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RESEARCH PAPER

Processing of Nimesulide-PEG 400-PG-PVP Solid Dispersions: Preparation, Characterization, and In Vitro Dissolution

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ABSTRACT

The objective of this investigation was to study the influence of dissolution enhancers such as polyethylene glycol 400, propylene glycol, polyvinylpyrrolidone K30, sodium lauryl sulfate, and Tween 80 on in vitro dissolution of a model active pharmaceutical material—nimesulide. Preliminary studies were conducted using a physical blend of nimesulide, and the adjuvants and solid dispersions were prepared using solvent evaporation and cogrinding methods. Aqueous solution of adjuvants was first triturated with nimesulide, followed by mixing with lactose and microcrystalline cellulose, and finally water was evaporated under vacuum in a cogrinding method. A 3^3 factorial design was adopted in a cogrinding method using the concentration of polyethylene glycol 400, propylene glycol, and polyvinylpyrrolidone K30 as independent variables. Tween 80 and sodium lauryl sulfate were added in all the batches. Full and reduced models were evolved for different dependent variables. The reduced models were validated using two checkpoints. Angle of repose $< 35^\circ$, percentage of drug released in 30 min (Q_{30}) > 40%, 45 min (Q_{45}) > 50%, and 120 min (Q_{120}) > 60% were used as constraints for the selection of an optimized batch. Contour plots are presented for the selected dependent variables. Polyvinylpyrrolidone was found to be more effective in increasing the drug dissolution, compared with polyethylene glycol 400 and propylene glycol. The granule flow was adversely affected when high levels of liquid adjuvants were used in formulations. Wettability study was conducted to measure wetting time for pure drug and the optimized batch. Improved drug dissolution was attributed to improved wetting and the solubilizing effect of adjuvants from the pseudosolid dispersions of nimesulide. Significant improvement in drug dissolution was observed ($Q_{120} = 70\%$), compared with pure drug powder ($Q_{120} = 15\%$). In conclusion, dissolution of nimesulide can be modulated using an appropriate blend of pharmaceutical adjuvants.

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Key Words: Nimesulide dissolution improvement; Pseudosolid dispersions; Cogrinding methods.

INTRODUCTION

The number of sparingly soluble active pharmaceutical materials has risen sharply in recent years, and the formulation of such entities presents greater challenges to industrial pharmacists. Along with other factors, solubility of active pharmaceutical materials is a key determinant of its oral bioavailability. The two most commonly used approaches for improving bioavailability are particle size reduction and solubility improvement through systematic formulation approaches.

Knowledge of the biopharmaceutics drug classification system, included in the guidelines of the U.S. Food and Drug Administration, can be used by formulation scientists for developing an optimized dosage form. Lobenberg and Amidon[1] reported that the complete absorption of digoxin could be expected if the particle size of the drug is small enough (high D_n), whereas in the case of griseofulvin, micronization will not significantly improve the fraction of drug absorbed. For griseofulvin, besides the change in D_n, a change of D_o is also required to move up to the plateau of complete absorption.[1] The minimum solubility of nimesulide at pH 3 is $4.6\,\mu g\,mL^{-1}$ at 20°C.[2] Because data of solubility at 37°C are not available, data at 20°C were used to calculate D_o and D_n. The calculated values of D_o and D_n were found to be 87 and 0.1, respectively, for nimesulide. The calculated value of fraction of dose absorbed is about 0.2, which is very close to that of griseofulvin. The theoretical volume of sodium citrate buffer (pH 3) required for complete dissolution of 100 mg of nimesulide is 21.7 L. One may therefore conclude that micronization of nimesulide will not significantly improve the fraction of dose absorbed. Hence, drug solubility should be enhanced by adopting a suitable method.

The incorporation of drug into solid carriers has been reported to result in an increase in the dissolution of drug leading to improved bioavailability.[3] The drug in a solid dispersion might not be in microcrystalline state, but a certain fraction of the drug might be present in a molecularly dispersed state in the carrier matrix.[4] In either case, when the solid dispersion is exposed to an aqueous medium, the carrier gets dissolved first; later, the drug is released in the form of fine colloidal particles. Because of the greatly enhanced surface area obtained in this way, the dissolution rate and bioavailability of poorly water-soluble drugs are expected to be high from solid dispersions.

Many carriers have been examined for formulation of solid dispersions. Polyethylene glycol (PEG), propylene glycol (PG), and polyvinylpyrrolidone (PVP) are the most commonly used carriers. Polyethylene glycols have been used extensively as water-soluble carriers and stabilizers for pharmaceutical dosage forms because of favorable solution properties, low toxicity, and cost.[5] Low-molecular weight PEGs (PEG 200, 300, and 400) have been used as cosolvents for liquid dosage forms.[6] PEG 400 is one of the most commonly used vehicles in soft gelatin capsules.[7] Propylene glycol is used as a solvent in parenteral and nonparenteral pharmaceutical formulations. It is a more efficient solubilizer than glycerin.[8] It is used in the formulation designing of sparingly water-soluble drug.[9–13] Polyvinylpyrrolidone is used as a solubilizing, complexing, and dispersing agent in pharmaceutical preparation.[14] It is used as a crystallization inhibitor of drug during storage of the formulation and as a carrier for improving solubility of the drug from solid dispersions.[15–20] Soluble donor concentration and membrane transport of poorly soluble NCES (new chemical entities) was markedly improved by povidone, PEG, PG 300, and Tween 80.[21]

