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RESEARCH PAPER

# Process for Overcoming Drug Retention in Hard Gelatin Inhalation Capsules

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## ABSTRACT

*The quantity and consistency of drug delivery from dry powder inhalation devices that incorporate a pre-measured dose in a hard shell capsule of gelatin or other compatible material can be negatively affected by mold release lubricants used in capsule manufacturing. This paper describes a novel process employing supercritical $CO_2$ for selective extraction of the fraction of lubricant responsible for the observed high and inconsistent drug retention in capsules and the ensuing lack of reproducibility of drug delivery. The process allows for lubricant removal from seemingly inaccessible interior surfaces of assembled capsule shells without altering the structural or chemical properties of the capsules. Diffusion limitations are overcome through repeated pressure increase and decrease to generate significant convective flow of dissolved lubricant out of the capsule. Drug retention is alleviated only if nearly all the retentive fraction of the lubricant is removed. The effect of extraction with supercritical $CO_2$ on the structure of the internal surfaces of the capsules is investigated using scanning electron microscopy. Key performance parameters such as drug and carrier retention and fine particle mass are investigated using simulated inhalation tests. Laboratory and pilot scale extractions yielded similar results.*

***Key Words:*** *Drug retention; Dry powder inhaler; Hard gelatin capsule; Mold lubricant; Supercritical fluid*

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## INTRODUCTION

Dry powder inhalers (DPI) are routinely used for pulmonary delivery of locally acting drugs such as bronchodilators. One common approach for single dose systems involves the placement of a known quantity of drug substance into a capsule of gelatin or other compatible material. The capsule is then punctured or ruptured in a special device to expose the medicament to a turbulent air stream induced by patient inspiration. Entrainment of the powder in the air stream leads to pulmonary deposition upon completion of the breathing cycle. Any material that is not discharged from the capsule will obviously not reach the target site.

Ipratropium bromide monohydrate (IpBr) is an anticholinergic bronchodilator drug that is administered via oral inhalation at typical therapeutic doses of $<50\,\mu g$. In one type of dry powder system, IpBr, reduced to a suitable particle size for inhalation (typically $<5\,\mu m$), is blended with a coarser bulking agent such as lactose with an average particle size of $40\,\mu m$ before filling into the capsule. The bulking agent also serves as a drug carrier to facilitate the dispersion of cohesive drug particles (1), to aid in the flow of the powder out of the inhaler, and to allow for separation into individual respirable particles (deaggregation) upon inhalation.

Empty capsules are supplied to the pharmaceutical manufacturer as a two-part system of a mating body and cap, in an assembled state. Capsule filling machinery separates the two parts, introduces the formulation, and then locks or closes the cap on the body of the capsule. The locking mechanism effectively prevents the inadvertent separation of filled capsules.

Manufacturing of capsule shells involves dipping mold pins into a bath of molten gelatin, removing the pins from the bath, and then allowing the capsule-forming material to harden on the pins. The hard capsule shells are then removed from the pins. In order to remove the capsule shells without damage, the mold pins are coated with a lubricant prior to their dipping in the bath. Some lubricant thus remains on the inside surfaces of the capsules. This lubricant is known to cause the drug to adhere to the walls of the capsules and, consequently, to increase drug retention and affect the quantity and consistency of the inhalable fraction.

Rinsing capsules with organic solvents has been shown to remove this undesirable lubricant material (2,3); however, capsule caps or bodies cannot be efficiently extracted in bulk because they tend to inter-associate. This can block access for the organic solvent to parts of the shells and reduce the efficiency of the drying step. The requirement that the two halves of the shell be separated confines the use of this process to separate processing stages of disassembly, extraction, drying, and reassembly of individual capsules. Potential solvent contamination of the capsules as well as damage to the gelatin material by the organic solvent are also possible.

The lubricant extraction methods described in this study make use of supercritical $CO_2$ to extract lubricant material from either open, i.e., capsule cap and body disassembled, or assembled capsules (4). A supercritical fluid (SCF) is a substance above its critical temperature and critical pressure ($31.0^{\circ}C$, 73.8 bar for $CO_2$). A SCF such as $CO_2$ is relatively innocuous, inexpensive, and unreactive. Its gaslike space-filling and highly diffusive nature combined with its relatively high density and affinity for lipophilic material provides a unique ability to rapidly flow into an assembled capsule, solubilize the lubricant, and transport it out of the capsule with no phase change. Information on SCFs, including the solubility of lipidic material similar to mold lubricant in SCFs, is available in the technical literature (5).

