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RESEARCH PAPER

Evaluation of Solid Dispersions of Clofazimine

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ABSTRACT

Clofazimine (CLF) was formulated with polyethylene glycol (PEG) and polyvinyl pyrrolidone (PVP) as a solid solid dispersion (SSD) to increase the aqueous solubility and dissolution rate of the drug. Different molecular weights of PEG (1500, 4000, 6000, and 9000 Da) and PVP (14,000 and 44,000 Da) were used in different drug:carrier weight ratios (1:1, 1:5, and 1:9) and their effect on the dissolution performance of the drug was evaluated in USP Type 2 apparatus using 0.1 N HCl medium. The dissolution rate was compared with corresponding physical mixtures, a currently marketed soft gelatin capsule product, and free CLF. The effect of different methods of preparation (solvent/melt) on the dissolution rate of CLF was evaluated for PEG solid dispersions. Saturation solubility and phase solubility studies were carried out to indicate drug:carrier interactions in liquid state. Infrared (IR) spectroscopy and X-ray diffraction (XRD) were used to indicate drug:carrier interactions in solid state. Improvement in the drug dissolution rate was observed in solid dispersion formulations as compared to the physical mixtures. The dissolution rate improved with the decreasing weight fraction of the drug in the formulation. Polyvinyl pyrrolidone solid dispersion systems gave a better drug release profile as compared to the corresponding PEG solid dispersions. The effect of molecular weight of the PEG polymers did not follow a definite trend, while PVP 14,000 gave a better dissolution profile as compared to PVP 44,000. Improvement in saturation solubility of the drug in the solid dispersion systems was noted in all cases. Further, IR spectroscopy indicated drug:carrier interactions in solid state in one case and

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XRD indicated reduction in the crystallinity of CLF in another. It was concluded that solid-dispersion formulations of Clofazimine can be used to design a solid dosage form of the drug, which would have significant advantages over the currently marketed soft gelatin capsule dosage form.

Key Words: *Clofazimine; Solid dispersions; Dissolution*

INTRODUCTION

Clofazimine (CLF) is an anti-leprotic,[1] anti-inflammatory,[2] and anti-muscarinic[3] drug that is used primarily for its anti-mycobacterial actions. Clofazimine is practically insoluble in water[1,3] and is one of the most lipophilic drugs administered orally to humans.[4] It displays poor absorption characteristics, which have been attributed to its poor aqueous solubility.[5–7] Up to 50% of the oral dose of CLF in humans is recovered in feces.[8]

Clofazimine is presently marketed as a soft gelatin capsule containing micronized solid drug particles suspended in an oil–wax base[6] (Lamprene®, Ciba Giegy, India). Although one report has estimated the extent of CLF absorption from Lamprene® at 70% w/w,[7] it is generally recognized to be poor and variable.[9]

An alternative solid dosage form (tablet/hard gelatin capsule) that has better dissolution and absorption characteristics is expected to (1) improve the rate and extent of drug absorption, (2) reduce inter-subject variability in bioavailability, (3) reduce the effect of food and other gastro-intestinal variables on drug absorption, (4) improve pharmaceutical handling and storage of the dosage form (soft gelatin capsules per se have numerous production and storage problems), and (5) possibly reduce the dosage of the drug, thus reducing the cost of therapy and undesirable effects. Thus, an alternative solid-dosage form of Clofazimine is highly desirable.

Encapsulation of the drug as a micronized suspension in an oily vehicle in a soft gelatin capsule (which is the presently marketed dosage form of Clofazimine) is a well-known technique utilized for drugs with extremely poor solubility and dissolution characteristics. For example, Isotretinoin is marketed in such a form (Accutane®, Roche Labs, Nutley, NJ, USA). However, if the drug could be made into a granular powder with enhanced wettability and dissolution characteristics, it is preferred to the soft gel formulation. Another similarly insoluble drug, Acitretin, is marketed by the same company (Roche Labs) as a hard gelatin capsule dosage form (Soriatane®). These are the molecules where drug solubility is so poor as to be the rate-limiting step in drug absorption. The preference for a superior dosage form with the evolution of technology is indicated by the chronology of approvals of these products by the same manufacturer.[10]

Low drug solubility has been recognized as the primary rate-limiting step in the absorption of Clofazimine as well.[5–7] Further, there have been reports that have quantified the role of particle size of the drug on its bioavailability. For example, when CLF was administered as a coarse crystalline powder, absorption was about 20%, while when it was administered as a microcrystalline suspension in oil–wax base in the form of a soft gelatin capsule, about 70% was absorbed. These data indicate that a reduction in the particle size will markedly enhance the bioavailability of the drug. This is attributable primarily to the enhanced solubility or dissolution of the drug. A correlation between an improvement in aqueous dissolution of CLF to its enhanced systemic bioavailability (approximately 3 times), relative to that from Lamprene®, has also been shown in one case.[6]

The possible incorporation of Clofazimine into a solid solid dispersion (SSD) is expected to improve drug solubility/dissolution and pave the way for the formulation of a hard gelatin capsule/tablet dosage form. The first steps to such development include the evaluation of enhancement of solubility and dissolution characteristics of the drug by incorporation into the SSD, the stability of the systems, and selection of the optimum formulation. These are the subject of the present paper. Development of the dosage form and *in vivo* studies shall be the course of future work.

EXPERIMENTAL

Materials

Clofazimine (molecular weight: 473) used was of pharmacopeial grade as provided by Astra-IDL

Limited, India. All the excipients and chemicals used were of analytical reagent grade.

Methods

Two different types of polymer were used: polyethylene glycol (PEG) and polyvinyl pyrrolidone (PVP). The following molecular weight fractions were evaluated at 1:1, 1:5, and 1:9 drug:carrier weight ratios, for PEG: 1500, 4000, 6000, and 9000 and for PVP: 14,000 and 44,000 (molecular weight distribution was within ±5% of designated molecular weight in all cases). Polyethylene glycol formulations were prepared by both the melt and the solvent method, while only the solvent method was used for PVP formulations.

Preparation of Solid Dispersions by Melt Method

Five grams of CLF was heated to about 220°C, its melting point. The required quantity of the solid polymer was then added, under constant stirring, leading to the melting of the polymer and formation of a homogeneous liquid. The co-melt was rapidly solidified at about 0°C in a desiccated environment. The material was kept under these conditions for about 24 hr to stabilize. The co-melt was then pulverized, vacuum desiccated (−0.8 atm or −25 inch Hg, 24 hr), sized into different sieve fractions, and stored in a desiccator, until further use.

