Available online on www.ijddt.com
International Journal of Drug Delivery Technology 2016; 6(4); 142-150

ISSN: 0975 4415

Research Article

Evaluation of Formulation Parameters for Development of Aceclofenac Nanosuspension Using Doe Statistical Tool

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Available Online: 1st December, 2016

ABSTRACT
The objective of present study was to identify and evaluate formulation variables affecting characteristics of nanosuspension formulations. Full factorial design experimental methodology was used for development of aceclofenac nanosuspension. Formulation factors evaluated were drug to polymer (Polyvinyl alcohol) ratio, amount of surfactant (Sodium dodecyl sulphate) relative to drug and solvent employed for carrying the drug. Total 18 formulations were prepared and their saturation solubility in distilled water and z average particle size were regarded as responses in this study. The response surface methodology utilizing polynomial equation was used to quantify the effect of each formulation variables. All three variables exerted significant effect on particle size and saturation solubility. Optimized nanosuspensions were obtained using numerical optimization technique by the desirability approach. The optimum formulation parameters were found to be 400% w/w of drug to polymer ratio and 7.5% w/w of amount of SDS for both solvents. The best optimized formulation obtained from ethanol showed significantly improved saturation solubility 255.39 µg/ml, particle size 477.7 nm and better dissolution efficiency (DE_{05}) 59.77%. The absence of interactions between drug and polymers was confirmed by Fourier transform infrared (FTIR) spectroscopy. The results demonstrated that polyvinyl alcohol was successfully employed for the development of nanosuspension of aceclofenac with higher dissolution efficiency leading to better oral bioavailability.

Keywords: Nanosuspension; Factorial design; Design of experiment.

INTRODUCTION

Aceclofenac (AC), a phenyl acetic acid derivative, [[[2-[(2,6-Dichlorophenyl) amino] phenyl] acetyl] oxy] acetic acid is a non-steroidal anti-inflammatory drug (NSAID) indicated for the symptomatic treatment of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondilytis[1]. It falls in BCS-II class as it has good permeability and low dissolution that causes its oral bioavailability depending on its dissolution rate in gastro intestinal tract[2]. Therefore, oral bioavailability and therapeutic efficacy may be improved by enhancing its solubility and dissolution rate. There are various approaches[3-5] to improve the dissolution behavior but particle diminution to the submicron range is a new formulation approach to increase the saturation solubility, dissolution rate and in turn to enhance the oral bioavailability of poorly soluble drugs[6]. The nanosized particles of poorly water soluble drugs can have a remarkable effect on performance in terms of bioavailability enhancement, food effects elimination and dose escalation. It can result in improving efficacy and safety. Inter-subject variations in pharmacokinetic behavior of oral dosage forms could also be reduced by nanosizing of drug particles[7]. Nanosuspension can be fabricated either by top-down or bottom-up processes. The top-down process involves particle size reduction of large drug particles into smaller particles using various techniques such as media milling, micro-fluidization and high pressure homogenization. However, all these processes require high energy input so are highly inefficient. In addition to these conventional methods, controlled crystallization is a novel and promising method which provide an opportunity to produce highly pure crystalline drugs with narrow size distribution and desirable morphology[8]. In the bottom-up approach, the drug is dissolved in an organic solvent and is then precipitated on addition of an antisolvent in the presence of a stabilizer. The precipitation method results in smaller size and homogenous particles[9,10]. There are number of variables which affect physical properties of nanosuspensions during precipitation process. These effects are interdependent and governed by nature of materials and process parameters as well. Stabilizers play a very important role in controlling the particle growth during precipitation and later increasing the stability of system by preventing Ostwald ripening. Hydrophilic polymers have been found to be efficient to stabilize nanoparticle formulations[11]. Surfactant may assist these

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polymeric stabilizers in controlling particle growth and stabilization process[12]. There are some reports suggesting the effect of nature of organic solvent on size of the precipitated particles due to relative diffusion rates of polymer and drug molecules towards the solid–liquid interface[13]. In the present work an attempt was made to prepare nanosuspension stabilized by poly vinyl alcohol. Another objective was to evaluate the effects of drug to polymer ratio, amount of surfactant relative to drug and different organic solvents on characteristics of aceclofenac nanosuspension. A design of experiment (DoE) with 3^2 full factorial design was utilized to evaluate the effect of critical formulation variables and their interactions involved during nano precipitation of aceclofenac.

MATERIALS AND METHOD

Materials

Aceclofenac was a generous gift from INTAS Pharmaceuticals Limited, Selaqui, Dehradun (India). Polyvinyl alcohol (Mw: 14000 approx., viscosity 4% w/v aqueous solution: 4-6 cps at 20 °C), sodium dodecyl sulphate (Mw: 288.38, HLB value ≈ 20, critical miceller concentration: 8.2 mmol/L at 25 °C) were purchased from CDH (P) ltd, New Delhi (India). Ethanol (absolute) and acetone were purchased from Qualigens Fine Chemicals, Mumbai (India). All chemicals used were of analytical grade.