The aim of this study is to investigate whether any physical change results from subjecting capsules to high fluid pressures, to gain some understanding of the effect of lubricant content on drug retention, and to investigate whether supercritical $CO_2$ can be used to extract the fraction of lubricant responsible for the observed high and inconsistent drug and carrier retention in the capsules. A further aim is to use scanning electron microscopy (SEM) of capsule internal surfaces before and after extraction to elucidate the mechanism of drug retention.

## EXPERIMENTAL

Raw lubricant in its suspension form was provided by capsule manufacturer A. Its extraction was conducted to determine optimal extraction conditions for lubricant in capsules. Six lots of hard, pigmented, size 3, 0.3-mL gelatin capsules, from two manufacturers and having different powder retention characteristics, were used in this study. Capsule lots 1–3 are regular capsules from manufacturer A. Capsule lot 4 consists of regular capsules from

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***Table 1***

*Reference Conditions for SFE of Capsules at Either Constant Pressure (CP=172 Bar) or by Periodic Variation of Pressure in the Range of 172–103 Bar.* T=*35°C*

| SFE-Treated Capsule Lot # | Dynamic SFE Time (hr) | NPV/PV[a] | State of Capsules During SFE |
|---|---|---|---|
| 1-E[b,c] | 5 | 20/15 | Assembled |
| 2-E-1 | 1 | CP | Open |
| 2-E-2[b] | 2 | CP | Open |
| 2-E-3 | 2 | CP | Assembled |
| 2-E-4[b] | 5 | 20/15 | Assembled |
| 2-E-5 | 5 | CP | Assembled |
| 3-E-1 | 1 | CP | Open |
| 3-E-2[b] | 2 | CP | Open |
| 3-E-3 | 2 | CP | Assembled |
| 4-E[b] | 5 | 20/15 | Assembled |
| 5-E[b] | 2 | CP | Open |
| 6-E[b] | 2 | CP | Open |

[a]NPV: Number of pressure variations. PV: Period of variation (min).
[b]Extraction at optimum conditions.
[c]Extraction at pilot scale.

manufacturer B. Capsules from lots 5 and 6 are experimental (not regular) lots from manufacturer A. They contain a proprietary polar plasticizer substance used to preserve the elasticity of the capsules in low relative humidity (RH) environments. Capsule lots 1–4 are referred to as regular lots.

Capsules were extracted at either constant pressure or variable pressure in either their open or assembled state. Table 1 depicts the extraction conditions. Extracted lot X-E-Y refers to capsule control lot X extracted under conditions Y shown in Table 1.

Except for capsule lot 1 which was extracted at pilot scale (9000 capsules) using bone dry $CO_2$ (99.8% purity) at a commercial facility (Phasex, Lawrence, MA), all other lots were extracted at experimental scale (112 capsules) using supercritical fluid chromatography (SFC) grade $CO_2$ (99.9995%). Lubricant in capsules and residue from supercritical fluid extraction (SFE) of capsules were analyzed by high-performance liquid chromatography (HPLC). Capsules were hand-filled with the same batch of powder. Drug retention and delivery yielded by both SFE-treated capsules and control capsules as provided by their manufacturers were assessed using an Andersen cascade impactor (CI; Andersen Mark II, Andersen Sampler, Inc., Atlanta, GA).

A separate study involving different lots of drug and lactose and four other regular capsule lots from manufacturer A was used to investigate the effect of mold lubricant on drug retention.

## SFE Apparatus

Extraction experiments were conducted using an in-house-built SFE unit (Fig. 1). Briefly, the experiment starts by loading capsules or raw lubricant into a 350-mL vessel. The vessel is then closed and connected to the SFE unit which incorporates an isothermal water bath at 35°C that contacts valves, heat exchanger, and vessel. Liquid $CO_2$ at about 60 bar in a cylinder equipped with a syphon tube is then pumped into the SFE unit. When pressure reaches the desired supercritical level, an automated micrometering valve is used to control pressure in the vessel. Lubricant-loaded $CO_2$ expands through the micrometering valve to near atmospheric pressure. Extracted lubricant condenses out of the gas and is retained in an extract collection vial. Carbon dioxide is vented through a hood into the atmosphere. Dynamic extraction at either constant pressure, i.e., conventiona SFE, or by periodic variation of pressure is conducted for a definite period. At the end of the extraction period, pumping of $CO_2$