Rapid solidification and minimum heating time for PEGs were the critically controlled aspects of the process. Polyvinyl pyrrolidone solid dispersions were not prepared by the melt method, because PVP melts above 250°C and degrades before/at its melting point.

Preparation of Solid Dispersions by Solvent Method

Five grams of CLF and 5, 25, and 45 g of the polymer were dissolved in an adequate amount of chloroform. The solvent was then rapidly evaporated with the aid of mild heat (up to about 50°C) and surface airflow with constant vigorous stirring to form a uniform solid mass. The co-precipitate was crushed into small particles, desiccated under vacuum for 24 hr, pulverized (again, after formation of a more fragile mass), vacuum desiccated again for a day, sized into different sieve fractions, and stored in a desiccator, until further use. This procedure on a pilot/industrial scale may be carried out by spray-drying the drug/polymer solution, which is expected to yield small size particles.

Preparation of Physical Mixtures by Trituration Method

Both CLF and the polymer were sifted through a fine mesh (#100 BSS), mixed together (with trituration in a pestle–mortar), and stored in a desiccated environment.

Assay Procedure

Five milligram drug equivalent of the formulation was dissolved in 5 N HCl and diluted to 100 mL in a volumetric flask and then 5 mL of this solution was further diluted to 100 mL. Absorbance of the sample was noted at 535 nm and the assay was calculated using the calibration curve (it followed Beer Lambert's law up to 5 μg/mL). There was no excipient interference by this method and the solution stability was established up to 6 hr.

Drug Release Rate/Dissolution Studies

Dissolution (of samples equivalent to 2.5 mg of CLF) was carried out in 1 L of 0.1 N HCl in USP-II apparatus at 37°C and 50 rpm with sampling of the media up to 2 hr. Five milliliters of the sample was acidified with 5 mL of 10 N HCl, and the absorbance recorded at 535 nm. The conditions chosen were meant to provide the maximum simulation of *in vivo* conditions, while using the simple pharmacopeial apparatus. Since the gastric pH is ~1.2 and drug dissolution from a conventional immediate-release dosage form is expected to occur in the stomach, 0.1 N HCl was chosen as the dissolution medium. A low quantity of formulation was used for dissolution studies due to the limited solubility of Clofazimine in 0.1 N HCl (0.2590 μg/mL).

Evaluation of Stability

The intimate mixing of polymeric carriers with the drug may affect the storage stability of Clofazimine. Stability of CLF in the solid dispersions systems was, therefore, evaluated by analyzing the assay and dissolution characteristics of the systems after storage at 25°C/60% relative humidity (RH) (controlled room temperature) and 40°C/75% RH (accelerated storage conditions) for 3 months in HDPE bottle packs, and the data was compared

with the initial samples. The moisture content of the samples was also measured at all time points, using Karl Fisher titrimetry, to evaluate the possible variation in stability due to the different moisture content of the samples.

Phase/Saturation Solubility Studies

To evaluate the increase in solubility of Clofazimine in the solid dispersions or only by the presence of the polymer in the dissolution media, phase/saturation solubility studies were carried out as follows: 10 mg of CLF and corresponding (10, 50, or 90 mg) amounts of the carrier were stirred vigorously for 24 hr in sealed vials with 10 mL of 0.1 N HCl. The samples were centrifuged and the supernatant filtered through a 0.45 μm membrane filter. Five milliliters of the sample was acidified with 5 mL of 10 N HCl, and the absorbance recorded at 535 nm (phase solubility). Quantities of the SSDs, equivalent to 10 mg CLF content, were given the same treatment as above (saturation solubility).

Initial studies were run up to 7 days with sampling and analysis at 24 hr intervals in order to determine the time required for equilibration of samples (data not shown). Twenty-four hours was found to be an adequate time for equilibration.

Infrared Spectroscopy

Infrared (IR) spectroscopic analysis was carried out on the solid dispersions to evaluate possible interactions between the drug and the polymers. Infrared spectra of the samples were recorded in the solid state by the KBr disc method. Individual polymers, CLF, and drug/polymer physical mixtures were run as controls.

X-ray Diffraction

Decrease in crystallinity of the drug is often a predominant mechanism responsible for increased dissolution rates. The x-ray diffraction (XRD) analysis was carried out to evaluate possible reduction in crystallinity of CLF after formulation into solid dispersions with the polymers. Selected batches of the SSD were subjected to powder XRD using the copper K-α radiation generated at 20 mA and 40 kV potential. The diffracted x-rays were then detected in the 2θ range of 5–50°, and the results processed by a pre-loaded computer program.

RESULTS AND DISCUSSION

Polyethylene glycol and polyvinyl pyrrolidone were chosen as the hydrophilic polymers for the present studies as these highly water-soluble and non-toxic polymers are known to enhance dissolution rates of insoluble drugs.

Dissolution Studies

The Clofazimine solid dispersions presented better dissolution performance over corresponding physical mixtures (Fig. 1) and the pure drug. This may be due to an improved wettability of the drug particles, a significant reduction in particle size during the formation of SSD, and the intrinsically higher rate of dissolution of the soluble polymer component of the SSD, which would pull along the more insoluble but finely mixed drug into the dissolution medium.

Effect of Weight Fraction of Polymer on Dissolution Rate of Clofazimine

Three different drug:carrier weight ratios (1:1, 1:5, and 1:9) were used to assess the effect of increasing polymer concentration on the release profiles of solid dispersions and physical mixtures. In all the cases examined, an increase in weight fraction of the polymer resulted in an improvement in the rate and extent of drug dissolution. Figure 2 represents the data for PEG 4000, and PVP 14,000 solid dispersions by the solvent method, respectively. The possible reasons for this trend include facilitation of CLF dissolution by dissolved amounts of the carrier[11] and a decrease in the particle size of the drug in the carrier, with an increase in carrier concentration. Lack of inhibition of carrier dissolution in the solid dispersions with lower drug concentrations, especially by the melt method, can also be responsible for the observed trend. Further studies are needed to evaluate the mechanisms involved.