Design of Experiment (DoE)

Design of experiment was used to study the correlation between the independent variables and the responses, to assess the interaction effect of compositional variation, and to optimize the nanosuspension drug delivery system of aceclofenac[14]. There may be number of parameters to be controlled during precipitation process by solvent-antisolvent method. Preliminary experiments were carried out to recognize potential process variables before designing the experiment. The levels of formulation variables were also screened using these preliminary experiments. Drug to polymer ratio and amount of SDS were evaluated at three concentration levels. Particle size and viscosity of solution were found to be restrictive factors in selection of level of formulation parameters. The variables selected are shown in Table 1 along with their low, medium and high levels. A full factorial design was employed for response surface methodology (RSM). The experimental design space consisted of 18 experiments with two numeric factors (Drug to polymer ratio, amount of SDS relative to drug) at three levels and a category factor (solvent) at two levels. Other variables (immersion depth of sonication horn, volume of antisolvent, solvent addition time, sonication time, power and temperature of sonication) were kept constant to minimize fluctuations. Design expert 9.0.4.1 (Stat-ease Inc., Minneapolis, MN) was utilized to design and analyze DoE results.

Preparation of nanosuspension

Aceclofenac nanosuspension was prepared by precipitation-ultrasonication method[15]. Two batches (batch-I and II) were prepared using ethanol and acetone as organic solvents respectively. Drug was dissolved in organic solvent (either ethanol or acetone) and added drop wise (rate of addition: 1 ml/min) to aqueous solution of PVA containing a range of amount of SDS. Simultaneously sonication was applied (magnitude: 150w, pulse: 3s, probe: 6ϕ) for 5 minutes using probe sonicator (LARK, India), keeping position of probe at 2 cm from bottom. Concentration of polymer was fixed and drug amount was varied so as to get various drug to polymer ratio (D/P ratio). Drug crystals resulted were centrifuged (eltek, Microspin TC 4815 D centrifuge) at 15000 rpm for 10 minutes and re dispersed with aid of sonication in solution of stabilizers having same composition from which they were prepared. Temperature of system was maintained below ~10 °C throughout experiment.

Particle size analysis

Particle size analysis was performed using Malvern Nano Zetasizer (Malvern Instruments, Worcestershire, UK) based on photon correlation spectroscopy. It yielded the mean diameter of the bulk population (*z*-average) and the polydispersity index (PI) as a measure for the width of the size distribution. All nanosuspension samples were analyzed in their original solvent media. Sample was taken in disposable cuvette and placed in sample holder of the instrument. All measurements were carried out at 25 °C. The particle size data was reported as z-average particle size and used for modeling of design of experiment.

Saturation solubility of nanosuspension

An excess quantity of sample was placed in the bottles containing 10 ml distilled water. The bottles were agitated in a shaking water bath (100 agitations /min) for 24 hat room temperature[16]. The solution was then centrifuged at 15000 rpm for 10 minutes. Supernatant was filtered and analyzed spectrophotometrically at 273.8 nm after suitable dilution with distilled water. All solubility measurements were performed three times and average values were used for modeling of design of experiment.

In vitro dissolution

In vitro dissolution of pure drug and optimized nanosuspensions from each batch were carried using six station USP dissolution apparatus (Veego mech., Model DA: 6D) type II (paddle method). 900 ml distilled water (pH 6.8) at 37±0.5 °C was used as a dissolution medium to discriminate the dissolution rate of different formulations. Pure drug, P-2-II and P-5-II were subjected to dissolution in distilled water as dissolution media. Rotation speed of the paddle was 50 rpm. At predetermined time intervals, 5.0 ml sample was withdrawn and replaced with an equivalent amount of fresh medium to maintain a constant dissolution volume. The amount of dissolved drug was analyzed spectrophotometrically at 273.8 nm.

FTIR spectroscopy

FTIR spectra were recorded using the instrument Bruker, Alpha, FT-IR. Sample was ground, mixed thoroughly with potassium bromide for 3-5 minute in a mortar and compressed into disc by applying a pressure of 5 tons for 5 minute in hydraulic press. Samples were analyzed in the frequency range of 400-4000 cm^{-1} with the resolution of 4 cm^{-1}.

