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PREPARATION OF ESSENTIAL OILS LOADED GRANULE BY MELT GRANULATION

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ABSTRACT

A comparative study on three granulation methods; melt granulation, fluidized bed granulation and wet granulation was performed to fabricate an essential oils loaded granule. The granule properties such as particle size distribution and the loading efficiency of anethole from fennel and cinnamaldehyde from cinnamon showed that the melt granulation in a high shear mixer was the most feasible method among the three methods.

In melt granulation, the granule particle size was well controlled by polyethylene glycol 6000 (PEG) content of which the optimum value was found to be 20%. Impeller speed and massing time in high shear mixer had small contribution to the particle growth when PEG content was optimized, while PEG particle size had some effect. Finer PEG powder improved the uniformity of granule size. Moreover, the cooling method of the hot mass affected the final granule properties significantly. The cooling with a fluid bed dryer was the best method.

Both of the retention rates of anethole and cinnamaldehyde in the final granule were more than 95% of initial doses irrespective of cooling method. Further, the adoption of a fluid bed dryer enabled very rapid cooling of hot granule with negligible loss of essential oils.

INTRODUCTION

Few studies have examined the granulation techniques for volatile materials. The use of porous materials such as cyclodextrins or microsponges[1] are applicable

to formulate volatile substances as powder form, however, the efficient granulation method of these adsorptives have not been established. One need for efficient granulation of volatile substance is offered in preparation of herbal medicine as a pharmaceutical dosage form. The granulation of powdered herbs containing essential oils which have many pharmacological effects[2] presents two major problems. One is the deficiency of granule growth arising from the fibrous character of herbs and the other is the vaporization of essential oils in the granulation process. Our preliminary survey have revealed that the essential oils content in herbs formulated stomachics on the market was considerably lower than the values calculated from intact herbs.

One reason for the reduction of volatile substances in granulation may be attributed to the drying process when a wet granulation was executed. An efficient drying need long-time fluidization of wet granules, which may cause larger elimination of volatile materials. To avoid these reduction of useful materials, the dry compaction was thought to be an ideal granulation method since it comprised no drying process. The dry compaction, however, can hardly produce fine granules homogeneously and frequent compactions and sievings are ought to be needed to obtain final product. On the other hand, the melt granulation or solid dispersion techniques, designed for direct tableting,[3-4] drug release control[5-8] and stabilization of moisture-sensitive drugs[9] can be also carried out without drying process. While some studies have elucidated the process variables of melt granulation,[10] however, the technique is much less widely recognized and applied to manufacturing than other granulation methods.

The objective of this study is to examine the applicability of melt granulation to agglomerate herbs formulated powder in comparison with general wet granulation methods.

MATERIALS

Powdered fennel and powdered cinnamon were obtained from Alps Industrial. Three grades of polyethylene glycol 6000 (PEG); flake PEG, coarse PEG and fine PEG (Nippon Oil and Fats) and polyvinyl alcohol (PVA 205s, Kuraray) were used as binders. The physical properties of used materials are shown in Table 1.

METHOD

Granulation Methods

Three granulation methods; melt granulation, fluidized bed granulation and wet granulation, were examined. The formulations for each granulation are shown in Table 2.

TABLE 1
Physical Properties of Used Materials

Property	Cinnamon*	Fennel*	Corn starch	Lactose
Sw (m/g)	0.58	0.40	0.17	0.20
Ds (μm)	12.6	10.3	24.6	139.4
	Flake PEG	Coarse PEG	Fine PEG	PVA **
Dm(μm)	750	207	92.2	—
η (mPa·s)	1840	1844	1800	13

Sw, relative surface area obtained through air permeation data; Ds,relative surface diameter; Dm, median diameter obtained from sieving data; η, viscosity at 70℃. *, Powdered; **, used as 10% aqueous solution.

TABLE 2
Formulations for Various Granulation Methods

Material	Melt granulation	Fluidized bed granulation	Wet granulation
Cinnamon powder*	15	15	15
Fennel powder**	15	15	15
Lactose	10	10	10
Corn starch	40	50	55
PEG 6000	20	—	—
PVA (as 10% aq.)	—	10	5
Total (5 kg)	100	100	100

*, Contained 1.53w/w% cinnamaldehyde (bp. 246℃); **, contained 1.03w/w% anethole (bp. 232-234℃).