Effect of Type of Polymer on Dissolution Rate of Clofazimine

With the same (solvent) method of preparation, PVP solid dispersions presented better drug-release profiles over corresponding PEG solid dispersions

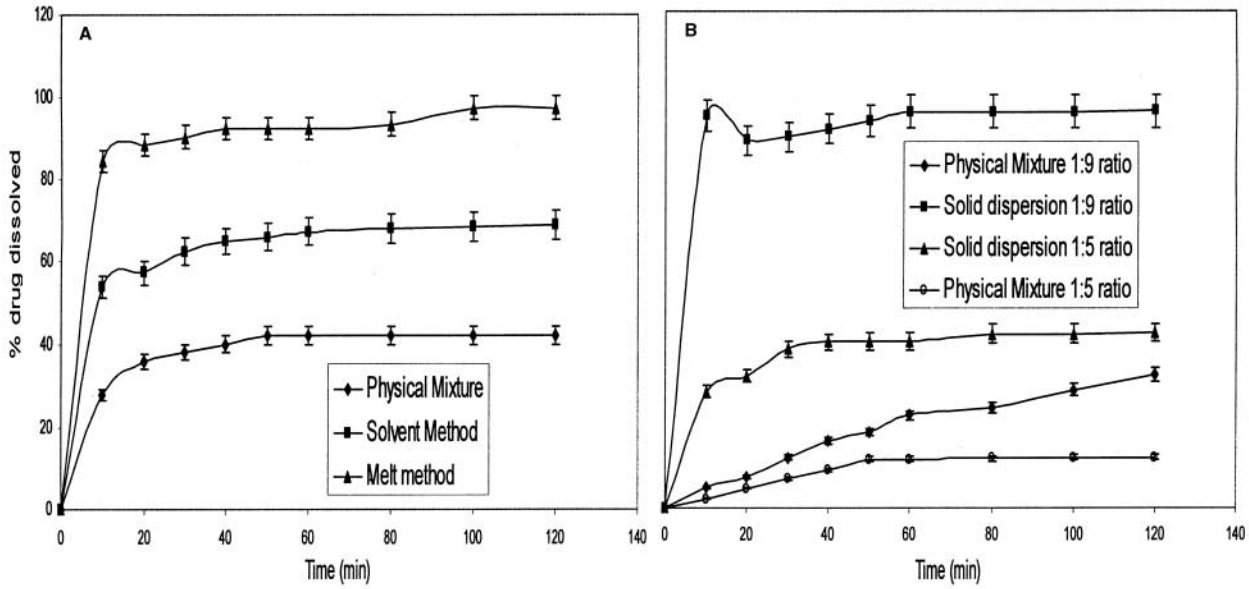

Figure 1. Dissolution profile of Clofazimine in solid dispersions vs. physical mixtures: (A) PEG 4000, 1:9 ratio; (B) PVP 14,000.

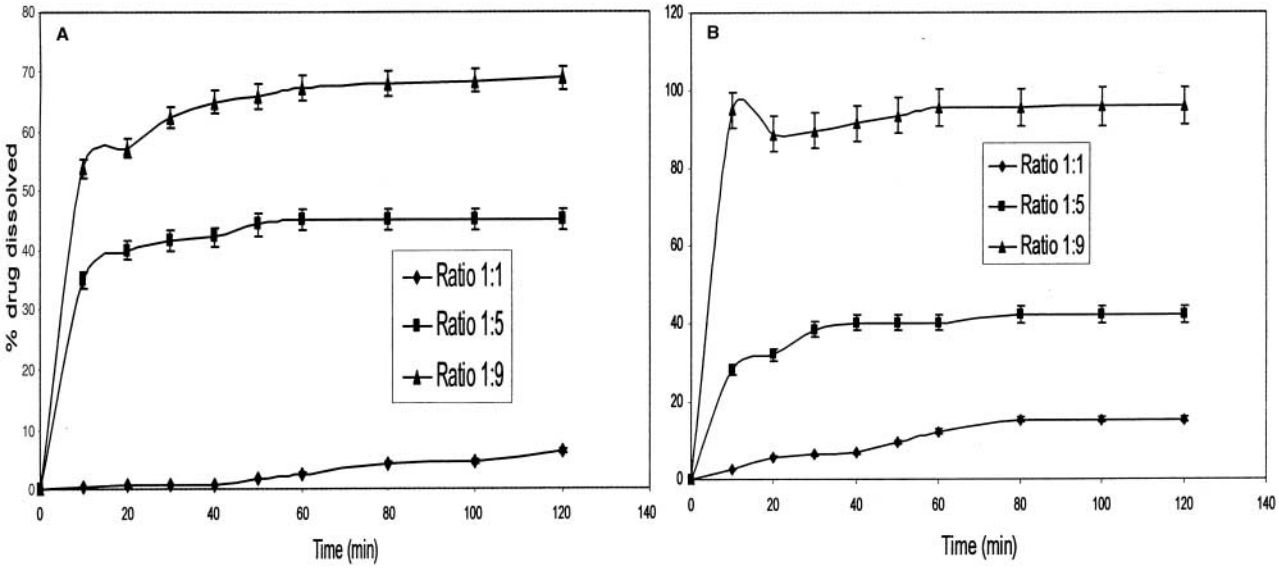

Figure 2. Effect of weight fraction of drug:carrier on Clofazimine release: (A) PEG 4000; (B) PVP 14,000.

at 1:9 drug:carrier weight ratio (Fig. 3). This was observed with both the molecular weight fractions of the polymers. This phenomenon may be due to the inherent differences between the two polymers in terms of intrinsic rates of dissolution and hydration, and possible complexation of the drug with PVP or decrease in crystallinity of the co-precipitated drug.

