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# Micromeritic studies on nicardipine hydrochloride microcapsules

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**Abstract**

In this study, nicardipine hydrochloride (N.HCl) microcapsules were prepared by means of coacervation phase separation technique using ethylcellulose (EC) as a coating material. Micromeritic investigations were carried out on nicardipine hydrochloride, ethylcellulose and nicardipine hydrochloride microcapsules in order to standardize the microcapsule product and to optimize the pilot production of dosage forms prepared with these microcapsules. Microcapsules we prepared had the ratio of 2:1 core:wall and then by sieving, were divided into two groups according to their particle sizes which were $>840$ $\mu$m and 476–840 $\mu$m. The bulk volume and weight, tapping volume and weight, fluidity, angle of repose, weight deviation, particle size distribution, density and porosity of nicardipine hydrochloride, ethylcellulose and nicardipine hydrochloride microcapsules were studied. To determine flowability, Hausner ratio and Consolidation index were also calculated from the results obtained. The findings of the study suggested that the micromeritic properties of the crude materials were significantly changed by the microencapsulation process. In addition, it was shown by scanning electron microscopy, that the changes were due to changes in the physicochemical properties of drug particles.

*Keywords:* Nicardipine hydrochloride; Microcapsule; Micromeritic properties; Particle population analysis; Drug content of gelatin capsules; Scanning electron microscopic studies

## 1. Introduction

The active substance of this investigation, nicardipine hydrochloride [2-(*N*-methylbenzylamino)ethylmethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,4,5-dicarboxylate)] is classified with the dihyrochloride derivatives and is a new calcium channel-blocking agent with coronary and peripheral arterial vasodilatory activity (Baky, 1985; Guerret et al., 1989; Merck, 1989). Nowadays, it is therefore effective in the treatment of angina and of mild to moderate hypertension. Several kinds of preparations have such as tablets, capsules and coated pellets have been suggested for use as oral extended release formulations (Bonferoni et al., 1992).

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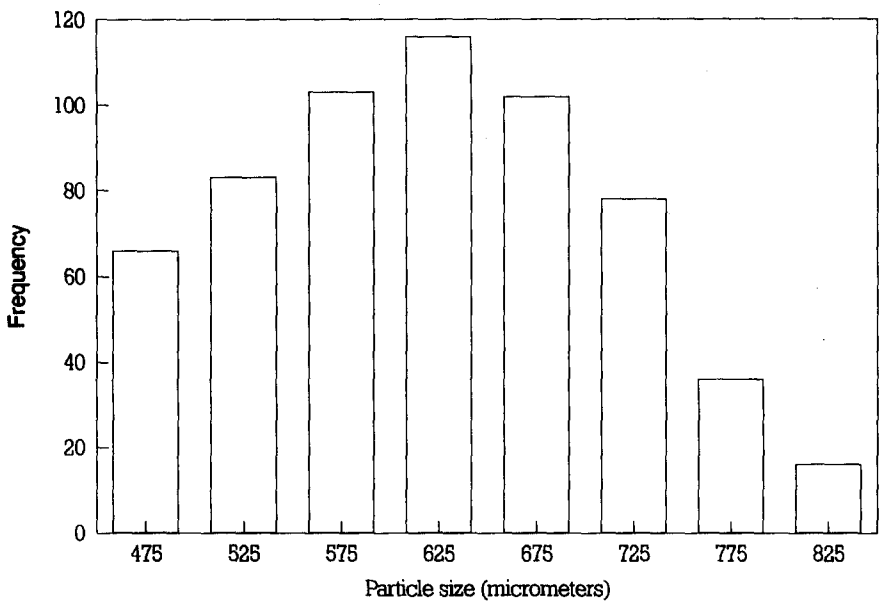


Fig. 1. Frequency distribution plots of particle size for microcapsules.