The concept of powdered solutions can be used to formulate liquid medication in free-flowing, dry-looking, and readily compressible drug powders.[22] The drug is released at a faster rate from the powdered solutions than that from the micronized powders, because the drug is present in a molecular state of subdivision in such systems. The increase in drug dissolution from liquisolid dispersions can be attributed to a number of factors, such as increased surface area and wettability.[23] The use of surfactants in pharmaceutical formulations is justified by the fact that bile salts and lecithin are physiologically present. They improve wettability[24] and solubility of many lipophilic substances.[25,26]

In the present study, nimesulide, a very slightly water-soluble nonsteroidal anti-inflammatory drug, was used as a model drug to develope a multicomponent, pseudosolid dispersion system. The major advantage of pseudosolid dispersion is improvement

of drug dissolution, because the drug exists in a dissolved and/or dispersed state in the carrier liquid. Polyvinylpyrrolidone K30, PEG 400, and PG were tried as dissolution enhancers in the previously optimized surfactant system of Tween 80 and sodium lauryl sulfate (SLS) for nimesulide.[27] To the best of our knowledge, no information is available on the improvement of dissolution of nimesulide using pseudosolid dispersion. Hence, the present work was undertaken for improving dissolution of nimesulide exploring the multicomponent, pseudosolid dispersion approach.

MATERIALS AND METHODS

Materials

Nimesulide, lactose I.P., microcrystalline cellulose (MCC), SLS I.P., PVP K30, and hard gelatin capsules were received as generous gifts from Alembic Ltd. (Vadodara, India), Cadila Healthcare (Zydus, India) Pvt. Ltd. (Ahmedabad, India), Rusan Pharm. Ltd. (Bombay, India), Helios Pharmaceuticals (Ahmedabad, India), and Restech Pharm. Pvt. Ltd. (Ahmedabad, India), respectively. Tween 80, PEG 400, and PG were from Laser Laboratories (Ahmedabad, India). Potassium dihydrogen phosphate from Loba Chemie Pvt. Ltd. (Bombay, India), disodium hydrogen phosphate dihydrate from Ranbaxy Laboratories Ltd. (S. A. S. Nagar, India), and chloroform from JC'S Chemicals (Vadodara, India) were used as received. Deionized double distilled water was used throughout the study.

Preparation Methods

All batches were prepared using 5 g of nimesulide. One hundred milligrams of nimesulide (100 mesh) were handfilled into 0-size hard gelatin capsules (batch P_1).

Physical Mixing Method

The physical mixture was prepared by mixing nimesulide (100 mg) and the excipients (240 mg lactose and 60 mg MCC) in a glass mortar by trituration and handfilled into 0-size hard gelatin capsules (batch P_2).

Solvent Evaporation Method

A blend of lactose (240 mg) and MCC (60 mg) was mixed with the solution of nimesulide (100 mg) in chloroform (1 mL). The solvent was allowed to evaporate at room temperature with occasional stirring. The semiwet mass was passed through a 40-mesh sieve, and the granules were subsequently dried at 60°C using a vacuum until a constant weight was obtained. The granules were handfilled into 0-size hard gelatin capsules (batch P_3).

Cogrinding Method

Batch P_4 was prepared by grinding nimesulide (100 mg), lactose (240 mg), MCC (60 mg), and water (0.5 mL). The cogrind dispersion was processed as shown in the solvent evaporation method. To investigate the influence of solubilizing agents such as PVP, PEG 400, or PG on drug dissolution, some preliminary batches were prepared. The aqueous solution (0.5 mL) of PVP, PEG 400, or PG (10–50 mg each) was triturated with nimesulide (100 mg) until a creamy homogeneous mixture was obtained. The mixture was further triturated with lactose (240 mg) and MCC (60 mg) for 10 min. The semiwet mass was passed through a 40-mesh sieve, and the granules were dried at 60°C using a vacuum until a constant weight was obtained. The granules were handfilled into 0-size hard gelatin capsules.

Experimental Design

To optimize concentration of the solubilizing agents, a 3^3 factorial design was adopted using the concentration of PEG 400 (X_1), PG (X_2), and PVP K30 (X_3) as independent variables at three levels: low (10 mg), medium (20 mg), and high (30 mg). Tween 80 (20 mg) and SLS (10 mg) were dissolved in the aqueous solution of solubilizing agents. Batches of factorial design were prepared by the cogrinding method using lactose (240 mg) and MCC (60 mg).

Angle of Repose

The angle of repose (AR) of various batches was measured using the fixed height funnel method.[28]

In Vitro Dissolution Study

In vitro release of nimesulide from the capsules was conducted according to the USP 23 basket apparatus (model TDT-60T, Electrolab, Bombay, India) at $37 \pm 0.5^{\circ}C$ and at 50 rev min^{-1} using 900 mL phosphate buffer (pH 7.4) as a dissolution medium ($n = 3$). Sample solution (2.5 mL) was withdrawn at the predetermined time intervals, filtered through a 0.45-μm membrane filter, suitably diluted, and analyzed by measuring absorbance of the solutions at 394 nm using a blank solution as reference by a Hitachi U-2000 UV-Vis double-beam spectrophotometer.[13] An equal amount of fresh dissolution medium was replaced after withdrawal of the test sample. The percentage of nimesulide dissolved was calculated using a regression equation generated from the standard data.