Both PVP 14,000 and PVP 44,000 enhanced the initial rate of dissolution of the drug from their SSDs, as well as the equilibrium amount of drug released, when compared to PEG batches. The initial

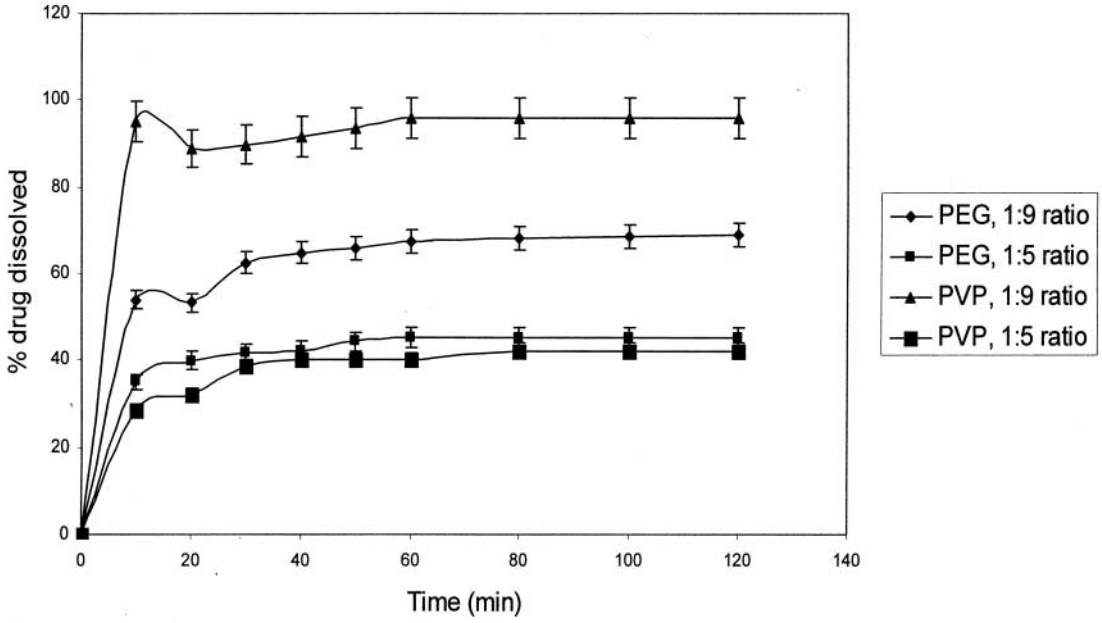

Figure 3. Effect of polymer types on Clofazimine release.

high drug release is observed at the 10-min time point, and gets reduced at subsequent time points. This may be because the equilibrium concentration that can be achieved with the given formulation in the solution is less than what was achieved at the first dissolution time point. Probably the initial rapid flux of the drug from the solid dispersion particles to the dissolution medium resulted in a high concentration, which got reduced with time. Slow dissolution was observed subsequently till the equilibrium concentration was reached. Further investigation is needed, however, to prove this phenomenon.

Effect of Polymer Molecular Weight on Dissolution Rate of Clofazimine

Depending upon the exact stereochemistry of the interstitial spaces in the polymer and their size, in relation to that of the drug, there exists a possibility of formation of interstitial solid solution of the drug in the polymer matrix. Formation of a solid solution is expected to enhance the rate of drug release tremendously. The size of the polymer varies in direct correlation with its molecular weight. Thus, a study of the effect of molecular weight fraction of the polymer can thus provide important clues regarding the optimal molecular size/weight of the polymer that should be used for maximum dissolution performance.

Dissolution profiles of batches fabricated with different molecular weights of PEG polymers were evaluated at 1:5 and 1:9 weight ratios using both solvent and melt methods of preparation. Also, different molecular weights of PVP polymers were evaluated at 1:5 and 1:9 weight ratios, respectively, using the solvent method. The PVP 14,000 batches gave consistently better dissolution profiles as compared to the PVP 44,000 batches (Fig. 4). This may be due to the difference in viscosity between these two weight fractions. A possible decrease in the drug diffusion rate through the diffusion layer with the increase in viscosity of PVP appears to be responsible for this.

With the solvent method of preparation, PEG 9000 batches gave the best release profiles, when compared with other PEG batches, at both 1:5 and 1:9 drug:carrier weight fractions. Moreover, the trend remained consistent when the drug:carrier weight ratios were increased from 1:5 to 1:9. Further, PEG 4000 batches gave better release profiles than PEG 6000 batches.

In the case of the melt method of preparation, PEG 4000 and PEG 6000 batches presented the best release profiles at both weight fractions (Fig. 4). The difference in release performance of PEG 4000

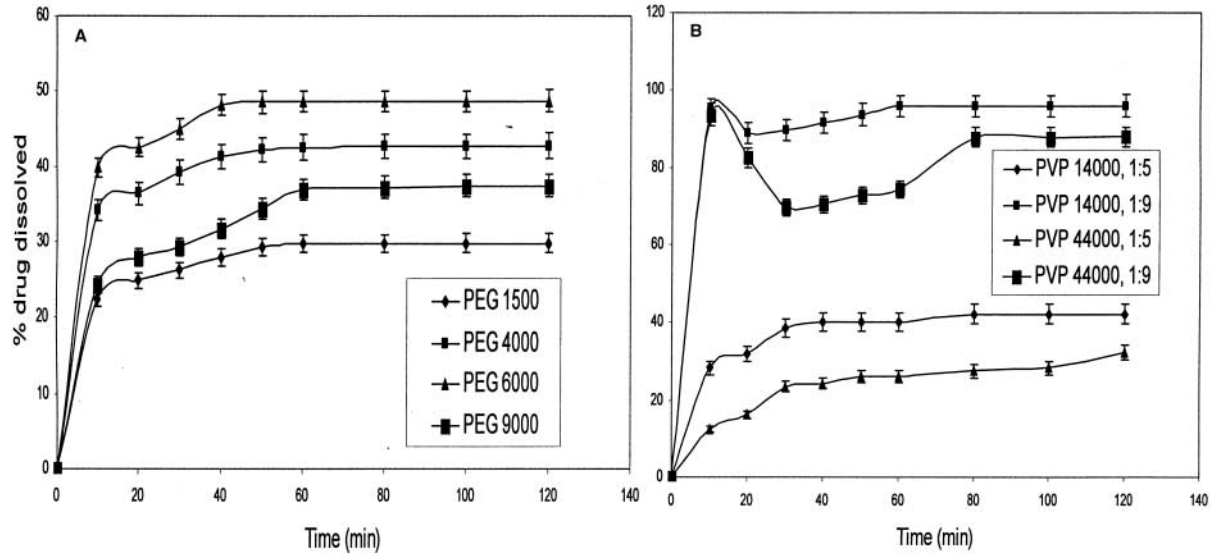

Figure 4. Effect of molecular weight of carrier on drug release: (A) PEG (1:5 weight ratio, melt method); (B) PVP (1:5 and 1:9 weight ratio, solvent method).

and PEG 6000 melt batches at 1:9 drug:carrier ratio is much reduced. This may be because of the drug concentrations in the media reaching the saturation solubility level.

