2289. doi: 10.1038/s41598-017-02523-4, PMID 28536446.
16. Sinha B, Müller RH, Möschwitzer JP. Bottom-up approaches for preparing drug nanocrystals: formulations and factors affecting particle size. Int J Pharm. 2013;453(1):126-41. doi: 10.1016/j.ijpharm.2013.01.019, PMID 23333709.
17. Gigliobianco MR, Casadidio C, Censi R, Di Martino P. Nanocrystals of poorly soluble drugs: drug bioavailability and physicochemical stability. Pharmaceutics. 2018;10(3):134. doi: 10.3390/pharmaceutics10030134, PMID 30134537.
18. Junyaprasert VB, Morakul B. Nanocrystals for enhancement of oral bioavailability of poorly water-soluble drugs. Asian J Pharm Sci. 2015;10(1):13-23. doi: 10.1016/j.ajps.2014.08.005.
19. Bose S, Schenck D, Ghosh I, Hollywood A, Maulit E, Ruegger C. Application of spray granulation for conversion of a nanosuspension into a dry powder form. Eur J Pharm Sci. 2012;47(1):35-43. doi: 10.1016/j.ejps.2012.04.020, PMID 22565066.
20. Ma YQ, Zhang ZZ, Li G, Zhang J, Xiao HY, Li XF. Solidification drug nanosuspensions into nanocrystals by freeze-drying: a case study with ursodeoxycholic acid. Pharm Dev Technol. 2016;21(2):180-8. doi: 10.3109/10837450.2014.982822, PMID 25427602.
21. Melzig S, Niedbalka D, Schilde C, Kwade A. Spray drying of amorphous ibuprofen nanoparticles for the production of granules with enhanced drug release. Colloids Surf Physicochem Eng. 2018;536:133-41. doi: 10.1016/j.colsurfa.2017.07.028.
22. hang X, Guan J, Ni R, Li LC, Mao S. Preparation and solidification of redispersible nanosuspensions. J Pharm Sci. 2014;103(7):2166-76. doi: 10.1002/jps.24015, PMID 24840928.
23. Butler EN, Kelly SP, Coupland VH, Rosenberg PS, Cook MB. Fatal prostate cancer incidence trends in the United States and England by race, stage, and treatment. Br J Cancer. 2020;123(3):487-94. doi: 10.1038/s41416-020-0859-x, PMID 32433602.
24. Cheong EJY, Nair PC, Neo RWY, Tu HT, Lin F, Chiong E, *et al.* Slow-, tight-binding inhibition of CYP17A1 by abiraterone redefines its kinetic selectivity and dosing regimen. J Pharmacol Exp Ther. 2020;374(3):438-51. doi: 10.1124/jpet.120.265868, PMID 32554434.
25. Rehman Y, Rosenberg JE. Abiraterone acetate: oral androgen biosynthesis inhibitor for treatment of castration-resistant prostate cancer. Drug Des Dev Ther. 2012;6:13-8. doi: 10.2147/DDDT.S15850, PMID 22291466.
26. Schultz HB, Meola TR, Thomas N, Prestidge CA. Oral formulation strategies to improve the bioavailability and mitigate the food effect of abiraterone acetate. Int J Pharm. 2020;577:119069. doi: 10.1016/j.ijpharm.2020.119069, PMID 31981706.
27. Solymosi T, Tóth F, Orosz J, Basa-Dénes O, Angi R, Jordán T, *et al.* Solubility measurements at 296 and 310 K and physicochemical characterization of abiraterone and abiraterone acetate. J Chem Eng Data. 2018;63:4453-8. doi: 10.1021/acs.jced.8b00566.
28. Gala U, Miller D, Williams RO 3rd. Improved dissolution and pharmacokinetics of abiraterone through KinetiSol® enabled amorphous solid dispersions. Pharmaceutics. 2020;12(4):357. doi: 10.3390/pharmaceutics12040357, PMID 32295245.
29. Schultz HB, Wignall AD, Thomas N, Prestidge CA. Enhancement of abiraterone acetate oral bioavailability by supersaturated-silica lipid hybrids. Int J Pharm. 2020;582:119264. doi: 10.1016/j.ijpharm.2020.119264, PMID 32278053.
30. Yang Z, Yang Y, Xia M, Dai W, Zhu B, Mei X. Improving the dissolution behaviors and bioavailability of abiraterone acetate via multicomponent crystal forms. Int J Pharm. 2022;614:121460. doi: 10.1016/j.ijpharm.2022.121460, PMID 35026315.
31. Aghrbi I, Fülöp V, Jakab G, Kállai-Szabó N, Balogh E, Antal I. Nanosuspension with improved saturated solubility and dissolution rate of cilostazol and effect of

solidification on stability. J Drug Deliv Sci Technol. 2021;61:102165. doi: 10.1016/j.jddst.2020.102165.

32. Sahu BP, Das MK. Nanosuspension for enhancement of oral bioavailability of felodipine. Appl Nanosci. 2014;4(2):189-97. doi: 10.1007/s13204-012-0188-3.
33. Maleki A, Hamidi M. Dissolution enhancement of a model poorly water-soluble drug, atorvastatin, with ordered mesoporous silica: comparison of MSF with SBA-15 as drug carriers. Expert Opin Drug Deliv. 2016;13(2):171-81. doi: 10.1517/17425247.2015.1111335, PMID 26636904.
34. Wheatley AM, Kaduk JA, Gindhart AM, Blanton TN. Crystal structure of abiraterone acetate (Zytiga), C26H33NO2. Powder Diffr. 2018;33(1):72. doi: 10.1017/S0885715618000015.
35. Kassem MAA, 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;18(4):983-96. doi: 10.1208/s12249-016-0604-1, PMID 27506564.

Cite this article: Rajendra P, Komal P. Amelioration of Dissolution Properties of Abiraterone Acetate via Nano-Sizing Employing High-Speed Homogenization Technique: An Optimization Study. Indian J of Pharmaceutical Education and Research. 2024;58(1s):s158-s166.