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Effect of particle size on the available surface area of nifedipine from nifedipine-polyethylene glycol 6000 solid dispersions

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Abstract

Solid dispersions containing 5%, 10%, 20%, 30% and 50% of nifedipine were prepared with polyethylene glycol (PEG) 6000 as carrier, respectively, by the fusion method. Drug release from four different size fractions of nifedipine-polyethylene glycol 6000 solid dispersions were examined. The probability parameters of Weibull distribution or log-normal distribution could be obtained from linear regression of the dissolution data. The effects of particle size on the dissolution rate of nifedipine were evaluated in terms of the time course of the available surface area ($S(t)$). The X-ray diffraction patterns showed that nifedipine was dispersed homogeneously in an amorphous state in the solid dispersions with nifedipine concentration up to 10%. The initial values and faster rate of decrease of $S(t)$ during the dissolution process were markedly enhanced in the solid dispersions with lower contents of nifedipine (5% and 10%) due to the formation of high energy metastable (amorphous) states of the drug and differences in the particle sizes had little effect on the values of the available surface area and the dissolution of the drug. Values of available surface area were particle size dependent for the solid dispersions with higher contents of nifedipine (20%, 30% and 50%) and the rate of decrease of $S(t)$ was enhanced as the particle size reduced.

Keywords: Particle size; Nifedipine; Polyethylene glycol; Solid dispersion; Dissolution; Available surface area; Weibull distribution; Log-normal distribution

1. Introduction

The mechanism for drug release from different particle size fractions of solid dispersions is very complex. It has been reported that there were no differences in the sulfathiazole dissolution from its 5% or 10% sulfathiazole-urea solid dispersions between the 840-2000 μm and 150-250 μm particle size fractions (Chiou and Niazi, 1971). That smaller sieve fractions gave faster dissolution was observed with dissolution of solid dispersions of sodium salicylate in PEG 3000 (Sjokvist and Nystrom, 1988). However, the fastest dissolution rates from 25% nifedipine-PVP solid dispersions was obtained from particles of 48–60 mesh size rather than from 12–16 mesh size or < 145 mesh size (Sugimoto et al., 1980). That such an optimal size

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range existed for maximum dissolution rates was also observed with dissolution of different size fractions of indomethacin-PEG 6000 solid dispersions (Ford and Elliott, 1985).

The time course equations of the available surface area ($S(t)$) generated in the dissolution process of solid dosage forms were derived (Kouchiwa et al., 1985) and subsequent values of $S(t)$ of a drug could be calculated from the dissolved amount and the dissolution parameters.

The aim of this study was to evaluate the dissolution characteristics of nifedipine from different particle size fractions of nifedipine-PEG 6000 solid dispersions using the time course of the available surface area ($S(t)$).

2. Materials and methods

2.1. Materials

Nifedipine (Industrie Chimiche Italiane, Lot 4616); PEG 6000 (Lux, Lot 041826); sodium dodecyl sulfate (Merck, Lot 3311901); all other chemicals were of reagent grade.

2.2. Methods

All experiments were carried out under subdued light to prevent light degradation of nifedipine.

2.3. Preparation of solid dispersions

Solid dispersions containing 5, 10, 20, 30 and 50% of nifedipine in the nifedipine-PEG 6000 systems were prepared by the fusion method. Both the drug and the carrier were mixed for 5 min in a laboratory V-shape mixer. The physical mixtures were heated directly on the hot plate at 80–85°C until completely melted. The fused mixtures were solidified by rapid cooling by immersion in a freezing mixture consisting of ice and sodium chloride. After cooling, the obtained solids were then stored for 24 h in a desiccator over silica gel. They were pulverized and sieved on a sieve shaker (Retsh, Germany) to give four different size fractions of powders: 600–425 μm, 425–250 μm, 250–150 μm and 150–90 μm.

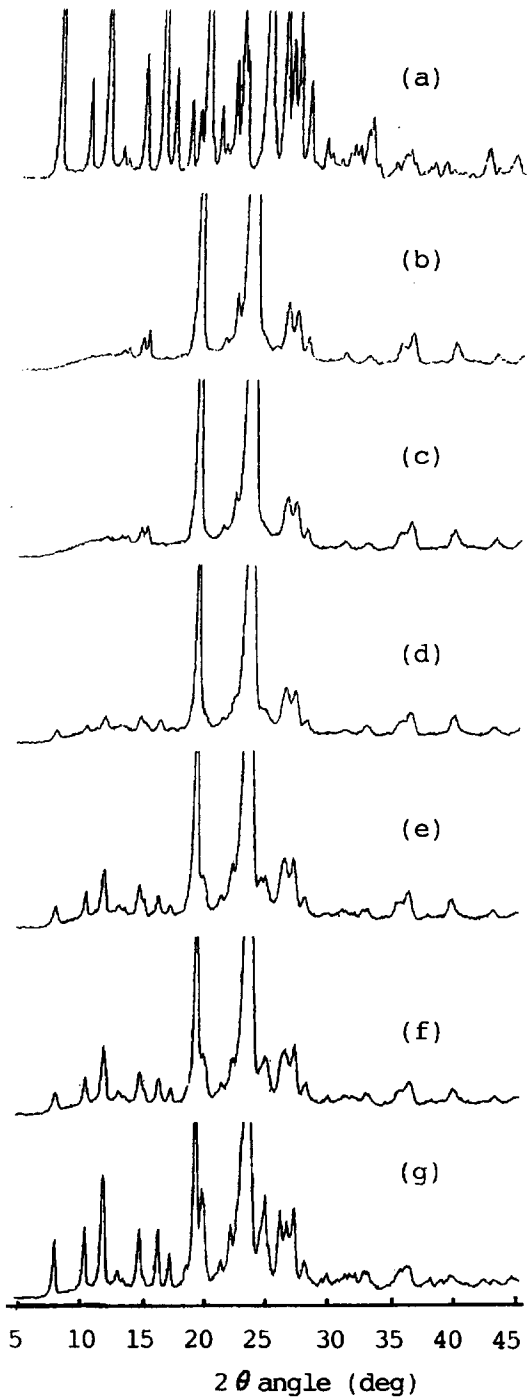

Fig. 1. X-ray diffraction patterns of nifedipine (a), PEG 6000 (b), nifedipine-PEG 6000 solid dispersions with 5% (c), 10% (d), 20% (e), 30% (f) and 50% (g) nifedipine.