An interesting change in trends of relative dissolution performance of different molecular weights of PEG polymers in two methods of preparation is noted. This may be due to the different nature of interaction between the drug and the carrier due to differences in temperature (210–230°C for melt method and less than 50°C for solvent method), presence/absence of a solvent, and time available for interaction (solvent > melt) during the preparation of the SSDs. Further studies are, however, needed to explain the exact reasons for these observations.

Infrared Spectroscopy

The interactions between the drug and the carrier often lead to identifiable changes in the IR profile of the solid dispersions. The solid dispersions (melt/solvent method), physical mixtures, polymeric carriers, and CLF were subjected to IR analysis in order to evaluate possible solid–solid interactions between the drug and the carrier. The data was compared with the standard spectrum for CLF, and characteristic peaks associated with specific structural characteristics of the molecule[5,12] and their presence/absence in the polymeric carrier as well as the solid dispersions and corresponding physical mixtures were noted. This was expected to provide information regarding the specific structural features of the drug molecule interacting with the excipients used.

The representative IR spectra are shown in Fig. 5. It was observed that the drug peaks at 1508 and 1620 cm^{-1} are present in PEG 4000 solid dispersion (1:9 ratio, solvent method) while they are absent when the dispersion is prepared by the melt method. The drug peaks of 1560 and 1587 cm^{-1} are present in PEG 6000 solid dispersion (1:9 ratio, solvent method) while they are absent when the dispersion is prepared by the melt method. The absence of the 1560 cm^{-1} peak (which corresponds to the bending vibrations of N–H hydrogen in the Clofazimine molecule) may be due to hydrogen bonding between the nitrogen atom of the drug with the oxygen atom in the polymer.

These observations indicate possible hydrogen bonding/complexation interactions between the drug and the carrier. Further studies are needed, however, to characterize the exact nature of interactions/complexes.

Effect of Particle Size of the Formulation on Drug Release Rate

To evaluate the role of particle size of the solid dispersions on their dissolution behavior, two differ-

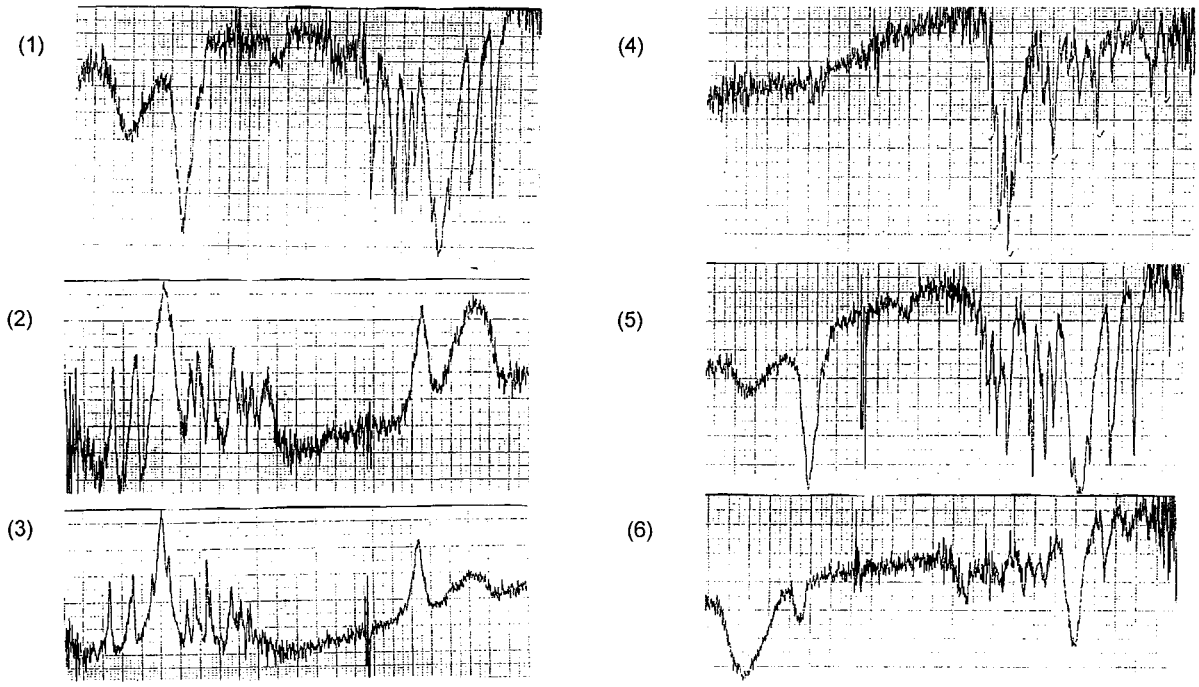

Figure 5. Infrared spectroscopic data of Clofazimine and its solid dispersions: (1) PEG 4000; (2) PEG 4000 solid dispersion by solvent method; (3) PEG 4000 solid dispersion by melt method; (4) Clofazimine; (5) PEG 6000 solid dispersion by solvent method; (6) PEG 6000 solid dispersion by melt method.

Table 1

Particle Size Fractions of the Solid Dispersion Used for Dissolution Studies

		Retention on Sieve (%)	
Sample No.	Mesh # BSS	Fraction A	Fraction B
1	44	0–1	0–1
2	60	0–2	0–1
3	85	96–100	0–2
4	100	1–4	0–3
5	120	1–2	97–100
6	150	0–1	0–2

ent particle size fractions (A and B, Table 1) of the solid dispersions at 1:5 and 1:9 weight ratios of PEG 4000 (melt as well as solvent method of preparation) and PVP 14,000 (solvent method of preparation) were subjected to comparative dissolution studies (Fig. 6). A decrease in particle size resulted in an increase in the dissolution rate in all the cases examined. Further, the effect was more pronounced for the solvent method of preparation for PEG batches than for the melt method. Also, the effect of particle size reduction in increasing dissolution is more dramatic in the case of PVP batches as compared to PEG batches. This could be due to the drug/carrier interactions in solid state in PEG formulations with the solvent method of preparation, leading to a reduced effect of the particle size variation on dissolution of the formulation, and greater increase in drug powder wettability by PVP than PEG. Further studies are, however, needed to test these hypotheses.

The dissolution studies were also carried out on the soft gelatin product available in the market (Lamprene®) in order to compare the profile with the solid dispersion formulations. The drug release rate obtained was low (<50% in 90 min) and variable (relative standard deviation, RSD >10%).