RESULTS AND DISCUSSION

Particle size analysis

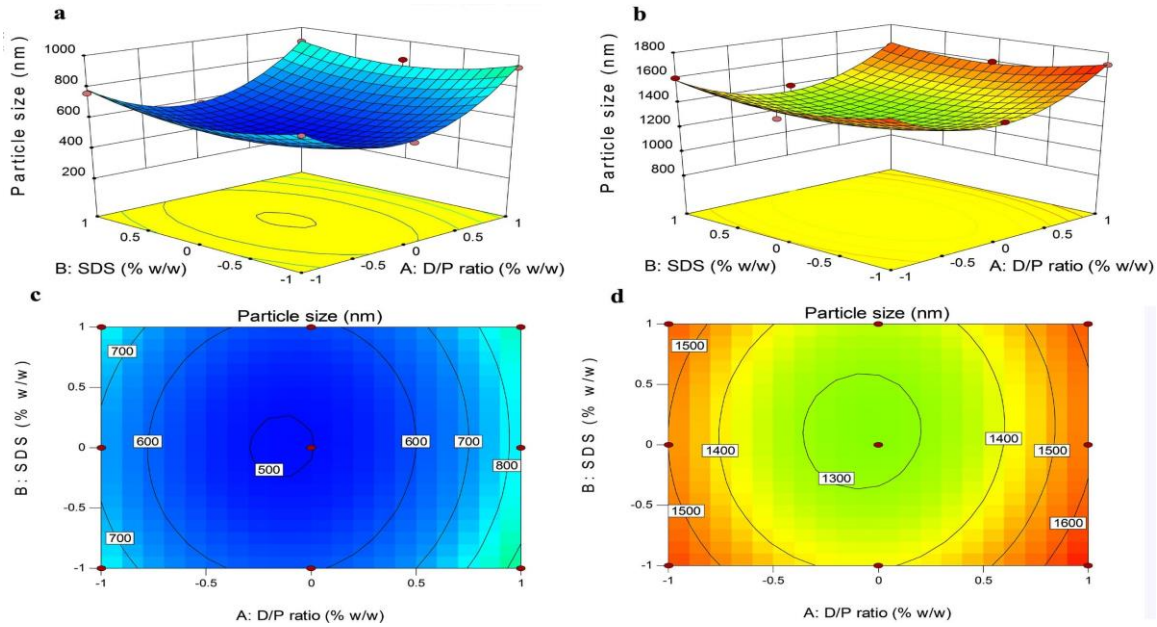

Figure 1: Response surface plots and contour plots showing effect of variables on particle size of nanosuspensions obtained from ethanol (a and c) and acetone (b and d).

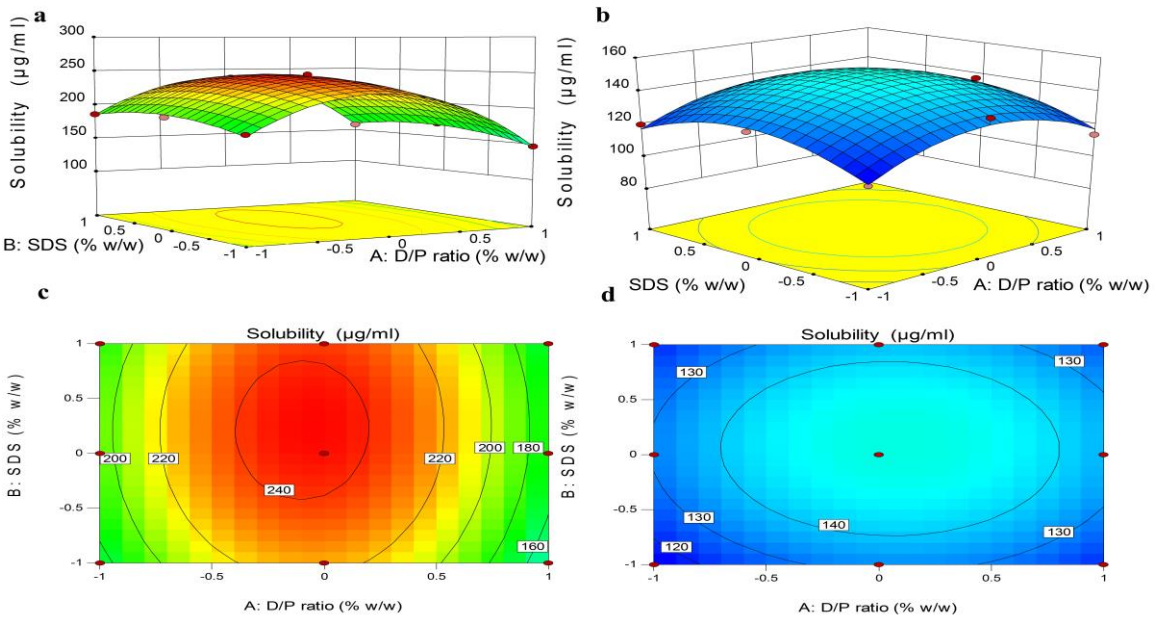

Figure 2: Response surface plots and contour plots showing effect of variables on solubility of nanosuspensions obtained from ethanol (a and c) and acetone (b and d).

Particle size (z average) of all nanosuspension formulations are represented in Table 2. Nanosuspensions were obtained with a broad range of particle size. Particles obtained using ethanol showed the least particle size among all the formulations.

Saturation solubility of nanosuspension

Saturation solubility of aceclofenac in distilled water was found to be 63.76 µg/ml. Nanosuspensions observed a marked increase in saturation solubility. All the nanosuspensions showed a significant enhancement in solubility in distilled water. Nanosuspensions obtained using ethanol exhibited the higher solubility in distilled water among all the formulations. Table 2 displayed the average saturation solubility of all the formulations.