Table 1
Solubility of nifedipine in solid dispersions with PEG 6000

Content of nifedipine (% w/w)	Solubility at 37 ± 1°C (mg/l) (in water) mean ± S.D.	Solubility at 37 ± 1°C (mg/l) (in pH 4.5 with 0.25% SDS) mean ± S.D.
5	13.5 ± 1.1	81.7 ± 0.9
10	11.6 ± 0.9	80.6 ± 0.9
20	11.5 ± 0.8	79.5 ± 0.8
30	10.4 ± 0.9	80.7 ± 1.2
50	11.7 ± 0.7	81.3 ± 1.7
Pure nifedipine	8.7 ± 0.5	79.4 ± 2.9

2.4. X-ray powder diffraction study

Diffraction patterns of the samples were obtained by scanning at 2°/min through the 2 θ angle on a diffractometer (Shimazu XD-D1, Japan) using Cu-K α radiation. Only sieved fractions of 150–90 μm of the samples were reported.

2.5. Solubility study

The aqueous solubility of pure nifedipine and nifedipine from solid dispersions was determined spectrophotometrically at 340 nm in an aqueous solution or in an acetate buffer solution containing various concentrations of surfactant. Amounts of pure drug and solid dispersions corresponding to 20 mg nifedipine were added to 20 ml of medium in a brown test tube and then sonicated (Bransonic, 50 kHz, USA) for about 20 min. The samples were allowed to agitate for 48 h at 37 ± 1°C water bath shaker. At the end of this period, the sample solution was withdrawn and centrifuged. The supernatant was filtered by a syringe fitted with a 0.45 μm membrane filter (Nuclepore, USA), suitably diluted (if any) before measurement. The results presented are mean values of five determinations.

2.6. Dissolution study

The solid dispersed samples containing 10 mg of nifedipine were filled in colorless, transparent No. 3 hard gelatin capsules. The drug dissolution rate tests were carried out at 37°C in pH 4.5 acetate buffer solutions containing 0.25% sodium lauryl sulfate as dissolution medium by using USP XXII dissolution tester (Jasco DT-610, Japan) with a rotational paddle (Method 2) with speed kept constant at 100 rev./min. The amount of nifedipine dissolved from each predetermined time interval was monitored spectrophotometrically at 340 nm. The results presented are mean value of six capsules.

2.7. Determination of the dissolution rate constant per unit surface area (k)

A nifedipine compact having a diameter of 10 mm was prepared by compressing 100 mg of the drug powders at a pressure of 132.6 MN/m^2, using a hydraulic press (Carver press). It was then placed in a holder and embedded in paraffin and stuck perpendicularly to a rotating shaft so that one of the planar flat sides was exposed. The dissolution rate tests were conducted by the same method as was applied in the dissolution study.

3. Results and discussion

3.1. Solid state analysis

Fig. 1 shows the X-ray diffraction patterns of nifedipine-PEG 6000 solid dispersions with various contents of nifedipine. All the dispersions showed the presence of a characteristic peaks of PEG 6000 and the characteristic peaks for nifedipine in these patterns gradually increased

with an increase in nifedipine concentration. The lack of diffraction peaks of crystalline nifedipine in the solid dispersions with nifedipine concentration up to 10% indicated the presence of an amorphous state of drug in these dispersions. For each of nifedipine-PEG 6000 solid dispersions,

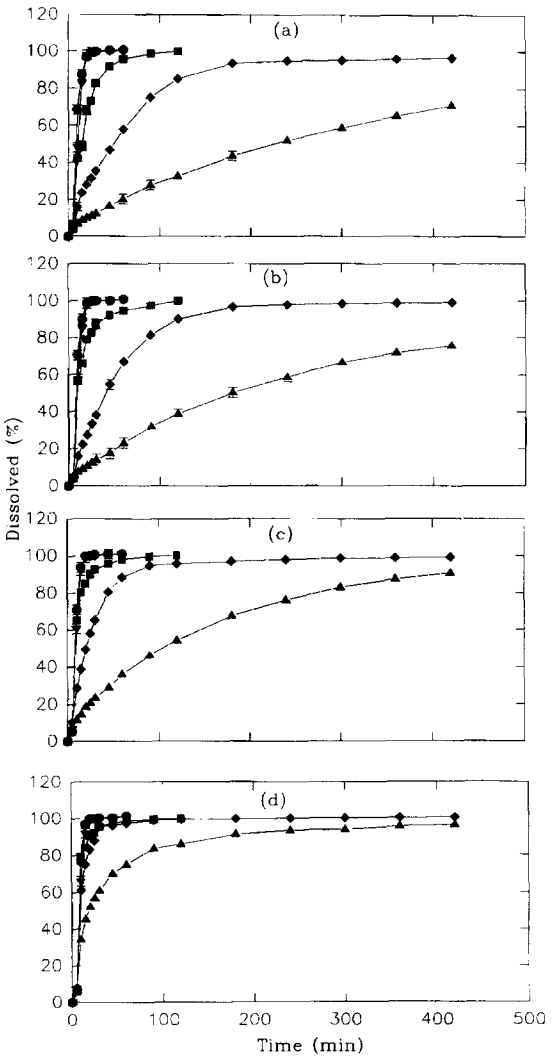

Fig. 2. Dissolution profiles of nifedipine from four different size fractions of nifedipine-PEG 6000 solid dispersions with various contents of nifedipine: (a) 600–425 μm, (b) 425–250 μm, (c) 250–150 μm and (d) 150–90 μm. ●, 5% nifedipine; ▼, 10% nifedipine; ■, 20% nifedipine; ◆, 30% nifedipine; ▲, 50% nifedipine.