Saturation Solubility Studies

An increase in the saturation solubility of the drug can explain the improved dissolution of solid dispersions, as per the Noyes and Whitney equa-

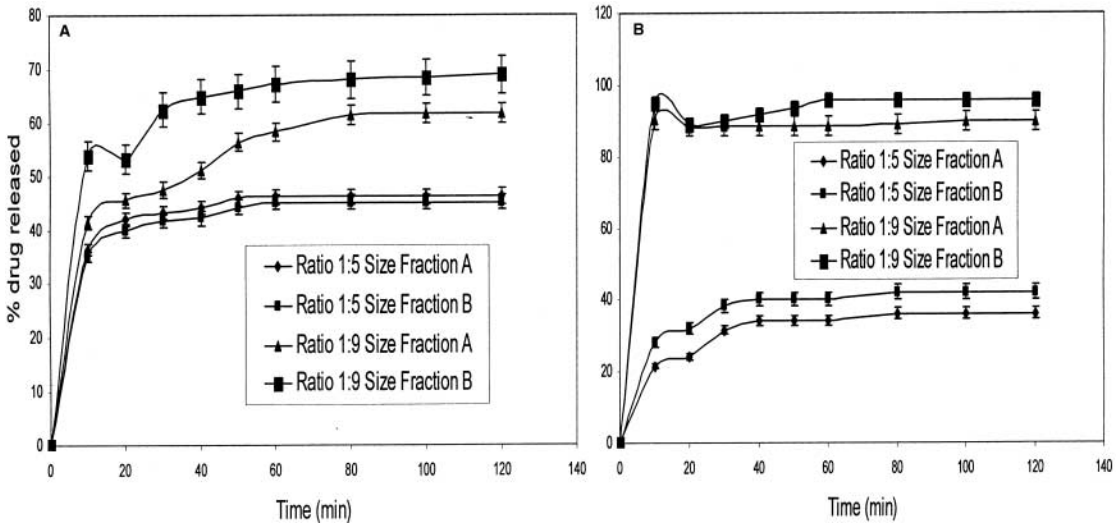

Figure 6. Effect of particle size of formulation on drug release: (A) PEG 4000 (solvent method); (B) PVP 14,000 (solvent method).

tion, since the saturation solubility of a compound is dependent on the size of the particles (if the particle size is less than 0.1 μm).[13] Since it is possible to achieve such reduction in particle size with solid dispersion systems, the saturation solubility studies were performed with these formulations (Fig. 7) using the untreated drug CLF as a control. More than 60 to 1600% increase in solubility was noted when the drug was formulated into solid dispersions. The best results have been obtained with PVP batches; and among the PEG batches, the melt method resulted in higher increases in drug solubility than the corresponding solvent method. Also, an increase in polymer weight fraction in the formulation was found to improve drug solubility. Thus, an improvement in saturation solubility of the drug could be one reason for the improvement in drug dissolution when CLF was formulated into solid dispersions.

Phase Solubility Analysis

The mechanisms responsible for improved drug dissolution may be classified as (1) drug/carrier interactions in solid state and (2) drug/carrier interactions in liquid state,[14] i.e., drug dissolution may be enhanced simply due to the presence of a second dissolved solute in the dissolution medium. When a physical mixture, for example, of the drug and the carrier is added to the dissolution medium it may simply happen that the carrier, which dissolves first, modifies the hydrophilic/lipophilic or wettability properties of the dissolution medium or it may form a weak complex with the drug at the particle surface, resulting in enhanced drug dissolution.[14]

Phase solubility studies were thus carried out to evaluate drug/carrier interactions in liquid state. Results are presented in Fig. 8. At drug:carrier weight ratios simulating the physical mixtures prepared, saturation solubility of the drug was enhanced in all cases, as compared to the control sample, pure drug Clofazimine. A 57–570% increase in drug solubility was observed as against 60–1600% for solid dispersions, as noted earlier. It was also observed that increasing carrier weight fraction results in an increase in drug solubility.

The maximum solubility achieved, however, remained lower than the saturation solubility achieved with the corresponding solid dispersion samples. This infers that the formation of solid dispersions of the drug does result in something more than just a mechanical mixture. Thus, drug/carrier interactions in liquid state are not solely responsible for improved drug dissolution from the solid dispersions.

X-ray Diffraction Analysis

X-ray diffraction analysis can be used to judge any changes in crystallinity of the drug when

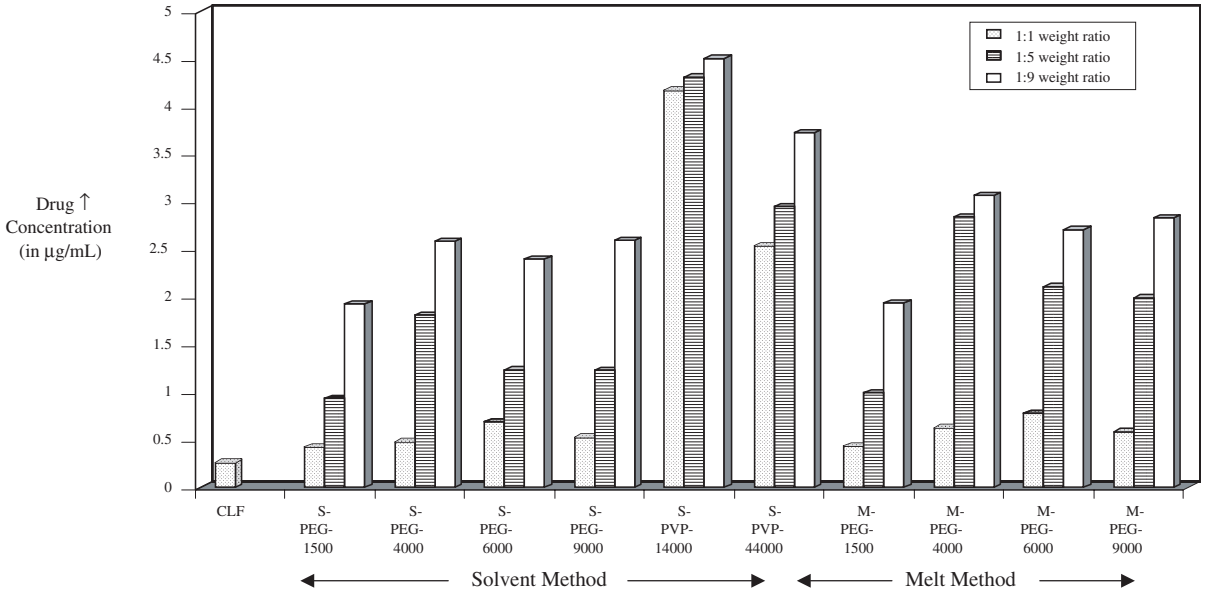

Figure 7. Results of saturation solubility studies.