Melt granulation was carried out with a 20 l scale jacket-equipped high-shear mixer (High-speed mixer FS-20, Fukae Industrial). The jacket was heated to 75℃ prior to granulation by the circulation of hot water regulated at 75℃. All ingredients were mixed by the impeller of which rotation rate were varied between 150 rpm (4 m/sec in circular velocity) and 450 rpm (12 m/sec) for up to 20 minutes with continuous jacket heating. Hot mass was then cooled by two methods. The jacket-cooling was executed by circulating water at 20℃ into the jacket at the flow rate of 800 ml/min. The fluidized-cooling was carried out by fluidizing the hot

granules using a fluid bed dryer (FLO-5, Freund) with an inlet air at 25℃ and 1.0 or 1.5 m^3/min in air feed rate followed to a decantation of hot mass from the high-shear mixer. Cooling was continued until the granule temperature decreased to below 50℃ in both methods.

Fluidized bed granulation was executed using a fluid bed dryer with 10% aqueous PVA solution as a binder solution. Inlet air at 80℃ was fed at the rate of 2 m^3/min. Shaking time was 6 seconds in every one minute. Binder solution of settled volume was sprayed continuously with 1.8 mmø nozzle at 1.5 kg/cm^2 in atomizing pressure at 20 ml/min in feed rate. Wet granules were then dried until the granule moisture became below 3%.

Wet granulation was carried out by massing the ingredients in a high-shear mixer at 230 rpm with a 10% aqueous PVA solution of settled volume as a binder liquid. Wet granules were then dried using a fluid bed dryer with an inlet air at 80℃ and 1.5 m^3/min in flow rate until granule moisture became lower than 3%.

Granules were sieved with #18 stainless-steel filters to remove lumps larger than 850 μm after each granulation.

Physical Properties

Relative surface area of each material were determined by the air permeation method. Viscosity of melting PEG and aqueous solution of PVA at 70℃ were measured with a rotational viscometer (Type BL, Tokyo Keisoku). Particle size distributions were observed by sieving. Granule water content was determined with a moisture balance (Type MO-1, Shimadzu). Scanning electron microscopic observation was conducted with a JSM-T20, JEOL.

Assay of Essential Oils

Accurately weighed granule around one gram was dispersed in 100 ml of co-solvent of acetonitrile, water and acetic acid (80:19:1) with stirring for 30 minutes. Cinnamaldehyde and anethole were then assayed simultaneously at 273 nm by a HPLC system (Jasco) on an octadecyl-sililated silica packed column (150 mm × 4.6 mm I.D.) with co-solvent of 0.01 M acetate buffer solution (pH 5.0) and acetonitrile (60:40) as a mobile phase.

RESULTS AND DISCUSSION

Comparison of Granulation Methods

1. Morphological study

Scanning electron microphotographs of granules prepared by melt granulation are shown in Fig. 1. Small and rugged particles were identified on the granule