Of primary importance to a formulator, when handling drug powder is the assessment of flow properties. Size, surface area and surface to volume ratio of a particle can be related to the physical, chemical and pharmacologic properties of a drug (Wells, 1988). Stability and dissolution rate of drug powders are dependent on their particle-size distribution, and the formulation of suspensions, emulsions and tablets also depends on the particle size of the dispersed material involved (Güclüyıldız et al., 1977; Rubinstein and Blane, 1977). The bulk density of a powder bed is not uniform. Therefore, the physical properties of the bed are not uniform either (Gold et al., 1966a; Podczeck et al., 1993). One of the aims of this paper has been to investigate the effect of the microencapsulation process on the compressibility and compactibility of crystalline drug and polymer powder. Therefore, bulk volume and weight, fluidity, angle of repose, weight deviation, particle size distribution, density and porosity of the crude materials and microcapsules should be determined as well in order to standardize the microcapsule product and to optimize the pilot production of dosage forms prepared with these microcapsules. The required sustained release can be obtained by either tableting the microcapsules or filling them in hard gelatin capsules. Therefore, we calculated the Hausner ratio and the Consolidation index of the powder flow to determine whether sufficient flowability is present.

In addition, the physicochemical differences of the drug and microcapsule particles were observed by scanning electron microscopy.

## 2. Materials and methods

### 2.1. Materials

Nicardipine hydrochloride (Yamanouchi Pharm. Co. Ltd., Japan); ethylcellulose (ethoxy number 48 and Type N-10) (Sigma, St. Louis, MO); cyclohexane (Merck, Darmstadt, Germany); the other chemicals used are of analytical grade.

### 2.2. Methods

#### 2.2.1. Preparation of nicardipine hydrochloride microcapsules

The method of preparation was developed by modifying the techniques of Jalsenjak et al.

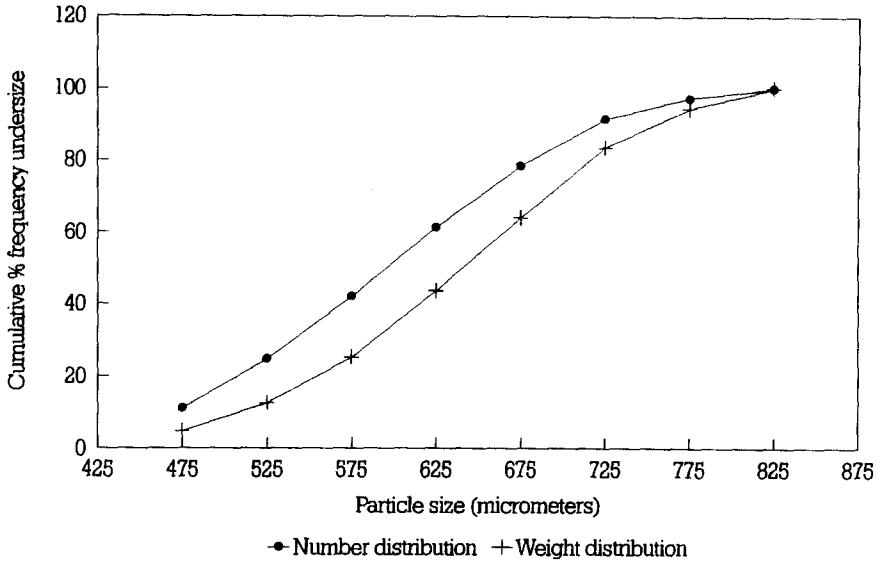


Fig. 2. Cumulative frequency plots of particle size for microcapsules.

(1976), Salib et al. (1976) and Sevgi et al. (1994).

Into a 500 ml three-necked flask, fitted with a stirrer, thermometer and a reflux, 200 ml of cyclohexane was placed. Four grams of ethylcellulose as coating material was added at 50°C by continuously stirring at 500 rev./min. The temperature was raised from 50°C to 70°C slowly over 20 min. Then, it was raised from 70°C to 80°C over a period of 75 min. The core material of nicardipine hydrochloride 8 g was then dispersed in the polymer solution with stirring at 500 rev./min over 10 min. The system was cooled within 30 min by continuous stirring; nicardipine hydrochloride microcapsules, coated with ethylcellulose, were separated by filtration and dried at 25°C.