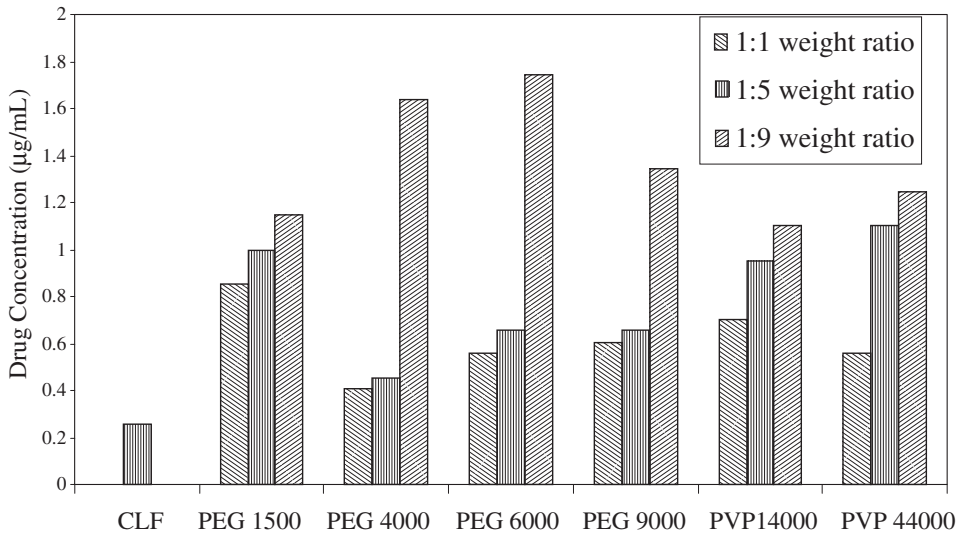

Figure 8. Phase solubility studies of Clofazimine (CLF) with carriers indicating increase in the solubility of the drug in the presence of the dissolved carriers.

formulated into a solid dispersion. Clofazimine is a crystalline drug: it exists in both monoclinic and triclinic crystal forms, and gives characteristic XRD peaks. Thus, XRD could be used to study any changes in crystallinity of the drug or its precipitation in an amorphous form, which could be one of the mechanisms responsible for improved dissolution. Various samples were subjected to XRD analysis (Fig. 9). While no significant difference was observed in the crystallinity of PVP and PEG 4000 batches (between physical mixtures and solid dispersions), PEG 9000 shows a change in intensity as well as number of peaks between the solvent and the melt method (melt = 11 > solvent = 8, whereas physi-

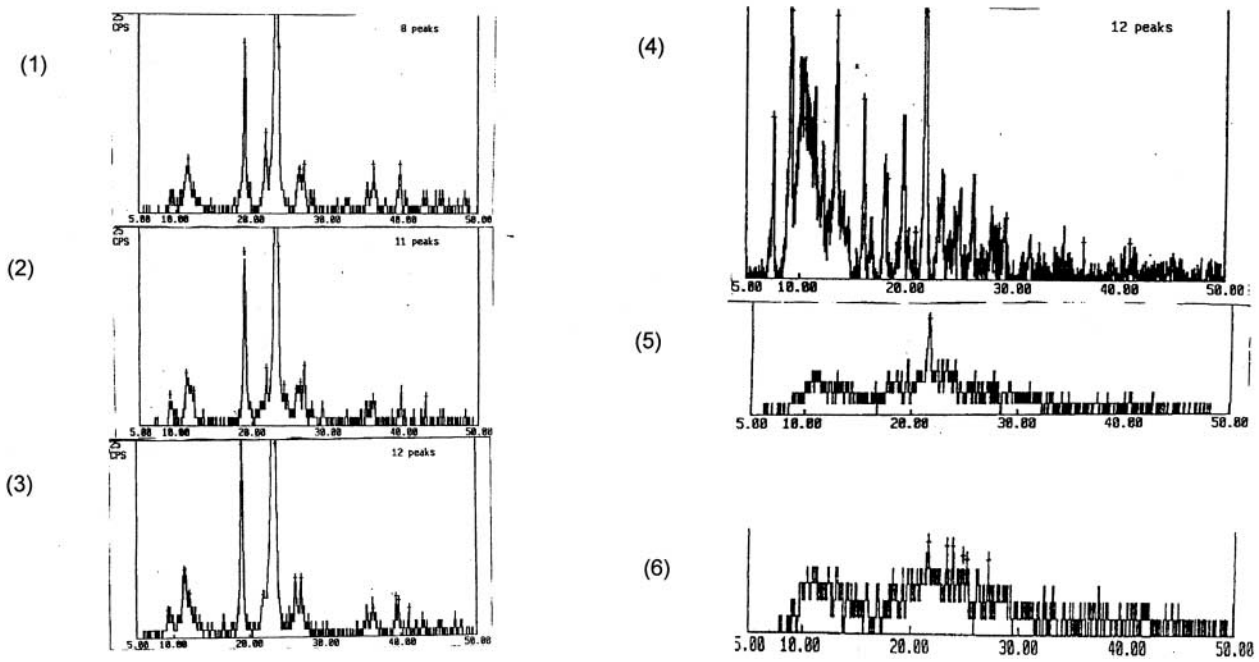

Figure 9. X-ray diffraction data of Clofazimine and its solid dispersions: PEG 9000 (1) physical mixture and solid dispersion by (2) melt and (3) solvent methods; (4) Clofazimine and PVP 14,000 solid dispersion by (5) solvent method and (6) melt method.