Wettability Study

Drug powder, powder mixture, or granules (3 g) was placed in a sintered glass funnel (33 mm i.d.). The funnel was plunged into a beaker containing water such that the surface of water in the beaker remains at the same level as the powder or granules in the funnel.[29] Methylene blue powder (100 mg) was layered uniformly on the surface of the powder or granules in the funnel. The time required for wetting methylene blue powder was measured. The average of three observations was used for drawing conclusions.

RESULTS AND DISCUSSION

Dissolution Study

The results of the dissolution study of batch P_1 showed that only 15% of nimesulide was released in 2 hr. Possible reasons for this poor drug dissolution are low aqueous solubility (≈ 0.01 mg mL^{-1}) and poor wettability (122 min), compared with lactose-MCC (4:1) mixture (19 min). Twenty percent of the drug was released from the physical mixture (batch P_2) in 2 hr. The improvement in drug dissolution may be attributed to the hydrophilic nature of the adjuvant and wicking action of MCC. To facilitate distribution of the drug in the carriers such as lactose and MCC, the solvent evaporation method was adopted (batch P_3). Approximately 25% of the drug was released in 2 hr from batch P_3. In batch P_4, the aqueous dispersion of nimesulide was cogrinded with the diluents and granulated. About 21% of the drug was released in 2 hr from batch P_4 (Fig. 1).

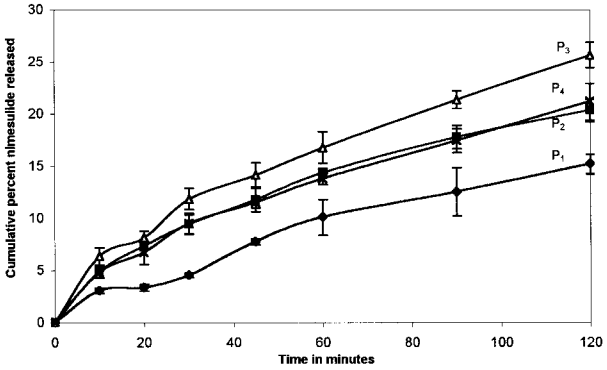

Figure 1. Dissolution curve for batches P_1–P_4.

Table 1. Results of student's *t*-test and similarity factor (f_2) for batches P_1–P_4.

Batch no.	t_{stat}	t_{cri}	f_2
P_4–P1	1.15	1.76	68.01
P_4–P_2	0.03	1.76	99.77
P_4–P_3	0.64	1.76	75.21

Flowability of the granules of batch P_3 (AR 31°) and batch P_4 (AR 32°) was found to be superior to that of batch P_2 (AR 45°) and batch P_1 (AR 47°). Batches P_1 and P_2 have a problem with weight variation, because the value of the AR was high. Improved flow of the processed material is attributed to the formation of aggregates of particles (40 mesh). The results of Student's t-test and similarity factor for batches P_1, P_2, P_3, and P_4 show insignificant differences between the batches (Table 1). The cogrinding method avoids the use of chloroform and therefore offers advantages such as reduced cost, improved safety, and environmental friendliness. Batch P_3 did not show significant improvement in drug dissolution in 30 min (11%) and 45 min (14%), compared with batch P_4 (10% and 12%, respectively). Hence, the aqueous cogrinding method was selected for further studies.

Optimization of the Solubilizing Agent

It was arbitrarily decided to obtain at least 60% of the drug release in 2 hr. Solid dispersions containing nimesulide (100 mg)-PVP (10–50 mg) were prepared by the cogrinding method that showed

improved drug dissolution, compared with batches P_1–P_4. Addition of 20 mg of PVP was found to be optimum in improving drug dissolution in 2 hr (31.43%). Addition of more PVP did not result in a proportional improvement in drug dissolution. Solubility of nimesulide in PEG 400 ($\approx$10 mg mL^{-1}) and PG ($\approx$3 mg mL^{-1}) is greater than that in water ($\approx$0.01 mg mL^{-1}). Hence, PEG 400 or PG was tried in the same concentration of PVP to improve the drug dissolution. The angle of repose of the batches varied from 30° to 35°. At a concentration of 50 mg of PVP, a viscous sticky mass was obtained from a higher viscosity of PVP, whereas cohesive granules were obtained when PEG 400 and PG were used at the same concentration. The increase in dissolution of nimesulide may be attributed to an increase in solubility and wettability (60–80 min). None of the preliminary batches (Fig. 2) showed $\geq$60% drug release in 2 hr; hence, combinations of adjuvants were used in the experimental design.