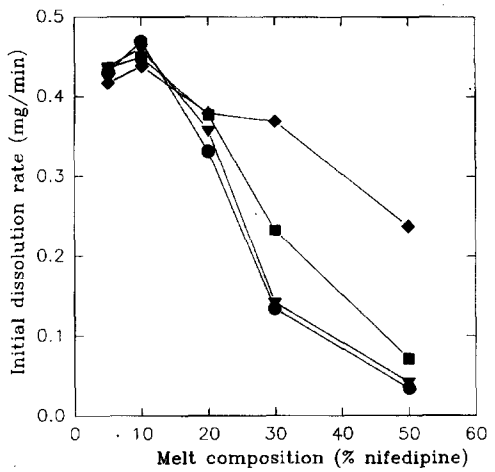

Fig. 3. The effects of nifedipine-PEG 6000 composition and particle size on the initial dissolution rates of solid dispersions. ●, 600–425 μm; ▼, 425–250 μm; ■, 250–150 μm; ◆, 150–90 μm.

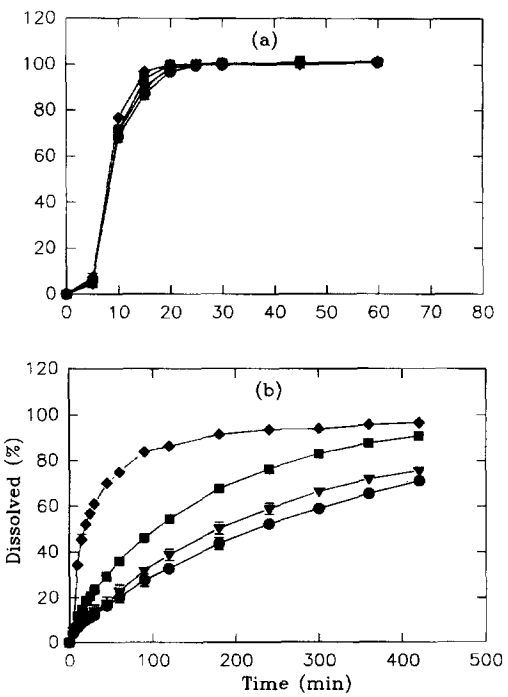

Fig. 4. Effect of particle size on the dissolution profiles of nifedipine from nifedipine-PEG 6000 solid dispersions with (a) 5% and (b) 50% nifedipine. ●, 600–425 μm; ▼, 425–250 μm; ■, 250–150 μm; ◆, 150–90 μm.

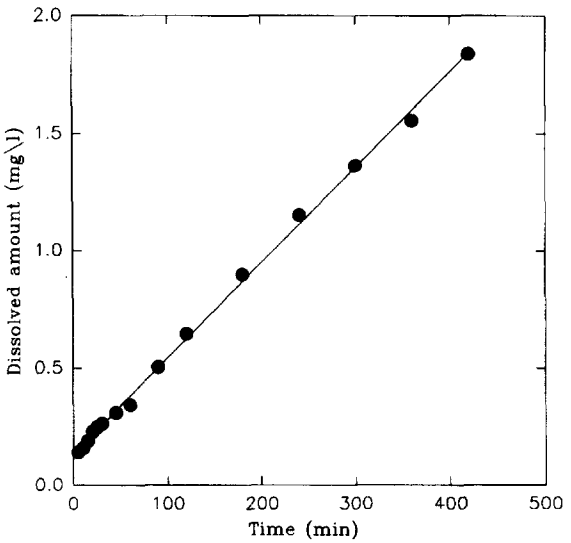

Fig. 5. Dissolution rate constant per unit surface area (k) of nifedipine.

there were no differences in their diffraction patterns among the four different particle sizes.

3.2. Solubility study

The solubility of pure nifedipine and nifedipine from solid dispersions is shown in Table 1. The solubility of pure nifedipine, obtained by the described method, is 8.7 mg/l in water or 79.4 mg/l in acetate buffer solutions containing 0.25% sodium lauryl sulfate. For all the solid dispersions tested, an increase in nifedipine solubility, compared with the solubility of the pure drug, was found.

3.3. Dissolution study

The dissolution profiles of nifedipine from the four different size ranges of nifedipine-PEG solid dispersion with various contents of nifedipine are shown in Fig. 2. The dissolution of nifedipine was markedly enhanced in the solid dispersions with lower contents of nifedipine (5% and 10%) rather than with higher contents of nifedipine (20%, 30% and 50%). The results confirmed the data from X-ray diffraction demonstrating that nifedipine could be dispersed homogeneously in an amorphous state in solid dispersions with low contents of nifedipine due to the inhibiting effect of PEG on drug crystallization (Save and Venkitachalam, 1992).