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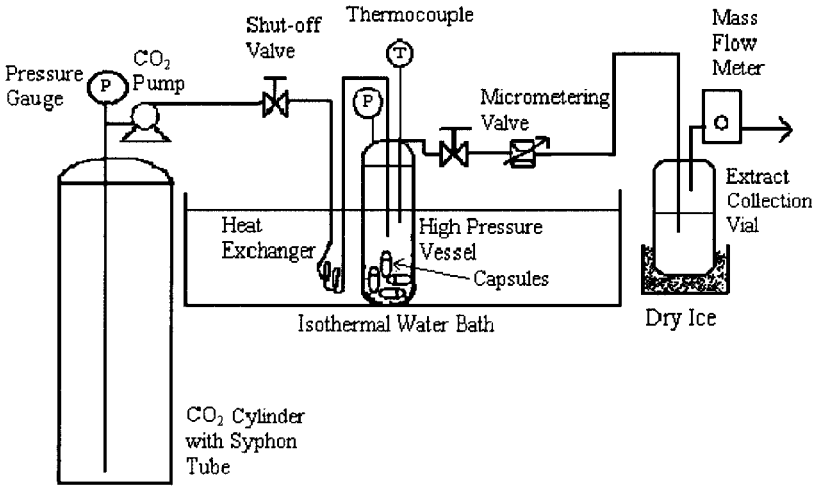


**Figure 1.** Schematic of SFE unit.

into the vessel is halted and pressure is slowly brought down to atmospheric level. Residual, unextracted material is then weighed and stored until ready for analysis. The extract lines are flushed with a mixture of 60% ethanol/40% tetrahydrofuran (THF), and the resulting extract is stored in amber bottles in a freezer.

## METHODS

### Cascade Impactor and Boehringer Ingelheim Inhalator™ System

A cascade impactor is a standard instrument that simulates the size classification function of the human respiratory system. It is used to characterize the behavior of gas suspended particulates and allow estimation of the amount of material possessing an aerodynamic size in the range associated with optimal pulmonary deposition. The CI used in this study is an eight-stage, 1 $ft^3$/min non-viable particle size sampler. It consists of a pre-separator stage that removes particles larger than 10 μm and a series of eight metal classifier stages with holes of decreasing size from the top to the bottom of the stack, separated by metallic collection plates.

For operation, a filled capsule is first inserted into the chamber of a device known as the Inhalator™. The same device is used by patients and for performance of in vitro testing. The inhaler is closed and the capsule is pierced with two prongs. The piercing button is then released and a vacuum pump is used to draw the sample in the capsule through the stack of stages. The smaller the particle, the longer it remains in the air stream and the lower the stage it can reach (6). In order to prevent particles from bouncing off the stage plates and being re-entrained in the air stream, collection plates and pre-separator were coated with an adhesive material [polyoxyethylene (23) lauryl ether in glycerol]. The plates were cleaned and recoated following each run. The pre-separator was recoated once every six runs.

The CI is equipped with a control system that allows air to be drawn through the inhaler for a defined duration. Air flow rate and sampling time were set to 28.3 L/min and 15 sec, respectively. Under these conditions, pressure loss due to flow resistance was 31 cm of water at a flow rate of 2.35 $m^3$/hr and an air pressure of 1000 mPa. Defined tolerances for pressure drops are confirmed prior to performing each test.

Approximately 5.5 mg of a powder blend consisting of 5.454 mg of lactose (Pharmatose 200M, DMV, Veghel, Netherlands) and 0.046 mg of IpBr were carefully hand-loaded into SFE-treated or control capsules. The capsules were locked and then shaken slightly to simulate the tumbling the capsules are subjected to between the time they are manufactured and the time they are used by a patient. Cascade impactor tests were then performed. Particles collected in stages 0–1 are larger than 5.8 μm and are not expected to reach the bronchiolar or alveolar regions of the lungs, and

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were therefore discarded. Fine particle mass (FPM), defined as the mass of drug or carrier particles with size $<5.8\,\mu m$ deposited in stages 2–7, is the fraction of material that possesses an aerodynamic size in the range that has been shown to be related to improvement in pulmonary function after inhalation of IpBr (7). These deposits were collectively extracted with 20 mL of 0.01 N HCl. The solution was then filtered through a 0.45-μm Gelman PTFE filter. High-performance liquid chromatography analysis was then used to determine the FPM. The FPM was evaluated for each individual capsule tested. Analysis for drug substance deposited on each individual stage is not possible because the quantities on some of the lower stages are often close to or below the detection limit.

Powder retention in a capsule was determined by first opening the capsule, then transferring the body and cap along with the residual powder into a 20-mL screw cap scintillation vial, adding 10 mL of 0.01 N HCl, sonicating in an ice bath for 1 min, filtering the solution through a 0.45-μm Gelman PTFE filter, and then analyzing by HPLC for IpBr and lactose. For each capsule lot, determination of retention and FPM in either extracted or control capsules was repeated at least six times.