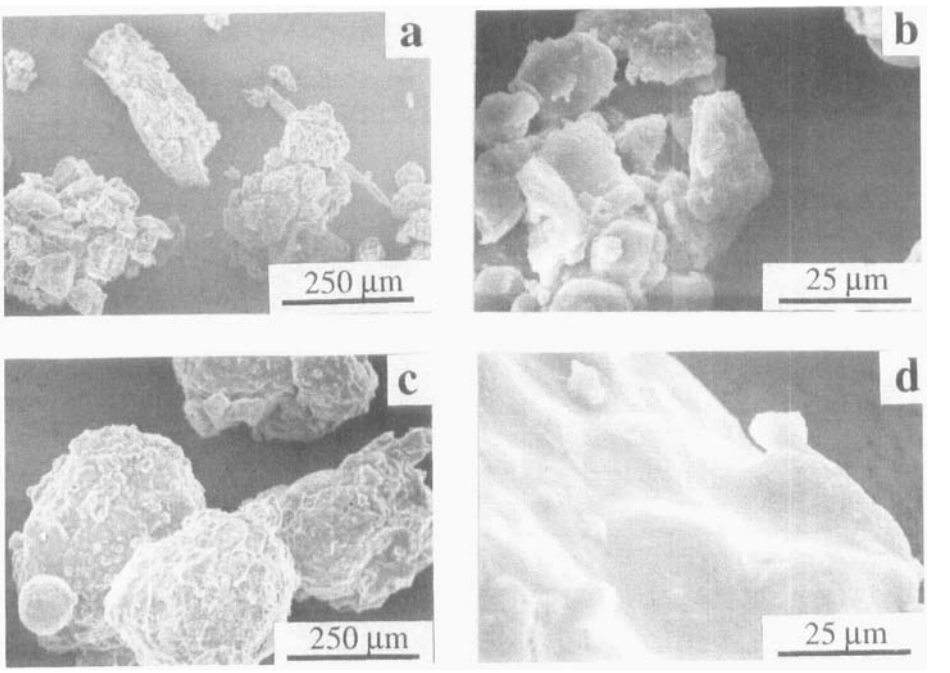

FIGURE 1
Scanning Electron Microphotographs of Melt Granulated Particles
Massing time; a, b, 5 min.; c, d; 10 min. Magnification; a, c, ×300; b, d, ×1000.

surface after massing for 5 minutes, which telling the existence of herb powder on the granule surface (Figs. 1a and 1b). By extending the granulation time up to 10 minutes, the surface roughness had disappeared under a PEG cover (Figs. 1c and 1d) . On the other hand, the granules prepared with the fluidized bed granulation and the wet granulation, lacking sealing material, showed starting materials on the surfaces of finished granules, resembling Figs. 1a and 1b. It was worthy of notice that fibrous herbs were exposed on the surface of finished granules prepared with these wet granulation methods.

2. Granule properties

The physical properties of prepared granules are shown in Table 3. From the resultant particle size, melt granulation and wet granulation produced feasible granules of which major fractions were found between 150 and 500 μm. Fluidized bed granulation attained little granule growth and generated much fine powder. An optimization of mechanical conditions for fluidized bed granulation was tried,

TABLE 3
Physical Properties of Prepared Granules

Property		Melt granulation		Fluidized bed granulation	Wet granulation
Size distribution (%)	850-500 μm	1.3*	0.8**	0.9	1.7
	500-250 μm	38.9*	18.7**	11.5	56.1
	250-150 μm	42.9*	51.6**	35.7	33.6
	150-75 μm	15.6*	27.3**	32.7	7.3
	<75 μm	1.3*	1.6**	19.2	1.3
Bulk density (g/ml)		0.67*	0.46**	0.32	0.58
Residual (%)***	Anethole	98.5*	97.3**	10.8	37.1
	Cinnamaldehyde	98.9*	98.0**	48.5	55.3

*, Jacket-cooling; **, fluidized-cooling; ***, residual rate versus starting mixture.

however, increase in binder feed rate and air feed rate caused an immobilization of wet mass and an augmentation of fine powder, respectively.

The residual rate of anethole and cinnamaldehyde varied dramatically according to the granulation method. In particular, anethole residual varied from 10.8% to 99.2%. This fact may be primarily attributed to the air flow in granulation and drying process. Continual fluidization is required for fluidized bed granulation method. Wet granulation also needs fluidization of wet mass in drying period. Moreover, granules prepared by these wet granulation methods showed the direct exposure of herbs on the granule surface. It was assumed that the high air flow across exposed herbs caused the vaporization of essential oils. Figure 2 shows the elimination profile of anethole through wet granulation as a function of time. Anethole eliminated about 5% in the granulation period and 40% in the drying period. Addition of sugar in place of lactose suppressed the anethole elimination slightly, however, the residual rate was still lower than that of melt granulated particle. The addition of fumed silica, which appeared to adsorb essential oils, was not effective neither. These results show that the fluidization of granules should be avoided to trap volatile oils at high rate when herbs receive air flow directly. And mild drying as to keep the wet granules under 50℃ for one day[11] could not be adopted from the view point of mass production. The high retention of essential oils in the melt granulated particles was partly explained by the coverage of the granule surface with PEG as shown in Figs. 1c and 1d. The