From the dissolution profiles estimates of the initial release rate of nifedipine were made and these are plotted and presented in Fig. 3. Fig. 4 shows the effect of particle size on the dissolution profiles of nifedipine from nifedipine-PEG 6000 solid dispersions with 5% and 50% nifedipine. It is clear from Figs. 3 and 4 that the differences in

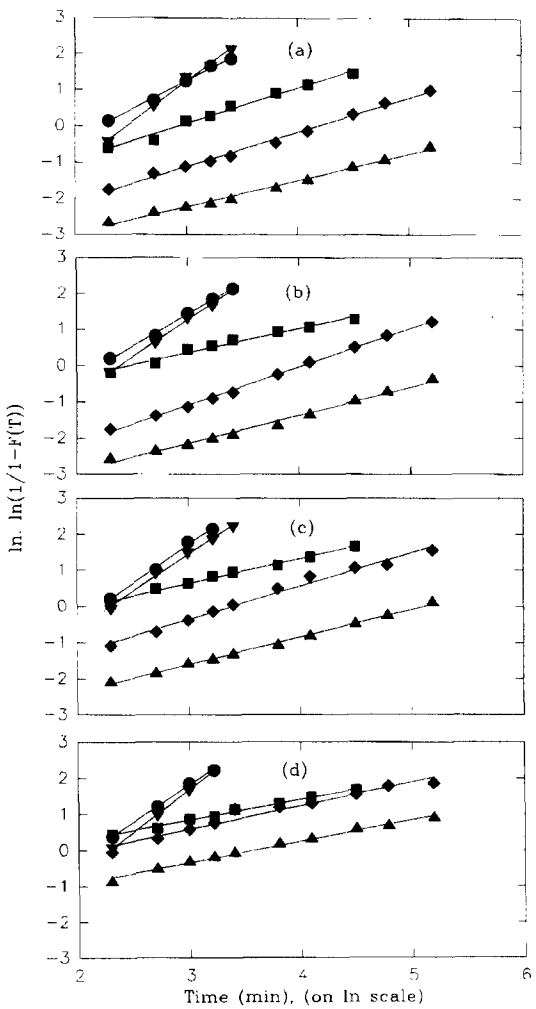

Fig. 6

Fig. 6. Weibull plots of four different size fractions of nifedipine-PEG 6000 solid dispersions with various contents of nifedipine: (a) 600–425 μm, (b) 425–250 μm, (c) 250–150 μm and (d) 150–90 μm. Symbols same as in Fig. 2.

Table 2
Probability parameters of the Weibull distribution from different size fractions of nifedipine PEG 6000 solid dispersions

Content of nifedipine (% w/w)	Size fraction	a	b	T_{20} (min)	T_{50} (min)	T_d (min)	r
5	600–425 μm	36.81	1.618	3.7	7.4	9.3	0.998
	425–250 μm	55.24	1.814	3.9	7.5	9.1	0.998
	250–150 μm	118.76	2.162	4.6	7.7	9.1	0.997
	150–90 μm	73.86	2.039	3.9	6.9	6.4	0.999
10	600–425 μm	311.14	2.326	6.2	10.1	11.8	0.997
	425–250 μm	142.44	2.078	5.3	9.1	10.9	0.999
	250–150 μm	112.68	2.055	4.8	8.3	9.9	0.997
	150–90 μm	214.85	2.349	5.2	8.4	9.8	0.999
20	600–425 μm	18.33	0.991	4.1	13.0	18.8	0.993
	425–250 μm	5.27	0.674	1.3	6.8	11.8	0.988
	250–150 μm	4.33	0.698	0.9	4.8	8.2	0.995
	150–90 μm	2.39	0.572	0.3	2.4	4.6	0.996
30	600–625 μm	36.77	0.841	12.2	47.2	72.9	0.991
	425–250 μm	47.32	0.938	12.3	41.3	61.1	0.993
	250–150 μm	10.88	0.695	3.6	18.3	31.1	0.973
	150–90 μm	3.98	0.656	0.8.	4.7	8.2	0.978
50	600–425 μm	98.37	0.780	52.4	224.3	358.9	0.997
	425–250 μm	99.97	0.815	45.1	181.4	284.4	0.998
	250–150 μm	55.55	0.799	23.4	96.5	152.6	0.999
	150–90 μm	6.78	0.532	2.2	18.3	36.5	0.993

a: the scale parameter; b: the shape parameter; T_{20}, T_{50} and T_d as the times when 20%, 50% and 63.2% of the available surface area has been generated during the dissolution process, respectively.

particle sizes of the solid dispersions with lower contents of nifedipine had little effect on the dissolution rates of the drug. This was attributed to the fact that this kind of solid dispersions possessed the same available surface area of nifedipine during the dissolution process due to the presence of the amorphous state of the drug. On the other hand, dissolution rates are particle size dependent for the solid dispersions with higher contents of nifedipine. The results indicated that smaller particles possessed higher dissolution rates than larger particles due to the former possessing a greater available surface area. It was thus proposed that the available surface area of drug generated may control the release of drug from solid dispersions.

3.4. Determination of k

The results of the dissolution rate constant tests on a nifedipine compact are shown in Fig. 5. An approximately linear relationship obtained between time and the dissolved amount of nifedipine. If $Cs > > C$ (sink condition), the Noyes-Whitney equation (Noyes and Whitney, 1897) could be rearranged and integrated into Eq. (1):

$$C = K \cdot S \cdot Cs/V \cdot t \quad (1)$$

By substituting the determined slope of the line (Fig. 5) into Eq. (1), $k = 5.87 \times 10^{-2}$cm/min was then obtained according to the previous method (Itai et al., 1985).

3.5. Weibull distribution

The Weibull distribution (Langenbucher, 1972) was applied to the dissolution data for linearization of dissolution profiles and expressed as follows:

$$F(t) = 1 - \exp(-(t^b/a)) \quad (2)$$

where $F(t)$ is the fraction of the total drug released at time t and a is the scale parameter and b is the shape parameter.Eq. (2) may be rearranged into

$$\ln \cdot \ln(1/(1 - F(t))) = b \cdot \ln t - \ln a \quad (3)$$

Table 3
Available surface area (cm^2) of nifedipine from nifedipine-PEG 6000 solid dispersions with various particle sizes by the Weibull distribution method