*2.2.2. Scanning electron microscopy study*

Structures of powder formed by nicardipine hydrochloride and its microcapsules were determined in an electron microscope. Particles were coated with 200 Å gold in a vacuum, they were examined and photographs taken with the JEOL-JSM-5200 scanning electron microscope.

*2.2.3. Micromeritic studies*

The bulk volume and weight, tapping volume and weight of the sieved microcapsules and the raw materials were determined (Münzel et al., 1959; Voight and Bornschein, 1982).

The fluidity and angle of repose of microcapsules and raw materials were determined (Gold et al., 1966b; Hiestand, 1966; Sunner et al., 1966; Güven, 1987).

Weight deviation and relative deviation of microcapsules and raw materials were determined (US Pharmacopeia XXII, 1990). The sieved fractions of microcapsules were extracted with a solution whose pH was adjusted to 1.2 and drug amounts were determined spectrophotometrically at 239.4 nm. The fractions of the microcapsules were filled into 10 hard gelatin capsules (size 0) and weighed and drug contents of the filled gelatin capsules were calculated. The size of the hard gelatin capsules needed was estimated from the Lindenwald–Tawashi nomogram (Güven, 1987). The USP XXII method was used for the determination of the weight deviations of hard gelatin capsules (US Pharmacopeia XXII, 1990).

According to particle population analysis, the particle size of the microcapsules was determined by a microscopic method using a particle size measurer (OMO, MOB-1-15$^{x}$). Not less than 600 particles were measured. The geometric mean di-

ameter and geometric standard deviation were calculated according to the number and weight distribution of the microcapsules taking into consideration the particle size distribution (Martin et al., 1969; Schwartz, 1974; Stockham and Fochtman, 1979; Barber, 1993).

The particle densities of sieved microcapsules and other materials were determined with a pycnometer by using cyclohexane and calculation with Eq. (1) (Voight and Bornschein, 1982).

$$\rho = \frac{\rho_{liquid} \cdot m}{m + (m_1 - m_2)} \tag{1}$$

Where: $\rho$, density of the nicardipine hydrochloride particles; $\rho_{liquid}$, density of cyclohexane; $m$, mass of the powder (1 g); $m_1$, mass of cyclohexane; $m_2$, mass of the cyclohexane contained nicardipine hydrochloride powder.

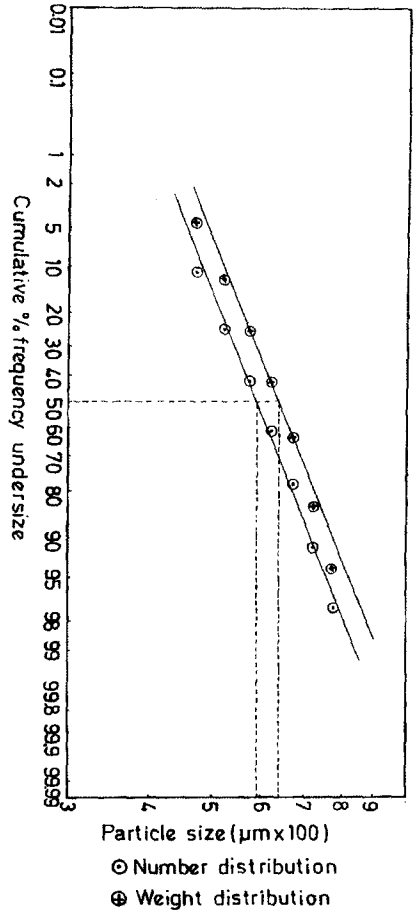


Fig. 3. Log probability plots of particle size for microcapsules.

The porosity of the microcapsules was calculated from the density values using Eq. (2) (Takenaka et al., 1980).

$$\epsilon = 1 - \frac{(C_{EC} \cdot \rho_{N.HCl} + C_{N.HCl} \cdot \rho_{EC})\rho_m}{\rho_{N.HCl} \cdot \rho_{EC}} \tag{2}$$

Where: $\epsilon$, porosity of the microcapsules; $C_{EC}$, weight per cent of ethylcellulose; $C_{N.HCl}$, weight per cent of nicardipine hydrochloride; $\rho_{N.HCl}$, density of the nicardipine hydrochloride particles; $\rho_{EC}$, density of the ethylcellulose particles; $\rho_m$, density of the microcapsule particles.