Experimental Design

A 3^3 factorial design was adopted using the concentration of PEG 400 (X_1), PG (X_2), and PVP K30 (X_3) as independent variables. Tween 80 (20 mg) and SLS (10 mg) were added in all the batches after dissolving them in the aqueous solution of the solubilizing agents. The results of dependent variables such as the AR and percentage of drug release at 30, 45, and 120 min (Q_{30}, Q_{45}, and Q_{120}, respectively) of the batches are shown in Tables 2 and 3. Response surface curvature can be examined when the variables are investigated at three levels. The design provided the following empirical second-order equation (Full model):

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 + b_{12}X_1X_2 + b_{23}X_2X_3 + b_{13}X_1X_3 + b_{123}X_1X_2X_3$$

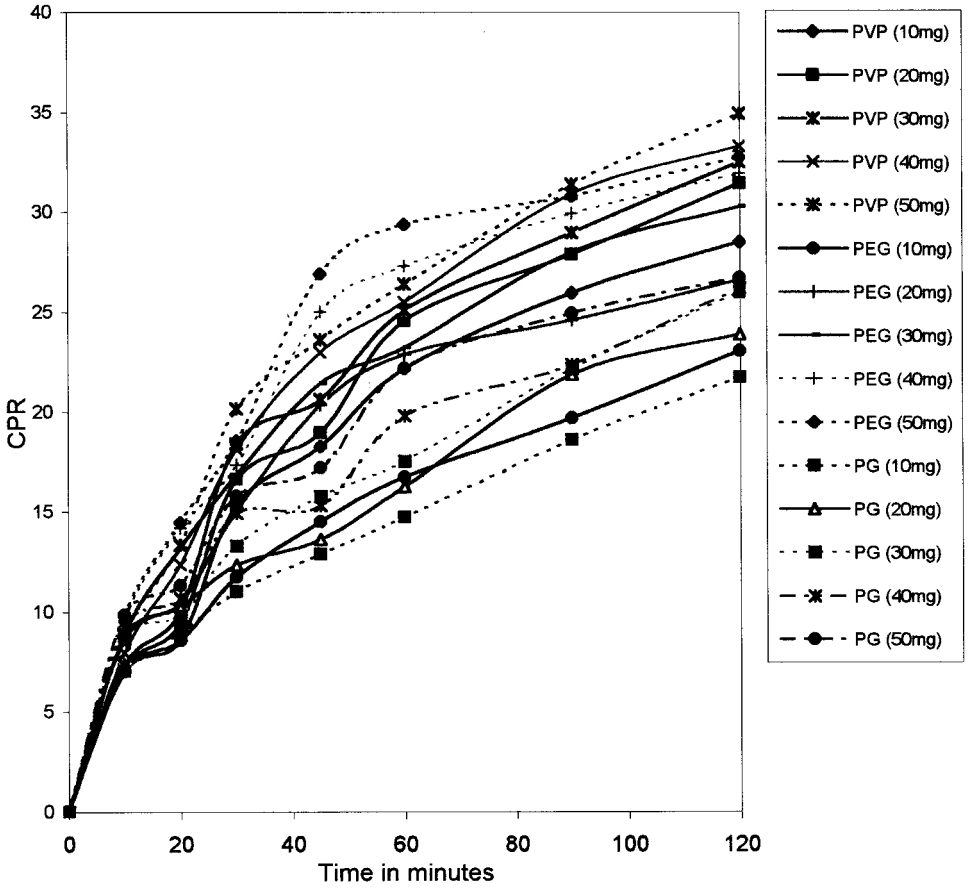

Figure 2. Dissolution curve for batches containing PVP, PEG 400, and PG.

Table 2. Experimental runs and measured responses.

Run no.	X_1	X_2	X_3	AR (°)	Q_{30}	Q_{45}	Q_{120}
1	−1	−1	−1	31.62	29.48	34.68	46.12
2	−1	0	−1	33.18	28.37	31.67	42.73
3	−1	1	−1	37.59	31.99	35.06	43.85
4	0	−1	−1	34.43	34.32	41.56	48.15
5	0	0	−1	34.50	33.12	41.07	49.93
6	0	1	−1	35.77	35.62	42.58	52.66
7	1	−1	−1	36.68	39.50	42.43	52.78
8	1	0	−1	38.11	38.60	44.60	54.33
9	1	1	−1	40.38	40.46	46.25	55.97
10	−1	−1	0	32.42	39.16	45.45	53.29
11	−1	0	0	33.85	34.62	44.16	54.47
12	−1	1	0	36.44	35.57	44.64	56.50
13	0	−1	0	35.76	44.25	49.56	62.38
14	0	0	0	33.96	40.54	51.86	63.20
15	0	1	0	35.55	44.52	54.78	64.37
16	1	−1	0	36.43	47.37	51.45	64.58
17	1	0	0	36.46	44.21	51.97	66.05
18	1	1	0	38.41	44.80	53.12	66.20
19	−1	−1	1	33.76	50.55	54.23	65.63
20	−1	0	1	34.71	48.68	52.35	66.08
21	−1	1	1	34.29	44.88	54.39	66.66
22	0	−1	1	33.11	48.67	55.34	68.47
23	0	0	1	33.68	50.54	55.66	69.20
24	0	1	1	34.85	52.51	56.43	69.04
25	1	−1	1	33.66	53.91	57.93	69.57
26	1	0	1	35.76	54.33	57.98	71.71
27	1	1	1	37.15	52.96	57.14	71.70

Factors and levels in the design

Independent variables	Levels		
	Low (−1)	Medium (0)	High (1)
PEG 400 (X_1), mg	10	20	30
PG (X_2), mg	10	20	30
PVP (X_3), mg	10	20	30

where Y is response; b_0 is the intercept; b_1, b_2, and b_3 are regression coefficients of the main effects; and b_{12}, b_{23}, b_{13}, and b_{123} are regression coefficients for interaction terms. The coefficients with second-order terms (b_{11}, b_{22}, and b_{33}) indicate the quadratic nature. The nonsignificant estimated coefficients should be dropped from the full model by adopting a significance test for the regression coefficient for the evolving refined model. Microsoft EXCEL® may be used to identify nonsignificant terms. A coefficient is significant if $t_i > t_{\mathrm{cri}\,(v)}$, where v is the degree of freedom of residual variance. The refined model may be used for calculation of residuals or for drawing contour plots. The full and refined models ($p < 0.05$) for AR, Q_{30}, Q_{45}, and Q_{120} are shown in Table 4.