Available surface area (cm^2)Time (min)														
5	10	15	20	25	30	45	60	90	120	180	240	300	360	420
I														
189.3[a]	135.8	61.3	20.2	5.2	1.1	0	0	0	0	0	0	0	0	0
200.1[b]	151.2	58.4	13.7	2.1	0.2	0	0	0	0	0	0	0	0	0
206.7[c]	178.9	51.6	5.7	0.2	0	0	0	0	0	0	0	0	0	0
235.7[d]	157.9	35.8	3.2	0.1	0	0	0	0	0	0	0	0	0	0
II														
184.3[a]	126.8	108.5	30.1	3.9	0.3	0	0	0	0	0	0	0	0	0
173.3[b]	155.8	88.3	24.4	3.8	0.3	0	0	0	0	0	0	0	0	0
173.8[c]	179.8	71.9	15.0	1.7	0.1	0	0	0	0	0	0	0	0	0
198.5[d]	179.7	65.5	7.2	0.3	0	0	0	0	0	0	0	0	0	0
III														
93.6[a]	71.4	54.6	41.8	32.1	24.7	11.2	5.1	1.1	0.2	0	0	0	0	0
99.3[b]	56.7	37.5	26.5	19.6	14.8	7.2	3.9	1.3	0.5	0.1	0	0	0	0
112.1[c]	58.4	35.5	23.1	15.8	11.1	4.4	1.9	0.5	0.1	0	0	0	0	0
96.6[d]	43.1	24.1	14.9	9.9	6.9	2.7	1.2	0.3	0.1	0	0	0	0	0
IV														
36.6[a]	30.2	26.2	23.3	20.9	19.1	14.7	11.7	7.8	5.3	2.7	1.4	0.8	0.4	0.3
37.5[b]	32.9	29.5	26.6	24.2	22.1	16.9	13.2	8.2	5.1	2.1	0.9	0.4	0.2	0.1
67.9[c]	46.2	35.2	28.2	23.3	19.6	12.6	8.7	4.6	2.6	1.1	0.4	0.2	0.1	0
105.8[d]	55.1	33.8	22.5	15.7	11.3	4.8	2.3	0.7	0.2	0	0	0	0	0
V														
12.3[a]	10.3	9.2	8.5	7.9	7.5	6.5	5.8	4.8	4.2	3.2	2.6	2.2	1.8	1.5
13.4[b]	11.5	10.4	9.6	9.0	8.5	7.4	6.6	5.5	4.7	3.6	2.8	2.3	1.9	1.6
22.4[c]	18.6	16.4	14.9	13.7	12.7	10.6	9.0	6.9	5.5	3.7	2.6	1.9	1.4	1.0
60.0[d]	37.2	27.2	21.5	17.7	14.9	9.9	7.2	4.4	2.9	1.5	0.9	0.6	0.4	0.3

I: 5% nifedipine; II: 10% nifedipine; III: 20% nifedipine; IV: 30% nifedipine; V: 50% nifedipine.[a]600–425 μm; [b]425–250 μm; [c]250–150 μm; [d]150–90 μm.

The ln·ln—ln plot of $1/(1\text{-}F(t))$ versus t becomes linear and parameters a and b can thus be obtained from the y-intercept and the slope of the line. Weibull plots of various particle sizes of nifedipine-PEG 6000 solid dispersions are shown in Fig. 6. It was found that Weibull plots for the solid dispersions with lower contents of nifedipine (5% and 10%) were sharper than that of higher contents of nifedipine. Values of the probability parameters a and b are presented in Table 2. It was evident from Table 2 that the larger values of a and b were obtained for the solid dispersions with lower contents of nifedipine (5% and 10%) rather than that of with higher contents of nifedipine.

Kouchiwa et al. (1985) derived time course equations for available surface area ($S(t)$) generated in the dissolution process as was shown in Eq. (4):

$$S(t) = b \cdot V/(a \cdot k)t^{b-1} \cdot \ln(Cs/(Cs - Wo/V)) \times \cdot \exp(-(t^b/a)) \quad (4)$$

By substituting the determined values (a,b) of the Weibull distribution into Eq. (4), the time course of the available surface area, $S(t)$, could be obtained.

The $S(t)$ values of nifedipine from four different particle sizes of nifedipine-PEG 6000 solid dispersions with various contents of nifedipine and the patterns obtained are shown in Table 3 and Fig. 7. The initial values of $S(t)$ and faster

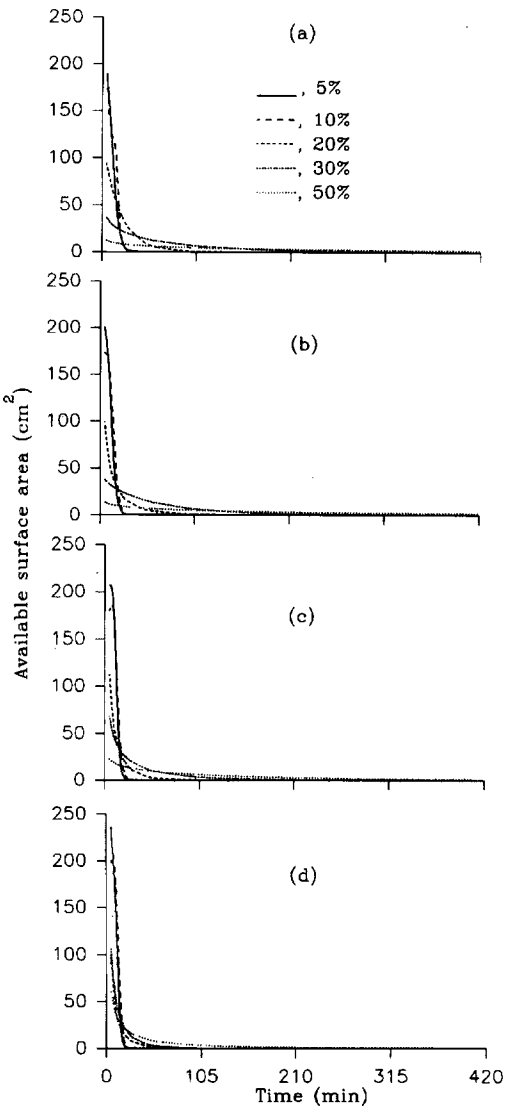

Fig. 7. $S(t)$ vs. t patterns of four different size fractions of nifedipine-PEG 6000 solid dispersions with various contents of nifedipine by the Weibull distribution method: (a) 600–425 μm, (b) 425–250 μm, (c) 250–150 μm and (d) 150–90 μm. Symbols same as (a).