Table 2

Evaluation of Storage Stability of the Formulation

Polymer	Drug/ Carrier Ratio	Assay (% w/w)			Dissolution (%) (30 min)			Water (by KF) (% w/w)		
		Initial	25°C/60% RH/3M	40°C/75% RH/3M	Initial	25°C/60% RH/3M	40°C/75% RH/3M	Initial	25°C/60% RH/3M	40°C/75% RH/3M
PEG 4000	1:9	99.8	99.7	98.2	101	100	102	1.46	1.48	1.45
PEG 6000	1:9	101.6	100.2	97.1	100	102	102	1.38	1.42	1.40
PVP 14,000	1:9	98.8	99.0	97.9	102	98	98	2.01	1.88	1.84
PVP 44,000	1:9	99.4	98.9	98.4	99	101	100	1.98	1.90	1.88

cal mixture = 12). This reduction of crystallinity may explain the higher drug release profile by the solvent method of preparation as compared to the melt method, whereas the melt method was found superior to the solvent method for all other molecular weight fractions of PEGs.

Stability of the Formulation

Representative formulations were tested for stability with respect to assay, dissolution, and water (by KF) at accelerated (40°C/75% RH) and controlled room temperature (25°C/60% RH) conditions for 3 months in HDPE containers with 1 g silica gel desiccant. The results are appended in Table 2. The results indicated the formulation to be stable under the tested conditions of storage.

Dissolution Data Interpretation

The dissolution data obtained for different batches was evaluated to find the Hixon–Crowell

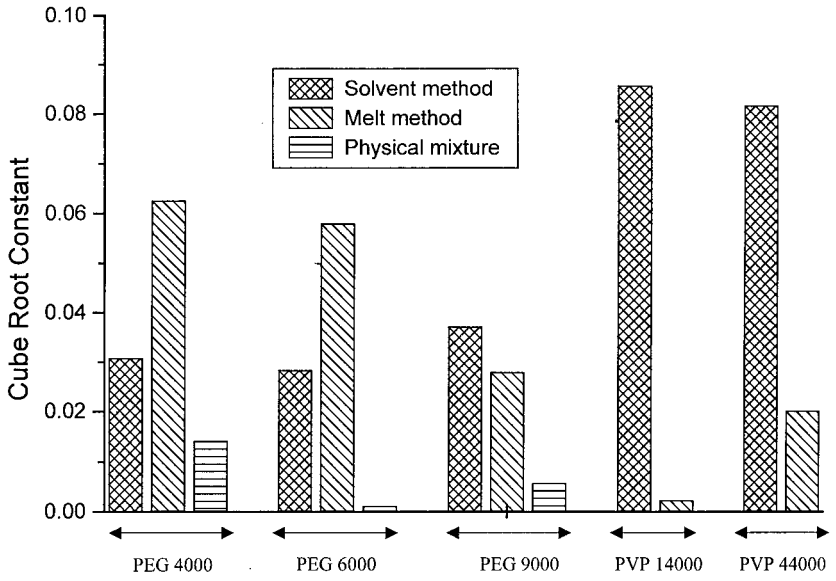

Figure 10. Comparison of Hixon–Crowell cube root constants for solid dispersion systems at 1:9 drug:carrier weight ratio.

cube root (initial) dissolution rate constant. This is based upon the amount of drug released within the first 10 min of dissolution study, when sink conditions are best maintained. This is significant in that the release of drug during later periods of dissolution study is affected by the maximum equilibrium solubility. Assuming the existence of sink conditions in *in vivo* circumstances, the Hixon–Crowell cube root (initial) dissolution rate constant remains a good criterion to judge a formulation.

The Hixon–Crowell cube root law describes the dissolution rate of powders in terms of the cube root of weight of particles, taken as:

$$M_o^{1/3} - M^{1/3} = Kt$$

with:

$$K = [N_p(\pi/6)]^{1/3} \frac{2KC_s}{P} = \frac{M_o^{1/3} 2KC_s}{dP}$$

where M_o is the original mass of drug particles; M is the mass remaining to be dissolved at time t; K is the cube root rate constant; C_s is the saturation solubility; d is the diameter of particles; N is the number of particles; P is the density of particles. Thus, larger values of K indicate better releasing formulations.

Figure 10 compares the dissolution rate constants of the drug and various formulations. The data indicates the solid dispersions prepared using PVP 14,000 and 44,000, at 1:9 drug:carrier weight ratio and PEG 4000 at 1:9 drug:carrier weight ratio (by the melt method) show the best drug release under sink conditions.

CONCLUSIONS

Improving the dissolution characteristics of insoluble drugs is important to achieve better bioavailability and reduced side-effects. The solid dispersion technique is an important tool in this direction. The present work shows that the dissolution rate of CLF improved markedly from almost none for the pure drug to almost 100% in some cases. Further, all the solid dispersion formulations performed better than the corresponding physical mixtures. Also, the saturation solubility of the drug when formulated into solid dispersion with the polymers was more than the phase solubility achieved in the presence of the polymers in the dissolution media. This indicated the presence of drug/carrier interactions in the solid state. Such interactions can be, for example, complexation between the drug and the carrier or reduction in crystallinity of the drug. The use of IR spectroscopy as an indication of complexation between the drug and the carrier or hydrogen bonding has been done by Taeye et al. for polyfunctional bases[15] and by Simonelli et al. for hydrochlorothiazide PEG solid dispersions.[16]

Reduction in crystallinity as indicated by XRD has also been studied in some cases.[16] The IR data of the solid dispersion systems prepared with CLF indicated the presence of such an interaction in one case, and XRD analysis indicated reduction in crystallinity in another.

It was noted that Povidone batches performed better than PEG batches when prepared by the same (solvent) method, and PVP 14,000 performed consistently better than PVP 44,000 in case of PVP solid dispersions. Increasing the drug:carrier weight ratio from 1:1 through 1:5 to 1:9 improved drug release profiles for all formulations and, for PEG batches, the melt method produced better releasing formulations than the solvent method. Also, the improvement in dissolution profile with reduction in particle size was more marked in the case of PVP batches than PEG batches.

An increase in saturation solubility of the drug was noted in all solid dispersion formulations. Phase solubility studies indicated the existence of drug/carrier interactions in liquid state, while IR analysis indicated the presence of drug/carrier interactions in solid state. It was thus concluded that improved drug dissolution could be achieved by formulating Clofazimine as solid dispersions with the carriers PEG and PVP. Some of the possible mechanisms responsible for the improved dissolution characteristics were noted. Solid dispersions of this drug can, therefore, be utilized for the development of an alternative solid oral dosage form of Clofazimine.

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