Angle of Repose

A coefficient with a positive sign shows a synergistic effect, whereas a coefficient with a negative sign shows an antagonistic effect. The main effects and regression coefficients b_{11} and b_{13} were found to be statistically significant. Hence, one cannot draw conclusions from the mathematical signs (positive or negative) of the main effects b_1, b_2, and b_3. The batch containing the independent variables at low

Table 3. In vitro dissolution profiles of batches of factorial design.

Run no.	Cumulative % of nimesulide released in:						
	10 min	20 min	30 min	45 min	60 min	90 min	120 min
1	14.36	19.67	29.48	34.68	40.53	41.64	46.12
2	14.45	20.91	28.37	31.67	35.06	39.98	42.73
3	14.48	21.73	31.99	35.06	39.71	41.16	43.85
4	14.55	28.07	34.32	41.56	43.77	45.89	48.15
5	15.02	23.04	33.12	41.07	44.74	48.10	49.93
6	15.73	23.94	35.62	42.58	46.62	49.17	52.66
7	15.52	27.02	39.50	42.43	48.55	50.52	52.78
8	15.70	26.78	38.60	44.60	49.15	51.33	54.33
9	18.32	26.21	40.46	46.25	51.80	53.70	55.97
10	16.69	25.45	39.16	45.45	48.26	52.54	53.29
11	18.93	25.50	34.62	44.16	47.44	49.17	54.47
12	20.74	26.43	35.57	44.64	46.18	53.54	56.50
13	16.16	25.91	44.25	49.56	52.26	57.12	62.38
14	17.60	29.69	40.54	51.86	57.77	61.03	63.20
15	23.78	32.80	44.52	54.78	59.71	62.65	64.37
16	23.72	34.41	47.37	51.45	59.74	62.59	64.58
17	20.12	34.23	44.21	51.97	56.70	63.53	66.05
18	22.22	34.55	44.80	53.12	58.65	63.17	66.20
19	22.89	32.23	50.55	54.23	61.71	63.78	65.63
20	22.65	31.44	48.68	52.35	57.47	62.87	66.08
21	21.98	29.87	44.88	54.39	58.03	61.94	66.66
22	22.93	28.36	48.67	55.34	58.87	64.99	68.47
23	23.15	31.86	50.54	55.66	58.69	63.53	69.20
24	24.45	31.70	52.51	56.43	61.23	65.02	69.04
25	25.66	34.64	53.91	57.93	60.73	66.44	69.57
26	24.16	33.65	54.33	57.98	60.48	67.02	71.71
27	25.19	34.72	52.96	57.14	60.84	65.95	71.70

Table 4. Summary of results of regression analysis of refined model.

Response		b_0	b_1	b_2	b_3	b_{11}	b_{22}	b_{33}	b_{12}	b_{23}	b_{13}	B_{123}	r^2
AR(°)	RM	34.62	1.40	1.25	−0.63	0.98	—	—	—	—	−0.75	—	0.7852
Q_{30}	RM	42.35	4.05	—	8.09	—	—	—	—	—	—	—	0.9406
Q_{45}	RM	51.08	3.68	—	7.86	−2.12	—	−1.81	—	—	−1.65	—	0.9678
Q_{120}	RM	62.21	4.31	0.89	9.53	−1.48	—	−2.08	—	—	−1.31	—	0.9809

RM, refined model.

levels showed the least AR (32° for batch 1), whereas the batch containing a high level of the variables X_1 and X_2 showed the highest AR (40° for batch 9). The result of particle size distribution (by the sieving method) of batches P_1, P_2, P_4, and 25 is presented in Fig. 3. The results of bulk and tapped densities and mean particle size of the batches are presented in Table 5. The photographs of batches P_1, P_2, P_4, and 25 are presented in Fig. 4. The particles of batch 25 are reasonably spherical in shape. PEG 400 and PG are liquid adjuvants, whereas PVP is a solid adjuvant. The liquid adjuvants adversely affected the AR, especially when used at a high level. It is worth noting that a low level of PEG 400 and PG may not show an appreciable improvement in drug dissolution. Figure 5 shows the contour plot for AR. The area that falls under the contour line of 35° shows different combinations of X_1 and X_2 that can give acceptable products. It is noted from the contour plot that the higher amount

of PEG 400 (X_1) can be tolerated if high levels of PVP (X_3) are used. The final selection of the batch was done after considering the other requirements of the dosage form (i.e., Q_{30}, Q_{45}, and Q_{120}).

Percentage of Drug Released in 30 Minutes (Q_{30})

The refined model shows that the interaction terms and the second-order terms are insignificant. It is concluded that coefficients b_1 and b_3 carry a positive sign; therefore, PEG 400 and PVP can improve the drug dissolution in the first 30 min. The lowest Q_{30} was observed when both polymers were used at low levels. The poor drug dissolution may be attributed to poor drug solubility and wetting when low levels of the polymers were used. The improved drug dissolution at high levels of PEG 400 and PVP is attributed to improved solubility and wetting of the drug particles. Figure 6 shows the contour plot for Q_{30}. The area that falls under the contour line of $Q_{30} > 40\%$ shows different combinations of X_1 and X_3 that can give acceptable drug dissolution.