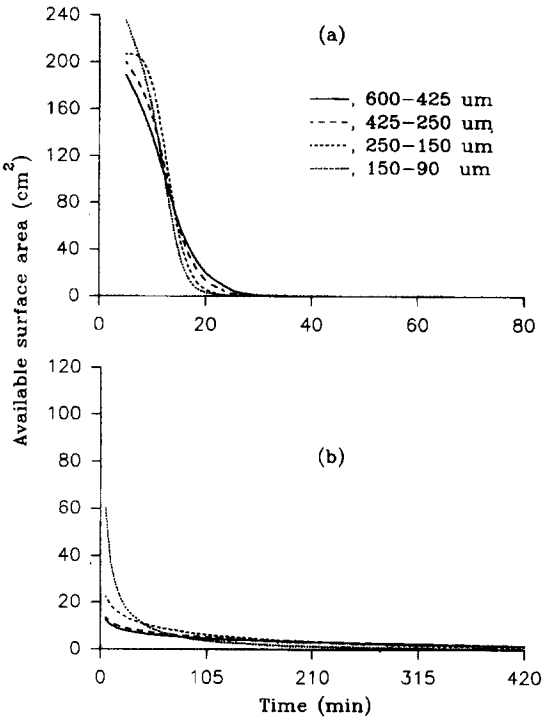

Fig. 8. Effect of particle size on the available surface area of nifedipine from (a) 5% and (b) 50% nifedipine-PEG 6000 solid dispersions by the Weibull distribution method. Symbols same as (a).

rate of decrease of $S(t)$ during the dissolution process were markedly enhanced in the solid dispersions with lower contents of nifedipine (5% and 10%). However, with higher contents of nifedipine, the enhancements were not so marked. This was attributed to the fact that the nifedipine could be dispersed homogeneously in an amorphous state in solid dispersions with low contents of nifedipine and thus $S(t)$ values generated during the dissolution process increased.

Fig. 8 shows the effect of particle size on the available surface area of nifedipine from 5% and 50% nifedipine-PEG 6000 solid dispersions by the Weibull distribution method. It was found that the differences in particle sizes of the solid dispersions with 5% nifedipine had little effect on the $S(t)$ value of the drug, whereas $S(t)$ values were particle size dependent for the solid dispersions with higher contents of nifedipine and the rate of decrease of $S(t)$ due to dissolution enhanced as the particle size reduced. This result indicated that the values of $S(t)$ generated were in good agreement with drug dissolution.

3.6. Log-normal distribution

Wagner (1969) demonstrated that the amount

of surface area available during an in vitro dissolution test may be characterized by a normal logarithmic distribution. By using the log-normal distribution, the two equations such as $F(t)$ and available surface area ($S(t)$) were developed by Kouchiwa et al. (1985) and were shown as follows:

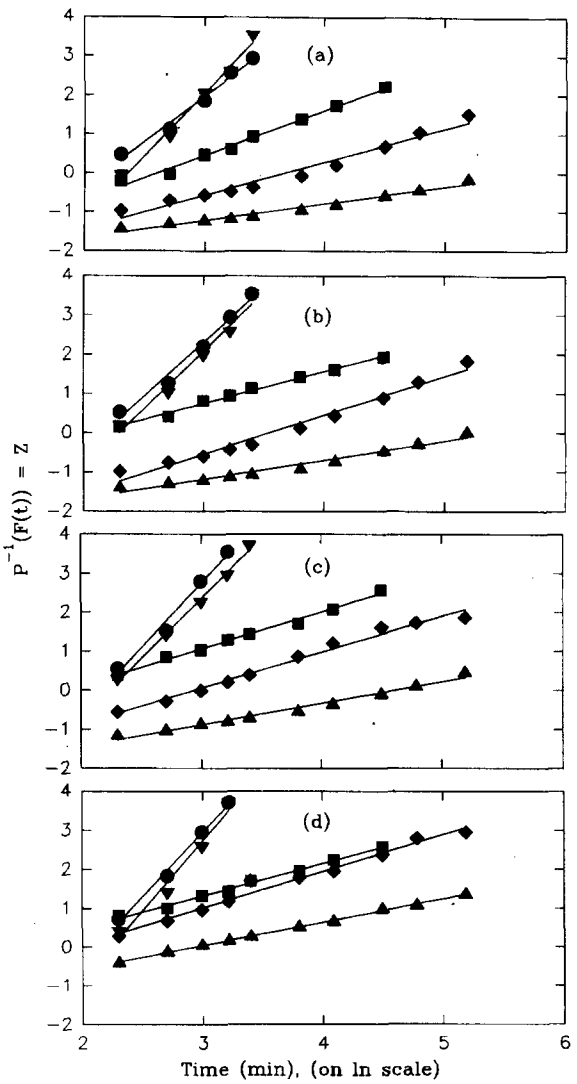

Fig. 9. Log-normal plots of four different size fractions of nifedipine-PEG 6000 solid dispersions with various contents of nifedipine: (a) 600–425 μm, (b) 425–250 μm, (c) 250–150 μm and (d) 150–90 μm. Symbols same as in Fig. 2.