The porosity of the nicardipine hydrochloride and ethylcellulose was determined by the bulk volume and true volume values calculated from Eqs. (3)–(5) (Fonner et al., 1966a,b; Sunner et al., 1966; Martin et al., 1969; Eaves and Jones, 1972).

$$\epsilon = \frac{V_b - V_p}{V_b} \tag{3}$$

Where: $\epsilon$, porosity of raw materials; $V_b$, bulk volume; $V_p$, true volume.

$$V_p = \frac{W}{\rho} \tag{4}$$

Where: $W$, mass of the powder; $\rho$, true density.

$$V_b = \frac{W}{\rho_b} \tag{5}$$

Where: $\rho_b$, bulk density.

Pharmaceutical preformulation equations were used to calculate the Consolidation index (Eq. (6)) and the Hausner ratio (Eq. (7)) (Fassihi and Kanfer, 1987; Wells, 1988).

$$\text{Consolidation index (Carr)\%} = \frac{\text{Tapped density} - \text{Fluff density}}{\text{Tapped density}} \times 100 \tag{6}$$

$$\text{Hausner ratio} = \frac{\rho_{B,\max}\,(\text{Tapped density})}{\rho_{B,\min}\,(\text{Fluff density})} \tag{7}$$

## 3. Results and discussion

Particle sizes of 300, 500, 586, 600 and 1000 microcapsules have been measured by some au-

Table 1
Micromeritic properties of powders and microcapsules (mean ± S.E.)

| | Pure drug (N.HCl) | EC | >840 μm | 476–840 μm |
|---|---|---|---|---|
| Bulk volume (ml/g) | 3.183 ± 0.062 | 2.329 ± 0.036 | 3.963 ± 0.027 | 3.470 ± 0.084 |
| Bulk weight (g/ml) | 0.314 ± 0.006 | 0.429 ± 0.006 | 0.252 ± 0.001 | 0.288 ± 0.007 |
| Tapping volume (ml/g) | 2.009 ± 0.024 | 1.933 ± 0.024 | 3.758 ± 0.074 | 3.234 ± 0.062 |
| Tapping weight (g/ml) | 0.497 ± 0.005 | 0.516 ± 0.006 | 0.266 ± 0.004 | 0.308 ± 0.005 |
| **Angle of repose (°)** | | | | |
| Amount 1 g | 33.88 ± 0.38 | 8.76 ± 0.68 | 20.66 ± 2.15 | 15.66 ± 0.81 |
| 2 g | 40.18 ± 0.62 | 9.13 ± 3.06 | 26.66 ± 1.62 | 30.33 ± 1.47 |
| 4 g | 50.57 ± 0.16 | 22.66 ± 1.11 | 31.66 ± 1.07 | 32.33 ± 1.47 |
| 6 g | 51.94 ± 0.80 | 28.57 ± 0.65 | | 31.66 ± 0.81 |
| 8 g | 54.20 ± 0.21 | 29.52 ± 0.20 | | 33.00 ± 0.70 |
| 10 g | 54.41 ± 0.33 | 29.93 ± 0.84 | | 32.33 ± 0.40 |
| **Flow time (s)** | | | | |
| Amount 1 g | 3.30 ± 0.07 | 0.46 ± 0.07 | 0.46 ± 0.03 | 0.30 ± 0.07 |
| 2 g | 16.80 ± 0.14 | 0.60 ± 0.00 | 0.93 ± 0.07 | 1.33 ± 0.17 |
| 4 g | 83.30 ± 0.35 | 1.00 ± 0.14 | 1.34 ± 0.04 | 1.60 ± 0.14 |
| 6 g | 130.80 ± 2.91 | 1.20 ± 0.28 | | 2.46 ± 0.07 |
| 8 g | 147.43 ± 3.74 | 1.50 ± 0.55 | | 2.66 ± 0.16 |
| 10 g | 199.06 ± 7.20 | 1.80 ± 0.24 | | 2.78 ± 0.13 |
| **Weight deviation (± mg)** | | | | |
| Volume 1 ml | 12.018 | 14.509 | 9.762 | 16.238 |
| 2 ml | 12.564 | 23.448 | 8.139 | 15.268 |
| 4 ml | 15.653 | 9.807 | 10.564 | 13.577 |
| 5 ml | 9.243 | 26.172 | 21.712 | 39.186 |
| 6 ml | 5.972 | 47.713 | 20.717 | 33.693 |
| **Relative deviation (± %)** | | | | |
| Volume 1 ml | 4.113 | 3.243 | 3.881 | 5.660 |
| 2 ml | 2.099 | 2.713 | 1.684 | 2.753 |
| 4 ml | 1.263 | 0.590 | 1.087 | 1.200 |
| 5 ml | 0.589 | 1.224 | 1.853 | 2.778 |
| 6 ml | 0.319 | 1.820 | 1.387 | 1.913 |
| True density (g/ml) | 1.062 ± 0.050 | 1.078 ± 0.021 | 0.987 ± 0.009 | 1.028 ± 0.044 |
| Porosity | 0.7705 ± 0.0055 | 0.6068 ± 0.0039 | 0.6010 ± 0.0052 | 0.6030 ± 0.0025 |