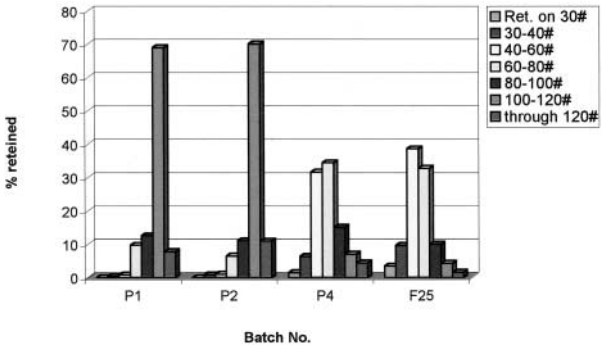

Figure 3. Histogram of particle size distribution of batches.

Table 5. Results of mean particle size, bulk, and tapped densities of selected batches.

Parameter	Batch P_1	Batch P_2	Batch P_4	Batch 25
Mean particle size (μ)	151.81	150.64	259.85	283.85
Bulk density (g/cm^3)	0.31	0.50	0.52	0.49
Tapped density (g/cm^3)	0.54	0.79	0.63	0.57

Percentage of Drug Released in 45 Minutes (Q_{45})

The refined model indicates that the main effect b_1 and b_3, the quadratic term b_{11} and b_{33}, and the interaction term b_{13} are significant. PVP seems to be more effective as compared with PEG 400 in controlling Q_{45}, because coefficient b_3 (7.9) was greater in magnitude compared with coefficient b_1 (3.7). Figure 6 shows the contour plot for Q_{45}. The area under the contour line of $Q_{45} > 50\%$ shows different combinations of X_1 and X_3 that give higher drug dissolution. The contour lines indicate that the addition of a higher amount of PEG 400 shows a higher drug dissolution if a high level of PVP is used.

Percentage of Drug Released in 120 Minutes (Q_{120})

The magnitudes of coefficients indicate that PVP is more effective than PEG 400 in controlling Q_{120}. Propylene glycol showed the least effect on drug dissolution ($b_2 = 0.89$). Figure 7 shows the contour plot for Q_{120}. The area that falls under the contour line of $Q_{120} > 60\%$ shows different combinations of X_1 and X_3 that can give high drug dissolution. The plot indicates that a higher amount of PEG 400 can give a higher drug dissolution if a high level of PVP is used.

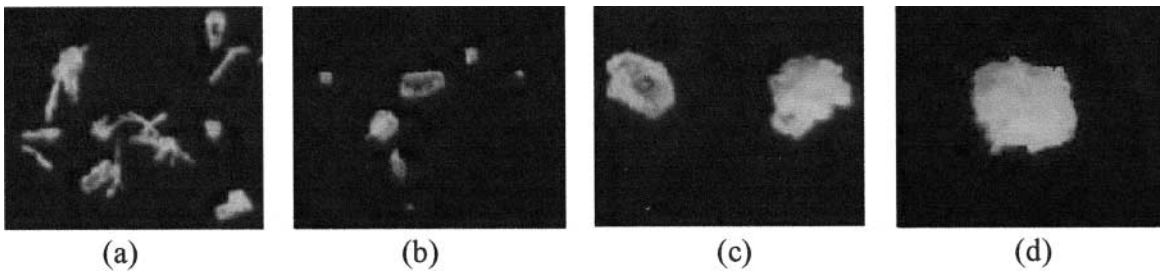

Figure 4. Photographs of batches (a) P_1, (b) P_2, (c) P_4, and (d) 25.

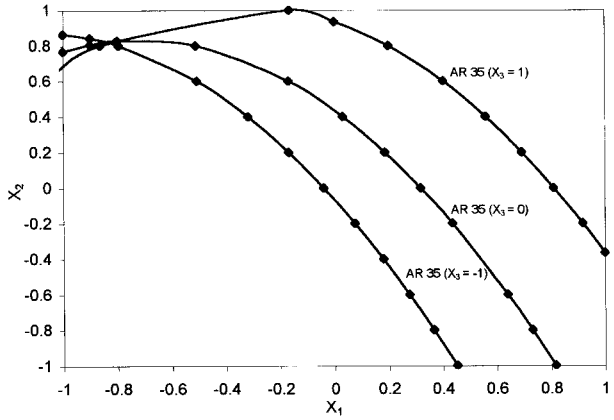

Figure 5. Contour plot for AR. X_1, X_2, and X_3 are levels of PEG 400, PG, and PVP K30, respectively.

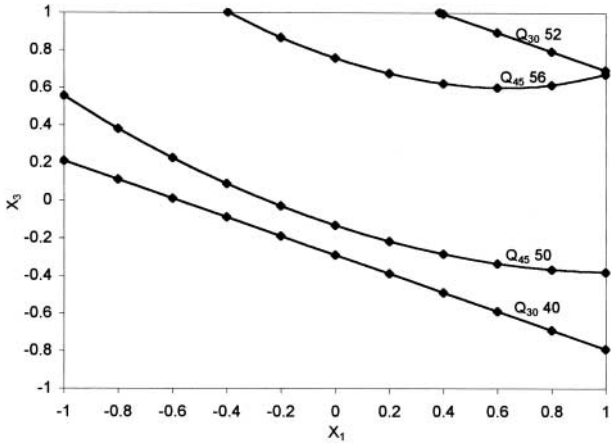

Figure 6. Contour plot for percentage of nimesulide released in 30 min (Q_{30}) and 45 min (Q_{45}). X_1, X_2, and X_3 are levels of PEG 400, PG and PVP K30, respectively.