$$F(t) = 1/(\sqrt{2\pi}\cdot\sigma)\cdot\int_0^{\ln t} \exp(-(\ln t - \ln\mu)^2/(2\cdot\sigma^2)) \times d(\ln t) \quad (5)$$

$$S(t) = V/(\sqrt{2\pi}\cdot\sigma\cdot k\cdot t)\cdot\ln(Cs/(Cs - Wo/V)) \times \cdot\exp(-(\ln t - \ln\mu)^2/(2\cdot\sigma^2)) \quad (6)$$

where μ is the logarithmic mean of t and σ is the standard deviation. On the other hand, $F(t)$ of the log normal distribution could be rewritten as

$$F(t) = 1/\sqrt{2\pi}\cdot\int_{-\infty}^{Z} \exp(-Z^2/2)\mathrm{d}Z = P(Z) \quad (7)$$

Eq. (7) could be rearranged as

$$Z = P^{-1}(F(t)) = (\ln t - \ln\mu)/\sigma \quad (8)$$

The linear relationships of $F(t)$ of nifedipine from nifedipine-PEG 6000 solid dispersions were obtained for the $P^{-1}(F(t))$-ln plot of $F(t)$ versus t and the approximate values of the probability parameters μ and σ were determined by linear regression. Log-normal plots of different size fractions of nifedipine-PEG 6000 solid dispersions with various contents of nifedipine are shown in Fig. 9. It was found that log-normal plots for the solid dispersion with lower contents of nifedipine (5% and 10%) were sharper than that of higher contents of nifedipine. The probability parameters μ and σ obtained from Fig. 9 are shown in Table 4. It is clear that the particle size effect of solid dispersions with higher concentrations of nifedipine on the probability parameters is more significant than that of lower contents of nifedipine. However, there were no differences in the probability parameters of solid dispersions with lower contents of nifedipine (5% and 10%) among the four size fractions.

By substituting the determined probability parameters (μ and σ) of the log-normal plots into Eq. (6), the time course of the available surface area ($S(t)$) could be calculated. Fig. 10 shows the $S(t)$ versus t patterns of the nifedipine-PEG 6000 solid dispersions during the dissolution process by the log-normal distribution method (Table 5). The solid dispersions with lower contents of nifedipine (5% and 10%) gave the larger values of $S(t)$ generated and the faster rate of decrease of $S(t)$ due to dissolution, whereas the solid dispersions

Content of nifedipine (% w/w)	Size fraction	σ	μ (min)	T_{max} (min)	r
5	600–425 μm	0.43	8.58	7.13	0.992
	425–250 μm	0.36	8.76	7.71	0.991
	250–150 μm	0.31	8.79	8.03	0.991
	150–9O μm	0.30	8.19	7.47	0.997
10	600–425 μm	0.31	10.59	9.62	0.992
	425–250 μm	0.36	9.38	8.24	0.993
	250–150 μm	0.32	9.36	8.45	0.997
	150–90 μm	0.28	9.37	8.67	0.986
20	600–425 μm	0.86	13.49	6.44	0.995
	425–250 μm	1.22	8.05	1.82	0.996
	250–150 μm	1.05	6.59	2.19	0.996
	150–90 μm	1.21	4.08	0.95	0.996
30	600–425 μm	1.21	39.47	9.13	0.991
	425–250 μm	1.01	34.57	12.34	0.995
	250–150 μm	1.23	18.01	3.96	0.989
	150–90 μm	1.07	6.81	2.17	0.989
50	600–425 μm	1.87	213.2	6.39	0.984
	425–250 μm	1.57	163.3	13.89	0.993
	250–150 μm	1.49	80.14	8.71	0.986
	150–90 μm	1.71	18.56	1.01	0.999

σ: standard deviation; μ: the logarithmic mean of t; T_{max}:peak time.

with higher contents of nifedipine gave the smaller values of $S(t)$ generated. The faster available surface area generated observed with lower contents of nifedipine was due to the formation of high energy metastable (amorphous) states of the drug. Fig. 11 shows the effect of particle size on the available surface area of nifedipine from 5% and 50% nifedipine-PEG 6000 solid dispersions by the log-normal method. It was found that the effects of particle size on the $S(t)$ generated from solid dispersions with higher contents of nifedipine were more significant than that of solid dispersions with lower contents of nifedipine. It is clear from Fig. 11 that the results are the same as shown in Fig. 8.

4. Conclusion

The differences in particle sizes of the solid dispersions with lower contents of nifedipine had little effect on the dissolution rates or available surface area ($S(t)$) of the drug during the dissolution process. This was attributed to the formation of high energy metastable (amorphous) states of the drug. Dissolution rates and values of available surface area ($S(t)$) were particle size dependent for the solid dispersions with higher contents of nifedipine (20%, 30% and 50%) and smaller particles possessed higher dissolution rates or higher initial values than larger particles. This may be attributed to the fact that PEG dissolved from the particles and left a hard surface layer rich in the crystalline form of nifedipine in which slower dissolution occurred. Therefore, dissolution or decreasing rate of $S(t)$ enhanced as particle size reduced.

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Table 5
Available surface area (cm^2) of nifedipine from nifedipine-PEG 6000 solid dispersions with various particle sizes by the log-normal distribution method