thors for particle size distribution (Kawashima et al., 1972; Nixon and Hassan, 1980a; Takenaka et al., 1980; Jalsenjak and Kondo, 1981; Morris and Warburton, 1982). In our study, a total of 600 microcapsules were measured and the number particle size distribution of the microcapsules is given in Fig. 1. The size varied from approximately 450 μm to 850 μm with a peak value between 600 μm and 650 μm.

The cumulative frequency plots of microcapsules in terms of number and weight distribution are shown in Fig. 2. The weight of microcapsules less than 510 μm is approximately 10%, less than 640 μm is 50% and less than 780 μm is 95%. The number of particles less than 475 μm is approximately 10%, less than 600 μm is 50% and less than 755 μm is 95%.

The log probability plots for the size of the microcapsules are shown in Fig. 3. A log normal distribution has several properties of interest. When the logarithm of the particle size is plotted against the cumulative per cent frequency on a probability scale, a linear relationship is observed. Such a linear plot has the distinct advantage that we can now characterize a log normal distribution curve by means of two parameters, the slope of the line and a reference point. The law has been reported to be obeyed by many particulate systems, including microcapsules (Takenaka et al., 1980; Senjkovic and Jalsenjak, 1981) although

Table 2
Drug contents of the microcapsules and the filled gelatin capsules (mean ± S.E.)

| | Particle size of microcapsules | |
|---|---|---|
| | >840 μm | 476–840 μm |
| Percentage of drug (g) | 12.52 ± 0.21 | 14.28 ± 0.23 |
| Microcapsule amount equivalent to 20 mg drug (g) | 0.160 ± 0.006 | 0.140 ± 0.0011 |
| Weight of empty gelatin capsules (g) | 0.0967 ± 0.0006 | 0.0963 ± 0.0005 |
| Weight of filled gelatin capsules (g) | 0.2551 ± 0.0009 | 0.2351 ± 0.0006 |
| Weight of microcapsules in gelatin capsules (g) | 0.1584 ± 0.0003 | 0.1358 ± 0.0003 |
| Drug content of the filled gelatin capsules (g) | 0.0198 ± 0.0001 | 0.0194 ± 0.0001 |

other workers with microcapsules have not found the law applicable (Nixon and Hassan, 1980b; Morris and Warburton, 1982).