Effect of formulation variables on particle size

A statistical design models including linear, factor interaction, modified, quadratic and cubic terms were generated for the response variable using multiple regression analysis approach[17]. On analyzing the data of all 18 formulations various polynomial equations, response surface and contour plots were generated. It was observed that all of the formulations didn't succeed to yield particles under 1 µm size. The responses obtained were evaluated by multiple regression analysis and F-statistic to identify

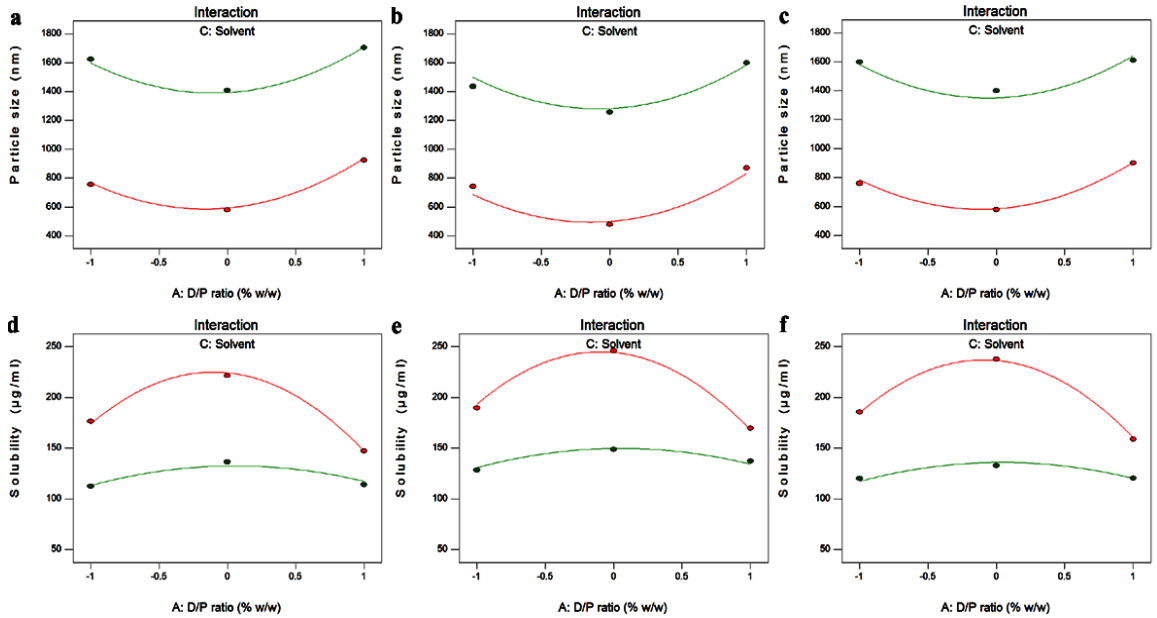

Figure 3: Interaction of solvent with D/P ratio for particle size (a-c) and solubility (d-f) when amount of SDS was kept at low (left), middle (middle) and higher (right) level. (— Acetone, — Ethanol)

statistically significant terms. All the variables are fitted to polynomial equation of quadratic model and ANOVA analysis was performed to find out significant factors. The coefficients of independent variables and p-values of probability>F are given in Table 3. The magnitude of coefficients and the mathematical sign it carries were used to identify the relative impact of the factors and their interaction. Model F-value of 223.21 ($p< 0.0001$) implies that the model is significant. Values of "Prob > F" less than 0.05 indicate model terms are significant. From coefficient table, it was observed that factors X_1, X_3 and X_1^2, X_2^2 had significant effect on the dependent variable. Coefficient of X_1 carried positive sign indicating positive effect of D/P ratio on particle size. Smaller particle size was obtained at low D/P ratio. Factor X_2 was found to be insignificant and its interaction terms were also insignificant. X_3 showed the highest effect with positive value indicating positive effect of solvent on aceclofenac nanosuspension i.e. ethanol produced smaller particle size compared to acetone. Contour and response surface graphs illustrated the effects of X_1 and X_2 on size of particles obtained through ethanol and acetone (Figure 1). Both variables showed nonlinear effect on particle size. Increase in value of X_1 from low (-1) to middle (0) level yielded low particle size and it showed a rise in particle size when value of X_1 was increased from middle (0) to high (+1) level. Particle size also showed nonlinearity with concentration of SDS although it was very less compared to X_1. Nonlinearity was also depicted by significant X_1^2 and X_2^2 factor in model design.

Effect of formulation variables on solubility

All the variables are fitted to polynomial equation of reduced cubic model and ANOVA analysis was performed to find out significant factors. The coefficients of independent variables and p-values of probability>F are given in Table 3. X_1, X_2, X_3, X_1X_3 and X_1^2, X_2^2, $X_1^2X_3$ are found to be significant parameters. D/P ratio, concentration of SDS and solvents significantly affected the response (solubility). D/P ratio inversely affected solubility. Solubility of nanosuspension was varied positively with concentration of SDS. X_3 showed the highest effect with negative value indicating negative effect of solvent on aceclofenac nanosuspension as ethanol produced particle with higher solubility compared to acetone. Solubility depends on the size as well as wettability of particles. Surfactant and hydrophilic polymers adsorbed over particle surface, aid in the wetting behavior of particles. Here solvent played a great role to aid the hydrophilic polymer to get adsorbed over surface particle at the time of precipitation. Both solvents showed a great variation in particle size and solubility of nanosuspension when PVA was used as a stabilizer for nanosuspension. The effects of X_1 and X_2 on response by contour plots and response surface graphs are shown in Figure 2 for particles obtained through ethanol and acetone. 3D surface graphs and contour plots clearly revealed the great effect of solvents on solubility of nanosuspension. Graph for ethanol is situated at greater height compared to that for acetone showing a positive effect of ethanol on solubility. Particles obtained through ethanol showed better solubility in water as compared to particles obtained through acetone. In case of ethanol, middle level of X_1 gave highest solubility at all the 3 levels of X_2 which indicated that X_1 had great effect on solubility. But in case of acetone, solubility seems to be consistent with change in D/P value. SDS was proved to be an important factor affecting solubility of nanosuspension in both cases. Circular area of maximum solubility value was found in the middle of both contour graphs revealing that highest solubility is confined circularly in between maxima and minima of X_1 and X_2.