Available surface area (cm^2)Time (min)														
5	10	15	20	25	30	45	60	90	120	180	240	300	360	420
I														
193.9[a]	200.2	61.2	15.4	3.9	1.0	0	0	0	0	0	0	0	0	0
150.9[b]	238.7	55.4	9.1	1.4	0.2	0	0	0	0	0	0	0	0	0
104.3[c]	278.8	41.7	3.6	0.3	0	0	0	0	0	0	0	0	0	0
161.6[d]	243.2	27.7	2.0	0.1	0	0	0	0	0	0	0	0	0	0
II														
31.6[a]	290.9	105.1	18.1	2.5	0.3	0	0	0	0	0	0	0	0	0
65.2[b]	273.8	87.1	15.9	2.6	0.4	0	0	0	0	0	0	0	0	0
84.1[c]	280.6	64.5	8.6	1.0	0.1	0	0	0	0	0	0	0	0	0
52.2[d]	319.9	52.9	4.1	0.3	0	0	0	0	0	0	0	0	0	0
III														
109.6[a]	100.4	70.6	48.0	32.9	23.1	8.9	3.9	1.0	0.4	0	0	0	0	0
139.4[b]	74.1	44.0	28.5	19.5	14.0	6.2	3.2	1.2	0.5	0	0	0	0	0
168.8[c]	80.7	42.8	24.9	15.6	10.3	3.6	1.6	0.4	0.2	0	0	0	0	0
149.9[d]	57.7	28.3	15.9	9.8	6.5	2.3	1.1	0.3	0.1	0	0	0	0	0
IV														
35.3[a]	39.8	36.7	32.4	28.2	24.6	16.7	11.9	6.6	4.1	1.9	1.0	0.6	0.4	0.3
29.4[b]	42.8	42.9	39.1	34.3	29.8	19.4	12.9	6.4	3.5	1.3	0.6	0.3	0.2	0.1
86.7[c]	66.5	49.2	37.2	28.8	22.8	12.6	7.7	3.5	1.9	0.7	0.3	0.2	0.1	0
105.8[d]	164.5	80.4	43.5	25.8	16.4	10.9	4.0	1.8	0.5	0.2	0	0	0	0
V														
9.8[a]	11.1	10.9	10.4	9.9	9.4	7.9	6.9	5.3	4.3	2.9	2.2	1.8	1.4	1.2
9.9[b]	12.0	12.3	11.9	11.4	10.9	9.3	7.9	6.0	4.8	3.2	2.4	1.8	1.4	1.2
21.8[c]	23.2	21.8	19.9	18.1	16.5	12.7	10.1	6.8	4.9	2.9	1.9	1.4	1.0	0.8
80.0[d]	50.4	35.6	26.9	21.1	17.2	10.4	7.1	3.9	2.5	1.2	0.7	0.5	0.3	0.2

I: 5% nifedipine; II: 10% nifedipine; III: 20% nifedipine; IV: 30% nifedipine; V: 50% nifedipine. [a]600–425 μm; [b]425–250 μm; [c]250–150 μm; [d]150–90 μm.

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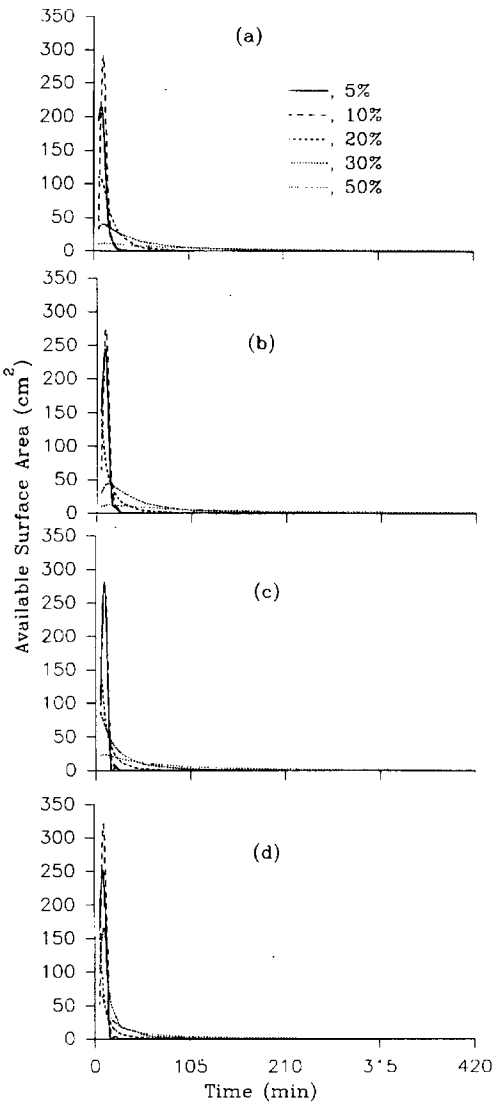

Fig. 10. $S(t)$ vs. t patterns of four different size fractions of nifedipine-PEG 6000 solid dispersions with various contents of nifedipine by the log-normal distribution method: (a) 600–425 μm, (b) 425–250 μm, (c) 250–150 μm and (d) 150–90 μm. Symbols same as (a).

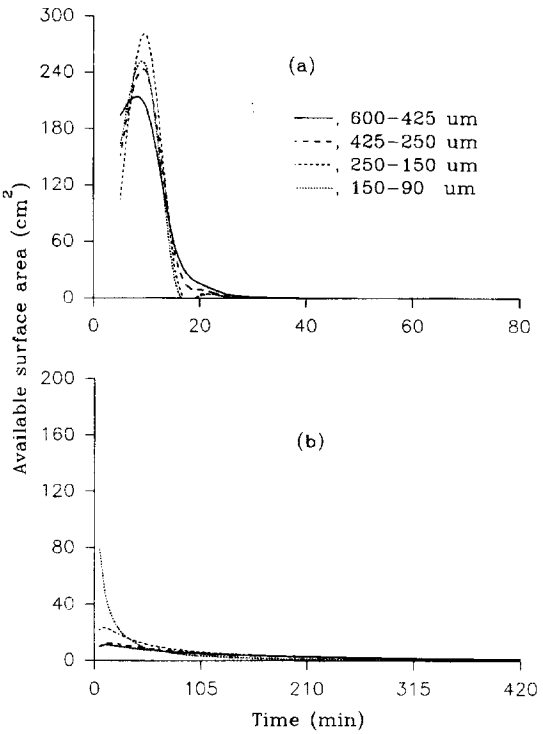

Fig. 11. Effect of particle size on the available surface area of nifedipine from (a) 5% and (b) 50% nifedipine-PEG 6000 solid dispersions by the log-normal distribution method. Symbols same as (a).

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