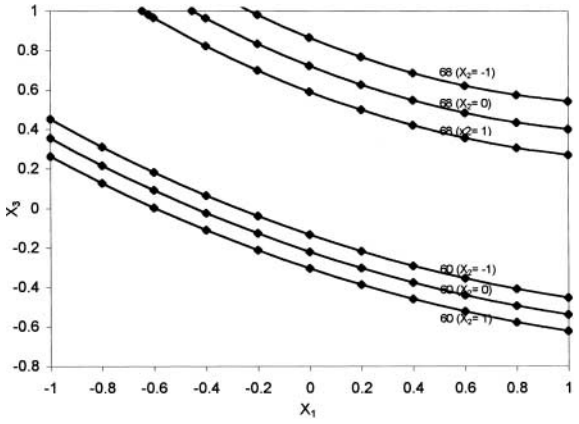

Figure 7. Contour plot for percentage of nimesulide released in 120 min (Q_{120}). X_1, X_2, and X_3 are levels of PEG 400, PG, and PVP K30, respectively.

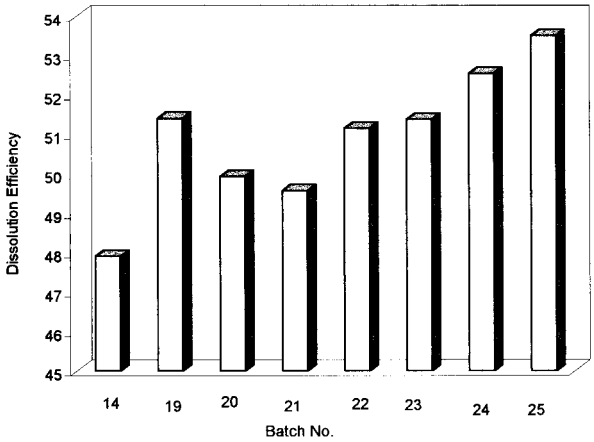

Figure 8. Histogram of dissolution efficiency of selected batches.

Table 6. Results of student's t-test and similarity factor (f_2).

Batch no.	t_{stat}	t_{cri}	f_2
25-14	0.75	2.18	56.34
25-19	0.29	2.18	75.15
25-20	0.45	2.18	69.11
25-21	0.50	2.18	65.15
25-22	0.33	2.18	71.71
25-23	0.26	2.18	78.58
25-24	0.14	2.18	86.69

The following constraints were arbitrarily used for the selection of an optimized batch: AR < 35°, $Q_{30} > 40\%$, $Q_{45} > 50\%$, and $Q_{120} > 60\%$. Batches 14 and 19–25 met the selection criteria. Batch 25 showed the lowest AR (Table 2) and the highest dissolution efficiency[30] among the selected batches (Fig. 8); hence, it was the optimized batch in the present study.

The similarity factor (f_2) was calculated using batch 25 as a reference batch.[31] The results of Table 6 show that the difference between batch 25 and batches 14 and 19–24 is statistically insignificant. The time required for water to penetrate in the wettability study was found to be 122 and 35 min, respectively, for pure drug powder and batch 25, which indicated that improved drug dissolution is because of increased wetting.

The liquisolid dispersion system containing drug and vehicle was studied by Spireas and Sadhu.[32] The drug remained in a solubilized state within the substrate of the liquisolid dispersion system. It is well

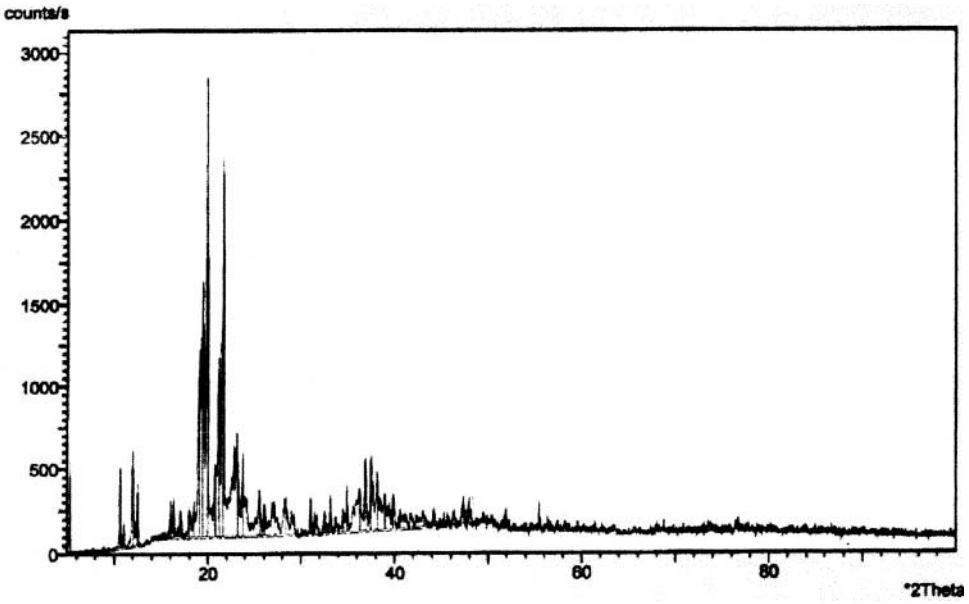

Figure 9. X-ray diffraction patterns of batch 25.