The geometric number mean diameters (dg) and geometric weight mean diameters (d'g), and the corresponding geometric standard deviations ($\sigma$g and $\sigma$'g) were calculated from Fig. 3, Eqs. (8) and (9) (Schwartz, 1974; Ismail and Tawashi, 1980; Barber, 1993).

$$\sigma = \frac{\text{diameter at 84.13\% probability}}{\text{diameter at 50.0\% probability}} \quad (8)$$

or

$$\sigma = \frac{\text{diameter at 50.0\% probability}}{\text{diameter at 15.87\% probability}} \quad (9)$$

In terms of regression analysis, to calculate the geometric standard deviation, the points at 15.87 and 84.13% probability are important (Fonner et al., 1966a; Carstensen and Musa, 1972; Hajratwala, 1982). It is recommended that probabilities between 16 and 84% be routinely included in the calculations. We found the values of the number distribution, dg = 595 μm and the weight distribution, d'g = 645 μm. Geometric standard deviations are calculated from the above results and they are $\sigma$g = 595/495 = 1.20 and $\sigma$'g = 645/540 = 1.19, respectively. It is reported that both of the calculated geometric standard deviations ($\sigma$g and $\sigma$'g) are the same or very similar (Martin et al., 1969; Barber, 1993; Ertan et al., 1995). The index of determination that indicates the fit to the straight lines remains the criterion by which one judges whether further analysis is necessary.

In Table 1, the bulk volume and weight, tapping volume and weight, angle of repose, flowing time, standard deviations, relative deviations, density and porosity values of the materials are shown. According to these results, the order of the bulk volume and weight of the materials are:

Ethylcellulose < (476–840 μm) < Pure drug < (>840 μm) for bulk volume (ml/g) and (>840 μm) < (476–840 μm) < Pure drug < ethylcellulose for bulk weight (g/ml). So ethylcellulose is the heaviest and the >840 μm microcapsules are the lightest. When the particle size of microcapsules increases, the bulk weight decreases.

Table 3
Interpretation of Carr's Index and Hausner Ratio for powders and microcapsule flow

| | Consolidation Index (Carr) | | Hausner Ratio | |
|---|---|---|---|---|
| | % | Flow | Ratio | Flow |
| Nicardipine hydrochloride | 36.82 | Very poor | 1.58 | Poor |
| Ethylcellulose | 16.86 | Good | 1.20 | Good |
| >840 μm microcapsule | 5.26 | Excellent | 1.05 | Good |
| 476–840 μm microcapsule | 6.49 | Excellent | 1.06 | Good |

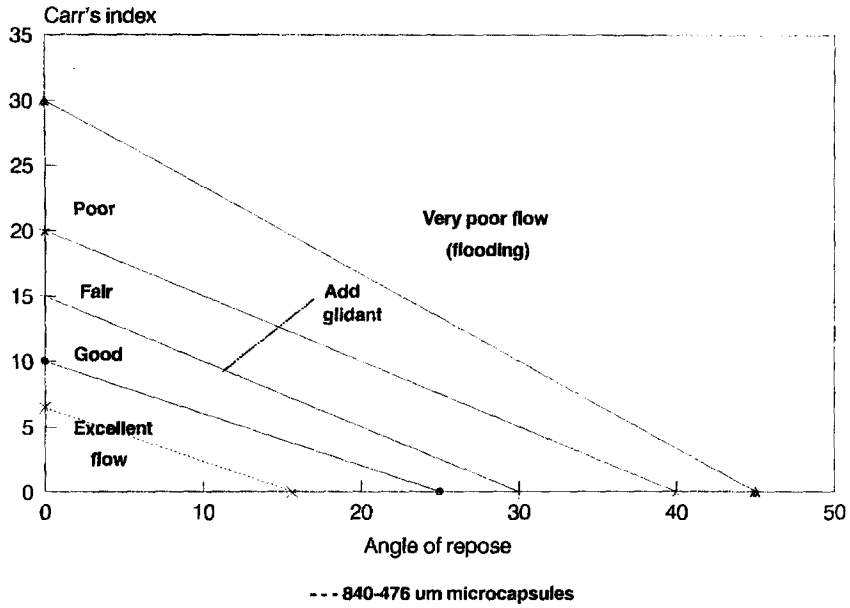


Fig. 4. Relationship between flow and angle of repose ($\theta$) and Carr's index.

It was found that: Ethylcellulose < Pure drug < (476–840 $\mu$m) < (>840 $\mu$m) for tapping volume (ml/g) and (>840 $\mu$m) < (476–840 $\mu$m) < Pure drug < Ethylcellulose for tapping weight (g/ml). Normally, the tapping volumes of all materials decrease according to the bulk volumes. The largest volume decrease was observed from the drug and this finding was supported by the porosity data.