Interaction of formulation variables for particle size

All the interaction terms were found to be insignificant. Interaction charts were generated for three level of D/P

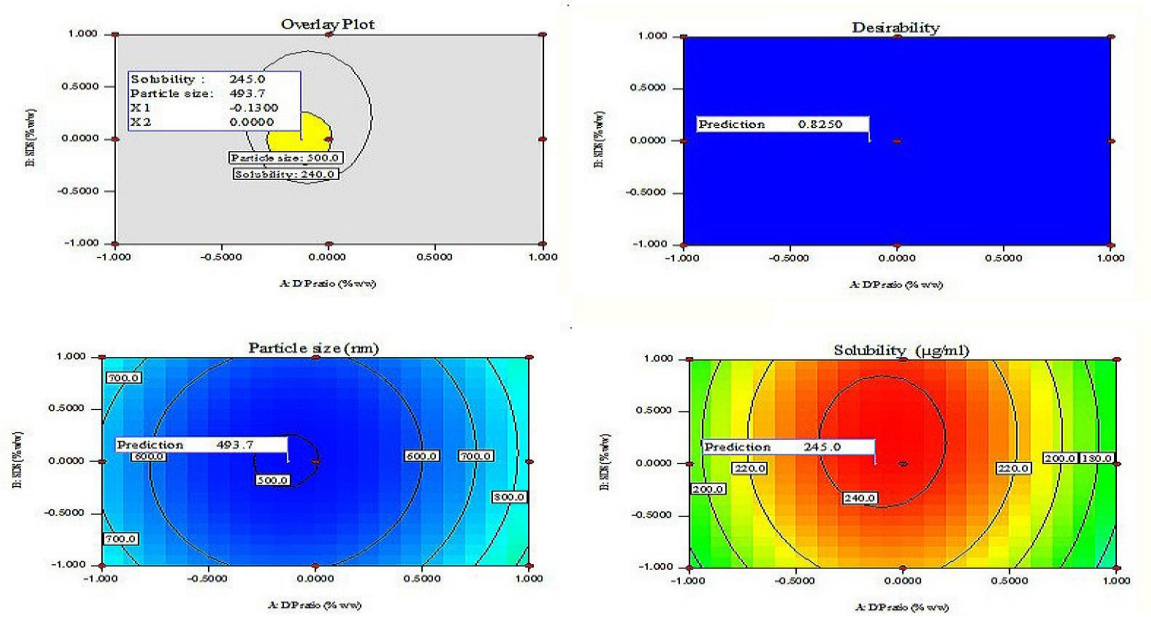

Figure 4: Optimization graphs for formulation stabilized by PVA (ethanol).

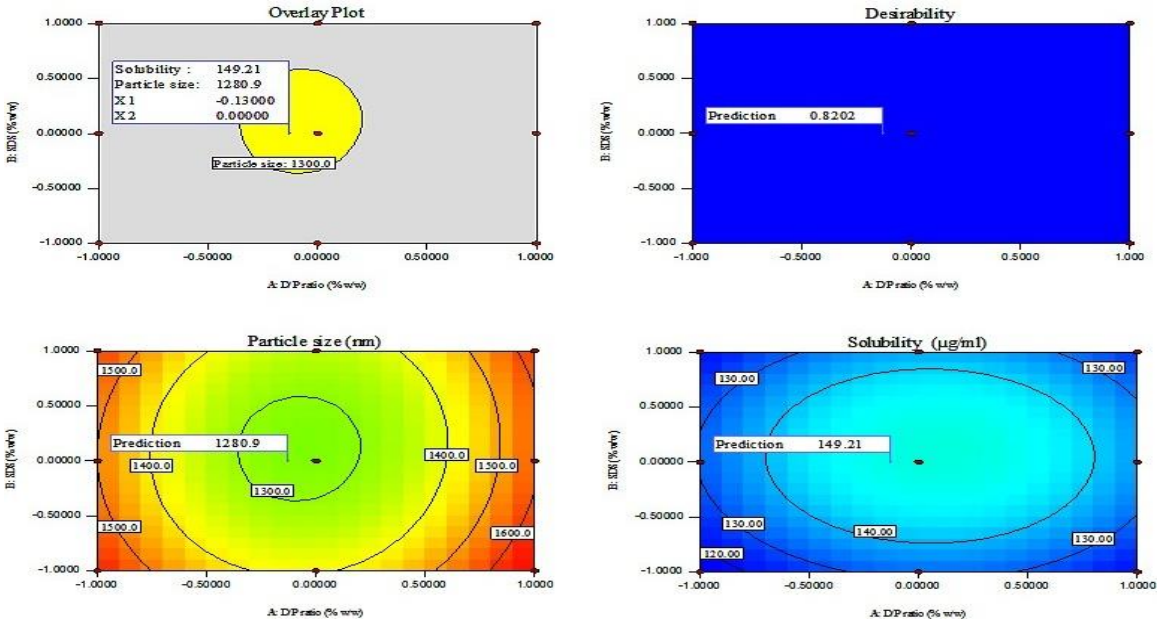

Figure 5: Optimization graphs for formulation stabilized by PVA (acetone).