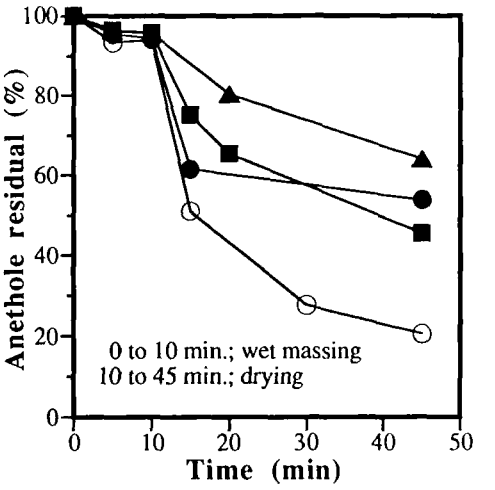

FIGURE 2

Residual Rate of Anethole through Wet Granulation

○, Without binder solution; ●, formulation in TABLE 2; ▲, with 15% sugar in place of lactose; ■, with 5% fumed silica added to the starting mixture.

melting PEG probably covered the starting mixture including the herbs very rapidly since the inside wall of the high shear mixer had been already heated to 75℃ where PEG readily melted. This process also enabled quick halt of scattering of herbs powder in the mixer. The PEG covering may also largely protect the incorporated oils against vaporization in the long-term storage.

From the results above, melt granulation was selected as the most suitable method to produce granules with feasible size and high retention of essential oils.

Optimization of Melt Granulation Process

To improve the reproducibility of melt granulation, the preparing condition unaffected by small variables in process is desired. Previous reports show that PEG content and impeller speed are the major determinants of particle growth in melt granulation. The optimum PEG content had been reported as below 15% when the starting materials were comprised of crystalline drugs, corn starch and lactose.[10] In the present study, however, the conventional PEG content was supposed to be insufficient with as much as 30% powdered herbs. The median diameters of granules prepared with various PEG contents are shown in Fig. 3. With 20% fine PEG, the median diameters of granules were nearly constant and

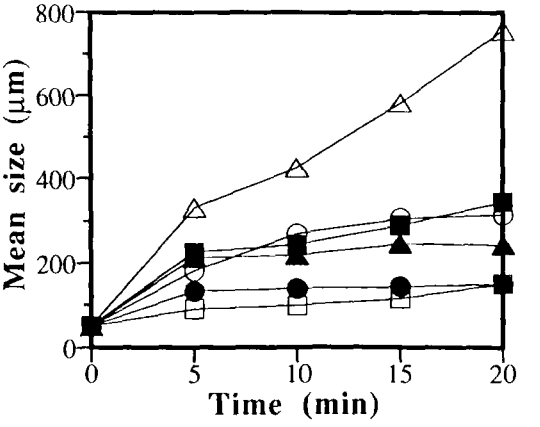

FIGURE 3
Effect of PEG Content and Impeller Speed on Granule Growth
□, 18%, 450 rpm; ●, 20%, 150 rpm; ▲, 20%, 300 rpm; ■, 20%, 450 rpm; ○, 22%, 150 rpm; △, 22%, 300 rpm.

maintained in the range between 150 and 300 μm irrespective of impeller speed after massing for longer than 5 minutes. With less PEG, 18%, scare growth in granule size was observed even with high speed agitation at 450 rpm. With more PEG, 22%, an agitation at 150 rpm showed moderate aggregation, however, higher speed agitation caused very rapid granule growth.

The above results indicated that the PEG content was the principal determinant of granule growth in the present study and the optimum PEG content was found at 20%. The speed and the duration of massing were fixed at 300 rpm (8 m/sec) and 10 minutes, respectively in the following study. They had little effect on the granule growth with 20% PEG.

Effect of PEG Size on Granule Growth

Fabrication of size-controlled granules in melt granulation may require a homogeneous distribution of melting PEG. Hence, a good dispersion of PEG powder in the starting mixture was seemed to be essential for ideal granulation. Of all the PEGs, fine PEG limited the size distribution of finished granule most strictly as the slant of lines in Fig. 4 shows. The flake PEG, which were poorly dispersed in the starting mixture, proved to be unsuitable as a binder since there were many lumps over 500 μm and fines which had not been agglomerated. This fact may be attributed to the insufficient dispersion of melting PEG which caused uneven