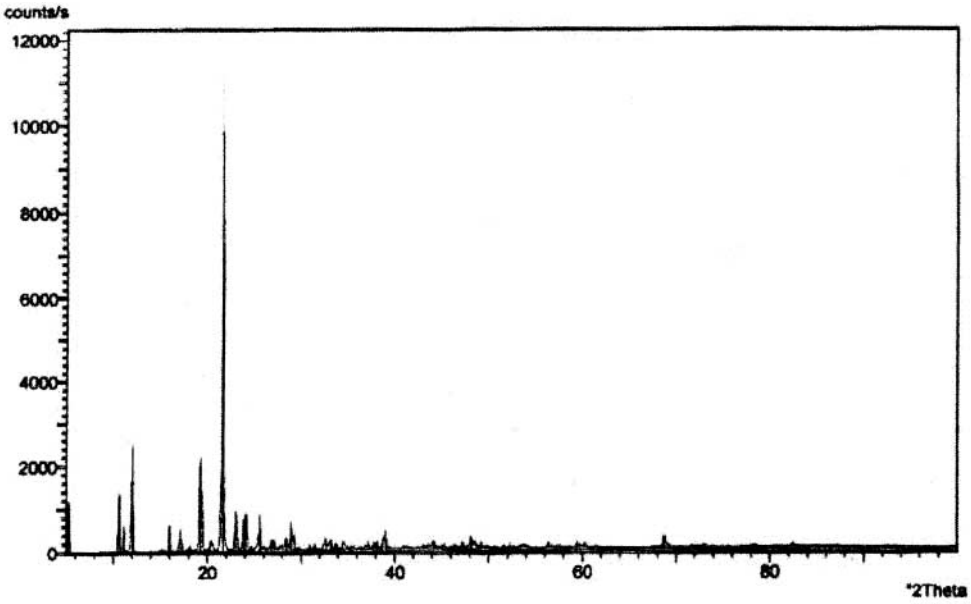

Figure 10. X-ray diffraction patterns of batch P_1.

known that better bioavailability of an orally administered poorly water-soluble drug can be achieved when it is in solution form. There is a possibility for the drug to precipitate out of the vehicle because of surface adsorption onto the carrier system. The precipitated drug particles may be in amorphous or solvated form possessing improved solubility.[33] The x-ray diffraction patterns (Figs. 9 and 10) show a smaller peak height of 2,737.38 counts/sec for batch 25, compared with the peak height of 1,1106.82 counts/sec for batch P_1. The results indicate that the drug in batch 25 is less crystalline, compared with batch P_1.[34] The solubility of the drug of batch 25 was found to be about 14 mg/100 mL of distilled water. Hence, increased solubility and dissolution of the drug were observed. Dissolution of the drug from pseudosolid dispersions may be also increased because of the presence of water-miscible adjuvant that acts

Table 7. Observed and predicted results of checkpoints.

	Batch C_1 ($X_1 = 0.6$, $X_2 = -1$, $X_3 = 0.8$)		Batch C_2 ($X_1 = 0.2$, $X_2 = -1$, $X_3 = -0.2$)	
Response	Observed	Predicted	Observed	Predicted
AR (°)	34.44	33.52	33.72	33.68
Q_{30}	50.19	51.25	41.34	41.54
Q_{45}	56.48	56.87	49.65	50.15
Q_{120}	68.70	69.04	60.70	60.19

as a wetting agent for the precipitated colloidal nanodrug particles. Drugs may be held within the powder substrate in partially solubilized and molecularly dispersed states. The partially solubilized and/or dispersed colloidal drug particles onto the carrier dissolve quickly in the dissolution medium from the pseudosolid dispersion system containing water-soluble agents like PEG 400, PG, PVP, and surfactants like Tween 80 and SLS. Because of improved wetting, solubilization, and increased surface area of the drug particles available for dissolution, the pseudosolid dispersion system of poorly water-soluble substances may be expected to display improved drug dissolution and enhanced bioavailability.

To validate the evolved mathematical models (reduced models for AR, Q_{30}, Q_{45}, and Q_{120}), two checkpoints were selected. Two batches (C_1 and C_2) were prepared and evaluated. Observed and predicted values are shown in Table 7. Calculated values are in good agreement with the observed values. Hence, it can be concluded that the evolved models may be used for theoretical prediction of responses within the factor space.

CONCLUSIONS

Cogrinding of nimesulide with an aqueous solution of PEG 400, PG, and PVP in the presence of the optimized concentration of Tween 80 and SLS was effective in improving dissolution of nimesulide. Polyvinylpyrrolidone K30 showed more dissolution-enhancing effects, compared with PEG 400 and PG. More than a four-fold increase in drug dissolution was observed in selected batches, as judged from Q_{120} values using pseudosolid dispersion of nimesulide. The study revealed that optimum levels of solubilizing agents should be used, because higher levels of liquid agents had adverse effects on flow of granules.

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