ratio with two different solvents. Figure 3 (a, b, c) revealed that effect of solvent was found to be prominent throughout the range of D/P ratio. These solvents showed distinct mixing behavior when added to aqueous polymer dispersion during the precipitation process. It was observed that acetonic drug solution didn't diffuse readily after addition to aqueous dispersion of polymer as compared to ethanolic drug solution. Although sonication was applied throughout the process but acetonic solution tended to form a layer over antisolvent and needed some time to go in bulk of antisolvent. Raghavan et al suggested that inhibition of crystal growth may depend on strength and number of hydrogen bonds between drug functional groups and polymer[18]. Aceclofenac has one carbonyl and one carboxylate group which can form hydrogen bonds with PVA. The availability of polymer approaching the drug surface should be enough at the time of nucleus growth to restrict the size of crystals. So this 'approaching polymer' was a critical parameter which affected particle size of crystals.

Interaction of formulation variables for solubility

Interaction of formulation variables were evaluated by observing the all coefficients for interaction terms. X_1X_2 and X_2X_3 were found insignificant. Only X_1X_3 interaction term showed significant effect on particle size. Coefficient for X_1X_3 was found to be positive and significant indicating the combined synergistic effect of solvent with D/P ratio on solubility. Solubility cannot be predicted solely based on particle size. The adsorption of polymer and surfactant at particle interface must also be responsible in quantification of solubility of particles. In addition to the stabilization of particles, stabilizers may assist in

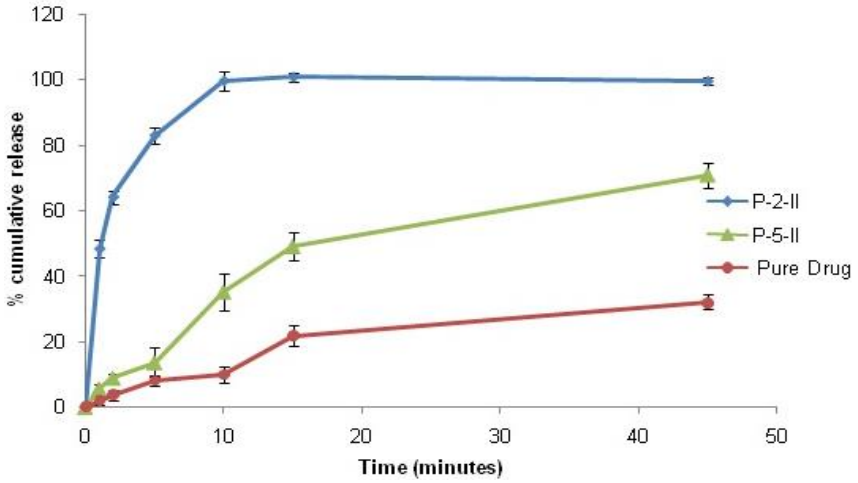

Figure 6: Dissolution profile of aceclofenac from nanosuspension formulations and pure drug in distilled water (pH 6.8).

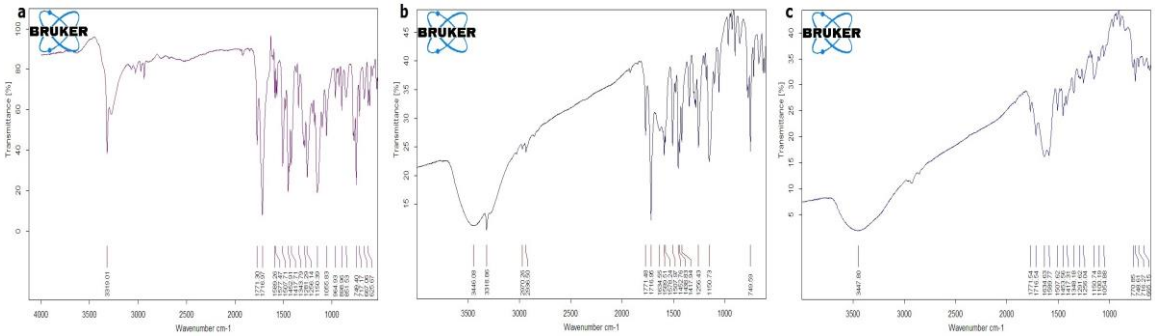

Figure 7: FTIR spectra of (a) Aceclofenac (b) Physical mixture of drug, PVA, SDS and (c) P-2-II.

enhancing the saturation solubility of the nanosized drug[19], as described by the Freundlich–Ostwald equation based on interfacial tension along with particle size.

$$S = S_{\infty} \exp\left(\frac{2\gamma M}{r\rho RT}\right)$$

where S =saturation solubility of the nanosized API, S_{∞}=saturation solubility of an infinitely large API crystal, γ is the crystal- medium interfacial tension, M is the compound molecular weight, r is the particle radius, ρ is the density, R is a gas constant and T is the temperature. Surfactants increased surface wetting of particles due to lowering of interfacial tension. This most likely resulted in a further enhancement of the saturation solubility. Interaction charts showed that solubility of particles obtained from ethanol was higher than solubility of particles obtained from acetone. But this difference is not at par the difference shown by particle size interaction charts as revealed in Figure 3(d, e, f). At higher level of D/P ratio the interaction curves for both solvents came out to approach each other and solvent effect on solubility appeared to be diminished. Adsorption of polymer and surfactants over surface of particles was not limited to crystallization phase only but it continued until adsorption equilibrium was established. Probably this yielded the solubility results which are not proportionally related to particle size.