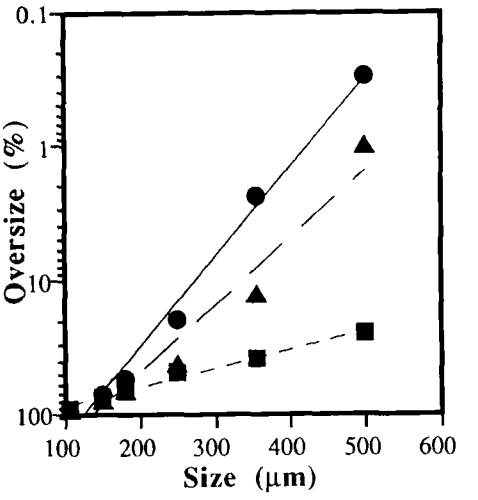

FIGURE 4
Effect of Particle Size of PEG on Granule Size Distribution
●, Fine PEG; ▲, coarse PEG; ■, flake PEG.

binding of starting materials. Schaefer *et al.*[10] have reported that the PEG size did not affected the granule size distribution of final product when the granulates were massed as long as 30 minutes, however, the effect of PEG size was not negligible when melt granulation was carried out with pre-heated high-shear mixer.

These results proved that the fine PEG powder was the most suitable binder to obtain the size-controlled granules in this study.

Optimization of Cooling Procedure

Melt granulation can be divided into two stages, hot massing and cooling. Hot massing stage has been well studied[3-10] and the optimum condition in the present study was established by adjusting the PEG content. On the other hand, previous reports on melt granulation technique had paid little attention to the cooling process. Less time-consuming and homogeneous cooling are essential to enlarge preparation batch size with melt granulation. *In situ* cooling as to spread the hot granules on a plate[12] takes long time and often results in cohesion or blocking of cooled granules, requiring frequent sieving to obtain feasible size granules. With a jacket-equipped high-shear mixer, circulation of chilled water into the jacket, the jacket-cooling, would be an ideal cooling method of melt granulates as it allowes

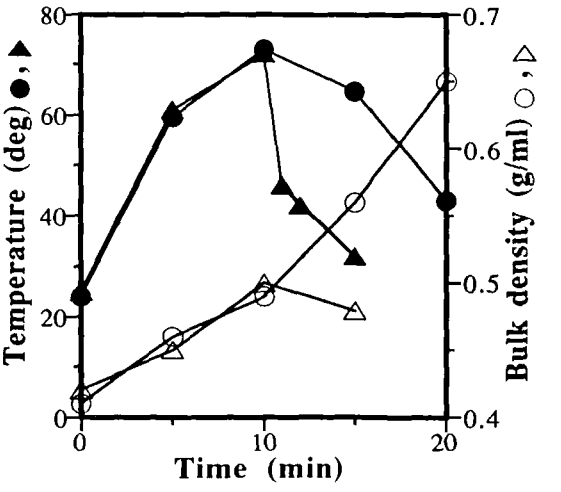

FIGURE 5
Effect of Cooling Method on Granule Temperature and Bulk Density
Cooling method; ●, ○, jacket-cooling; ▲, △, fluidized-cooling at 1.0 m^3/min.

completion of granulation in one vessel. In our study, however, the jacket-cooling took about 10 minutes to reduce the granule temperature to below 50℃ where PEG had been already solidified. Moreover, a rapid increase in bulk density of the granule was observed in the course of cooling (Fig. 5).

Problems such as blocking or densification of the hot mass seen with conventional cooling methods would mostly occur when the temperature of mass was neighbouring the freezing point of PEG with continuous agitation. Thus a cooling with fast passage through the freezing point of PEG was assumed to be the better method. Cooling the hot mass with a fluid bed dryer, the fluidized-cooling, showed much faster decrease in granule temperature as shown in Fig. 5. The temperature of granules decreased to 47℃ with a short fluidization for only one minute. Here, the flow rate of 1.0 m^3/min was the lower limit at which granules were able to be fluidized. The bulk density of granules, to the contrary, showed a little change in the cooling process. And scare lumps were observed with the final product as the particle size distribution in Table 3 shows. This fact proved that no blocking was proceeded with granules which had been once cooled to below 50℃.

These results demonstrated that the short-time cooling by a fluid bed dryer could provide the feasible granules in melt granulation with the simplicity in regulation of hardness, particle size and possibly disintegration time of prepared granules.