The particle size of microcapsules is larger than that of raw materials so the volume decrease is very small for microcapsules. The volume decrease is less when the mean particle size of the microcapsules increases. Our results and results in the literature are similar (Hiestand, 1966; Ertan et al., 1995).

Ethylcellulose had the smallest values for angle of repose and flow time while nicardipine hydrochloride showed the greatest values for both. As a result, flow time has been found to be smaller in microencapsulated nicardipine hydrochloride when compared to powdered form. So this result once again indicated the improvement of flow property in microcapsule form but in order to understand whether this improvement would be enough for producing gelatin capsules and tablets from microcapsules with the necessary amounts, the Consolidation index and Hausner ratio to the microcapsules should be examined.

The procedure for determining true density pycnometrically using organic solvents was followed. This method has been used in some studies (Eaves and Jones, 1972; Woodruff and Nuessle, 1972; Steiner et al., 1974; Carstensen and Chan, 1977)

The density of the materials is given in the following order, according to the our results: (476–840 $\mu$m) $\leq$ (>840 $\mu$m) < Ethylcellulose < Pure drug.

Normally, when the size of microcapsules increases, the density decreases. Ethylcellulose has the highest density and this is supported by the data for the bulk weight. Kawashima et al. (1972) found the true density values of microcapsules as 1.32–1.54 g/cm$^3$ and Takenaka et al. (1980) as 1.02–1.19 g/cm$^3$. The true density of our materials was 0.987–1.078 g/cm$^3$. So the literature results are similar to ours.

The porosity may be computed from a knowledge of the density. Density may be directly related to porosity (Eaves and Jones, 1972).

The highest porosity was observed for nicardipine hydrochloride and the porosity of ethylcellu-

Fig. 5. Scanning electron photomicrograph of nicardipine hydrochloride ( × 1500).

lose was higher than that of the microcapsules. When the size of microcapsules increases, a small change has been observed in the porosity.

It was observed from the calculated standard deviations and relative deviations that the standard error is less than 5% when filling the microcapsules into hard gelatin capsules. The size of gelatin capsules is found according to the Lindenwald–Tawashi nomogram. For all microcapsule size fractions, size 0 gelatin capsules could be used to fill the microcapsules. The weight deviation of the hard gelatin capsules in which the sieved microcapsules were filled, was found to be 90–110% of the capsule's weight which fits the USP XXII (US Pharmacopeia XXII, 1990). This was supported by the calculations of the relative deviations of the microcapsules. Drug contents of the microcapsules and the filling gelatin capsules are shown in Table 2. This table also shows the method for calculating the drug content in the microcapsules. Our results are in accordance with the general pharmaceutical limits which are given in Pharmacopeia XXII.

The flowability of the microcapsules was found to be excellent according to the Carr index of compressibility and good according to the Hausner ratio of the materials. This is shown in Table 3. These results were confirmed by the flow time values. The relationship between flow and angle of repose ($\theta$) and Carr's index is given in Fig. 4.

Photographs of nicardipine hydrochloride and its microcapsules from the scanning electron microscope are shown in Figs. 5–7. It is clear from these that by means of the microencapsulation process, the drug particle size increased and the shape of the microcapsule particle has become more spherical than the drug particles, so flowability of the microcapsules is greater than that of the drug particles as in previous findings (Kawashima et al., 1989; Chukwu et al., 1991; Messhali et al., 1991; Torrado-Duran et al., 1991).

From these results, it may be concluded that the process of microencapsulation has significantly increased the fluidity of the nicardipine hydrochloride, and for tableting the microcapsules or filling them into hard gelatin capsules for industrial applications, no glidant will be needed.

Fig. 6. Scanning electron photomicrograph of $>840$ $\mu$m nicardipine hydrochloride microcapsules ( $\times$ 35).

Fig. 7. Scanning electron photomicrograph of 476–840 $\mu$m nicardipine hydrochloride microcapsules ( $\times$ 35).

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