Optimization of formulation

Table 4 shows the polynomial equations in terms of actual factors for responses which were used to make predictions about the response for given levels of each factor. Here, the levels were specified in the original units for each factor. This equation could not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space. Numerical optimization technique by the desirability approach[20] was explored to produce the optimum parameters for the formulation. The formulation was optimized for the dependent (response) variables, particle size and solubility. This program suggested some formulations and predicted their responses with desirability values between 0 and 1. Criteria of parameters was set at particle size range (450 nm<size<700 nm) and maximum solubility (174 µg/ml<solubility<260 µg/ml) for ethanol and particle size range (1000 nm<size<1300 nm) and maximum solubility (100 µg/ml <solubility<160 µg/ml) for acetone. Formulations with D/P ratio, 400% w/w (code level; -0.130) and SDS, 7.5% w/w (code level; 0) were found to fulfill the desirability requisite (Figure 4, 5) for both solvents and considered as optimum formulations. Suggested optimized formulations were prepared according to the predicted model and evaluated for the responses (particle size and solubility) to evaluate reliability of the response surface model. The result in Table 5 demonstrates a reasonable relationship between

Table 1: Factorial design parameters and experimental conditions for optimization of nanosuspension stabilized by PVA.

Factors type	subtype	Factors	Levels used, Actual (coded)		
			Low (-1)	Medium (0)	High (+1)
Numeric	Continuous	X_1- D/P ratio (Aceclofenac/ PVA)	200% w/w	430% w/w	660% w/w
Numeric	Continuous	X_2- Concentration of SDS	0.0% w/w	7.5% w/w	15% w/w
Category	Nominal	X_3- solvent	Ethanol	-------	Acetone

Table 2: The factor and responses of model nanosuspension formulations utilizing 3^2 factorial design.

Formulation code (X_1,X_2,X_3)	Particle size (nm)	Solubility (µg/ml)	Formulation code (X_1, X_2, X_3)	Particle size (nm)	Solubility (µg/ml)
PV-1-I (-1,-1,-1)	756.9	176.48	PV-4-I (-1,-1,+1)	1623.2	112.41
PV-1-II (-1,0,-1)	740.8	189.84	PV-4-II (-1,0,+1)	1435.0	128.54
PV-1-III (-1,+1,-1)	760.2	185.52	PV-4-III (-1,1,+1)	1600.4	120.04
PV-2-I (0,-1,-1)	580.4	221.45	PV-5-I (0,-1,+1)	1408.7	136.44
PV-2-II (0,0,-1)	479.3	246.19	PV-5-II (0,0,+1)	1257.1	148.83
PV-2-III (0,+1,-1)	578.3	237.50	PV-5-III (0,1,+1)	1399.6	132.81
PV-3-I (+1,-1,-1)	923	147.35	PV-6-I (+1,-1,+1)	1705.3	113.87
PV-3-II (+1,0,-1)	871	169.60	PV-6-II (+1,0,+1)	1599.0	137.23
PV-3-III (+1,+1,-1)	900.2	158.68	PV-6-III (+1,+1,+1)	1609.9	120.35

Table 3: Coefficients of factors for particle size and their p-values.

Particle size (Quadratic model)			Solubility (Reduced cubic model)		
Source	Coefficient	p-value Prob > F	Source	Coefficient	p-value Prob > F
Intercept	+890.47	----	Intercept	197.07	----
X_1-D/P	+57.66	0.0010	X_1-D/P	-5.48	0.0034
X_2-SDS	-12.41	0.3298	X_2-SDS	3.91	0.0157
X_3-Solvent	+391.56	< 0.0001	X_3-Solvent	-47.34	< 0.0001
X_1X_2	-12.34	0.4246	X_1X_2	0.14	0.9244
$X_1 X_3$	-15.06	0.2428	$X_1 X_3$	7.22	0.0008
$X_2 X_3$	-8.81	0.4832	$X_2 X_3$	-2.16	0.1144
X_1^2	+259.84	< 0.0001	X_1^2	-40.55	< 0.0001
X_2^2	+90.14	0.0019	X_2^2	-14.80	0.0003
			$X_1X_2 X_3$	-0.43	0.7741
			$X_1^2 X_3$	23.26	< 0.0001
			$X_2^2 X_3$	-0.75	0.7240

Table 4: Prediction polynomial equations in terms of actual factors for responses.