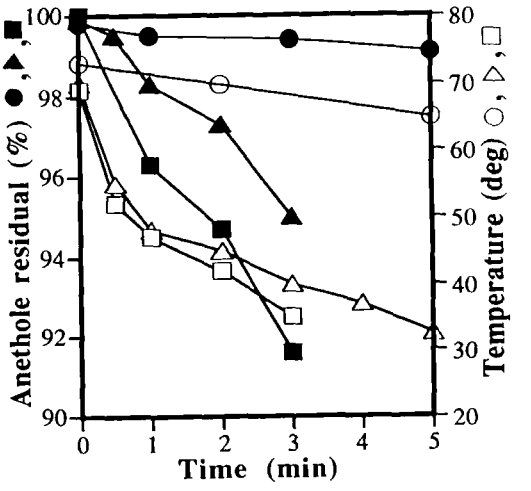

FIGURE 6
Effect of Cooling Method on Residual of Anethole
Cooling method; ●, ○, jacket-cooling; ▲, △, fluidized-cooling at 1.0 m^3/min; ■, □, fluidized-cooling at 1.5 m^3/min.

Residual of Essential Oils through Melt Granulation Process

The major concern in the present study is the elimination of essential oils through granulation process as well as granulation of powdered herbs. Of the two essential oils, anethole was easiler to be lossed on fluidization as can be concluded from the results shown in Table 3. Thus the anethole was chosen as an indicator of oils elimination. The elimination of anethole during hot massing was almost negligible for it could be finished in a closed system. The anethole residual in the granule right after the hot massing varied narrowly between 98.5 and 99.5% as the values before cooling shows in Fig. 6. On the other hand, time-course anethole residual was slightly affected by the cooling method. The jacket-cooling was superior to the fluidized-cooling in retention rate of anethole over the whole cooling interval. With the fluidized-cooling at 1.0 m^3/min in air flow rate for one minute, however, the residual rate of anethole was compatible with that of granules cooled by the jacket-cooling. Here, the granule temperature had already decreased to below 50℃, which meant the completion of cooling. The residual rate of cinnamaldehyde was also high (98.5%) in the cooled granule. When the air flow rate was augmented to 1.5 m^3/min, the granule temperature decreased similarly to cooling at 1.0 m^3/min though the elimination of anethole was slightly faster.

The results above showed that a rapid cooling with a fluid bed dryer at low flow rate could realize the protection of oils elimination as well as rapid cooling.

CONCLUSION

Size-controlled granules containing medicinal herbs were prepared by melt granulation followed by rapid cooling with a fluid bed dryer. Vaporization of essential oils contained in the herbs was almost completely prevented from vaporization throughout the granulation process.

These results suggest that the melt granulation is a useful technique for the agglomeration of powdered materials which contain volatile substances. The use of suitable reservoirs for other volatile medicines or excipients will provide new kinds of drug dosage forms with the present technique.

REFERENCES

1. Ukita, K., Kuroda, M., Honda, H. and Koishi, M., Chem. Pharm. Bull., 37, 3367 (1989).
2. Schilcher, H., Therapiewoche, 36, 1100 (1986).
3. El-Banna, H.M., Eshra, A.G. and Hammouda, Y., Pharmazie, 32, 511 (1977).
4. Ford, J. L. and Rubinstein, M. H., Int. J. Pharm., 8, 311 (1981).
5. Rubinstein, M.H. and Musikabhumma, P., Drug Dev. Ind. Pharm., 6, 451 (1980).
6. McTaggart, C.M., Ganley, J.A., Sickmueller, A. and Walker, S.E., Int. J. Pharm., 19, 139 (1984).
7. Flanders, P., Dyer, G. A. and Jordan, D., Drug Dev. Ind. Pharm., 13, 1001 (1987).
8. Sjökvist, E. and Nyström, C., Int. J. Pharm., 67, 139 (1991).
9. Musikabhumma, P., Rubinstein, M. H. and Khan, K. A., Drug Dev. Ind. Pharm., 8, 169 (1982).
10. Schaefer, T., Holm, P. and Kristensen, H. G., Drug Dev. Ind. Pharm., 16, 1249 (1990).
11. Choi, W.S., Proceedings of Second World Congress Particle Technology, 337 (1990).
12. Kinget, R. and Kemel, R., Acta Pharm. Technol., 31, 57 (1985).