Solvent	Response	Polynomial equations in terms of actual factors
Ethanol (-1)	Particle size	+498.9+72.72*[D/P ratio]-3.60*[SDS]-12.33*[D/P ratio]* [SDS]+259.8*[D/P ratio]^2+90.14*[SDS]^2
	Solubility	244.4-12.70*[D/P ratio] +6.070*[SDS]+0.5727*[D/P ratio]* [SDS]-63.80*[D/P ratio]^2-14.05*[SDS]^2
Acetone (+1)	Particle size	+1282.0+42.60*[D/P ratio]-21.22*[SDS]-12.34* [D/P ratio]* [SDS]+259.8*[D/P ratio]^2+90.14*[SDS]^2
	Solubility	+149.7+1.743*[D/P ratio]+1.745*[SDS]-0.2888*[D/P ratio]* [SDS]-17.29*[D/P ratio]^2-15.55*[SDS]^2

the experimental and predicted values, which confirmed the practicability and validity of the model.

In vitro dissolution

Table 6 showed results of dissolution testing of pure drug and optimized nanosuspension formulations (P-2-II, P-5-II) from each batch. Amount of drug released at 05 minutes (Q_{05}) and 45 minutes (Q_{45}) were calculated for comparison of dissolution pattern at initial as well as later stages. A model independent parameter, the dissolution efficiency (DE) till 05 minutes was calculated to compare dissolution profiles[21].

$$\text{Dissolution efficiency} = \frac{\int_{t1}^{t2} y \cdot dt}{y100.\, dt}$$

where y is the percentage of dissolved product. DE is then the area under the dissolution curve between time points, t_1 and t_2 expressed as a percentage of the curve at maximum or 100% dissolution, y_{100}, over the same time period. Nanosuspension formulations showed promising and improved dissolution rate of drug compared to pure

Table 5: Optimized nanosuspension formulations and their response variables.

Parameters	P-2-II	P-5-II
Solvent	Ethanol	Acetone
D/P ratio	400% w/w (-0.130)	400% w/w (-0.130)
SDS	7.5% w/w (0)	7.5% w/w (0)
Particle size (Predicted)	493.7 nm	1281 nm
Particle size (Observed)	477.7 nm	1254 nm
% RE	3.34%	2.15%
Solubility (Predicted)	245.0 µg/ml	149.2 µg/ml
Solubility (Observed)	255.39±3.98 µg/ml	135.73±2.69 µg/ml
% RE	4.07%	8.93%

Table 6: Dissolution parameters of nanosuspensions in distilled water.

Formulation	Q_{05}	Q_{45}	DE_{05}
P-2-II	82.92±2.33	99.41±1.10	59.77 ±0.60##
P-5-II	13.66±4.65	70.72±3.82	8.79±2.17*
Drug	7.99 ±1.56	31.95±2.25	4.210±0.782

*p<0.05, #p<0.001, ##p<0.0001

drug in distilled water (Figure 6). Aceclofenac has very low solubility (63.75 µg/ml) in distilled water which provided non sink condition and a clear difference was observed between the dissolution rate of nanosuspension and pure drug. Dissolution efficiencies of all formulations were compared statistically (one way ANOVA) with pure drug. All the formulations showed a significant improvement in dissolution efficiency compared to pure drug. P-2-II released almost completely followed by P-5-II and pure drug. Pure drug released only 31.95% after 45 minutes but nanosuspension formulations showed improved dissolution within that span of time. More than 80% drug was released by P-2-II within first 05 minutes and attained greater DE_{05} compared to pure drug. The rank order of DE_{05} was found as P-2-II>P-5-II>Pure drug.

FTIR of nanosuspension

IR spectra of pure aceclofenac, physical mixture and nanosuspension (P-2-II) are shown in Figure 7. Pure aceclofenac showed characteristics peaks at 3319.01 cm^{-1} attributed to secondary N–H rocking vibrations, signal at 1589.26 cm^{-1} attributed to C=C stretching of the aromatic ring, at 749.40 cm^{-1} because of C\Cl stretching, at 1716.97 cm^{-1} attributed to C=O stretching of the carbonyl group, at 3028 cm^{-1} and at 2935 cm^{-1} attributed to C\H stretching (due to both aromatic and aliphatic stretching vibrations, respectively)[22]. Characteristic peaks, although of smaller intensity, were resulted in the spectrum of nanosuspension. Higher amount of polymer might have suppressed the signal of drug. The results revealed no considerable changes in the IR peaks of aceclofenac in the prepared nanosuspension when compared to pure drug thereby indicating the absence of any interaction. A broad peak at 3447.6 cm^{-1} may be attributed to hydrogen bond between drug and polymer.

CONCLUSION

In present work the formulation attributes were studied which affected the key characteristics of formulation i.e. particle size and solubility in distilled water. Drug to polymer ratio and concentration of SDS played a decisive role in the formulation design. Smaller crystals were obtained when ethanol was used as compared to crystals obtained from acetone. PVA was able to control the particle growth during precipitation but showed different behavior in two organic solvents. Nanosuspension formulations were found to have greater solubility in water than pure drug. The effect of this higher solubility was reflected in dissolution behavior of nanosuspensions. A remarkable higher drug release was shown by nanosuspension formulations when compared to that of pure drug. The results evidenced that nanosuspension stabilized by PVA can be used for improving the solubility, dissolution rate and bioavailability of the drug.

ACKNOWLEDGEMENTS

The authors acknowledge INTAS Pharmaceuticals Limited, Dehradun, India for providing Aceclofenac as gift sample.

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