### Gravimetric Evaluation of Capsule Retention

In one case (capsule lot 2-E-5), a rough estimate of powder retention was obtained using a simple method which consists of holding between fingers the cap and body of a filled capsule open sides down, vigorously emptying into a waste container by tapping both hands five times on the edge of the container, and then gravimetrically determining powder retention. Evaluation of powder retention is repeated five times. The validity of this method was ascertained by comparison with retention in lots 2 and 2-E-2, which was also determined using the CI test apparatus. When used in a systematic fashion, this method has been shown to give a reliable estimate for the propensity of capsules to retain a powder.

### HPLC Analysis of Drug and Carrier

Analysis for IpBr was conducted using a $4.6\times150\,mm^2$ Zorbax SB-C18 reverse phase column and a mobile phase of 0.008 M 1-pentane sulfonic acid sodium salt/acetonitrile 82:18 (v/v) at a flow rate of 1.5 mL/min. Column temperature was 35°C, injection volume was 100 μL, ultraviolet (UV) detection wavelength was 210 nm, and run time was at least 10 min.

Analysis for lactose was conducted using a $7.8\times300\,mm^2$ Bio-Rad Aminex HPX-87H ion exclusion column and a mobile phase of 0.012 N sulfuric acid at 1.0 mL/min. Column temperature was 40°C, injection volume was 100 μL, detection was accomplished by refractive index, and run time was at least 15 min.

### Measurements on Capsules: Weight Loss, Brittleness, and SEM

Weight loss of capsules due to SFE was determined by gravimetry immediately following their removal from the extraction vessel. Capsule brittleness, which is related to capsule elasticity and flexibility, was evaluated before and after SFE using a capsule impact tester. The instrument consists essentially of a pin attached to the bottom of a lever swinging from different heights and impinging upon a capsule. The minimum height at which the capsule is pierced by the pin determines the energy needed to pierce the capsule. The higher the energy (mJ) needed to pierce the capsule, the lower the capsule brittleness.

A scanning electron microscope (SEM, Hitachi S-4000) was used to examine changes in capsule internal surface brought about by the SFE treatment. Capsules were cut using a heated wire and then adhered to an aluminum stub using double-sided silver tape. The internal surface was then sputter-coated with a thin layer of platinum.

### SFE of Assembled Capsules: Processing Considerations

Extraction of assembled capsules by conventional SFE at constant pressure yielded little lubricant extract and only marginal reduction in capsule retention. It was determined that condensation of solubilized lubricant back onto the capsule internal surfaces during pressure letdown to atmospheric level following the extraction period is at least partially responsible for the lack of improvement in the retention properties of the capsules. Strong diffusion limitations between the lubricant-laden $CO_2$ phase in the capsule and the bulk $CO_2$ phase outside the capsule greatly limited the ability to evacuate solubilized lubricant out of the capsule.

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One way to overcome strong diffusion limitations is to create conditions under which convective flows take place. The ability to vary the density of supercritical $CO_2$ through periodic changes in pressure with no phase change was used to develop a method for establishing such flows. The method consists of repeatedly increasing and decreasing pressure over a specified range. Fresh $CO_2$ from the bulk phase is forced into the capsule $CO_2$ phase during pressure buildup and lubricant-laden $CO_2$ phase is forced into the bulk $CO_2$ phase during pressure reduction. Besides extraction of lubricant from assembled capsules, this pressure modulation technique can be used to extract any soluble material from closed or nearly closed containers, including vials, bags, and drums (8). A mass transfer model is used to determine conditions under which convective flows enhance extraction efficiency (9). It is found that small-magnitude pressure changes, which do not induce the precipitation of solubilized material, are sufficient to effect a considerable enhancement in extraction efficiency.

## RESULTS AND DISCUSSION

### Determination of Optimal Extraction Conditions

Study of the extractability of raw lubricant material was used to determine the conditions under which lubricant in capsules will be quantitatively solubilized. A low supercritical temperature of 35°C was selected to avoid thermal degradation of capsules. Residues of extraction of $0.35 \pm 0.03$ g of raw lubricant extracted at pressures $\geq 172$ bar and extraction times $\geq 2$ hr at 1.6 standard liters per minute of $CO_2$ appeared as a solid, glassy material. A maximum of 80% of the lubricant mass is soluble in $CO_2$ at 35°C and pressures $\geq 172$ bar. Residues obtained at pressures $<172$ bar and extraction times $<2$ hr appeared as viscous suspensions. Hence, in the absence of diffusion limitations, 2 hr of dynamic extraction at 172 bar should lead to essentially optimal extraction of the liquid, soluble fraction of the lubricant in capsules. This fraction is hypothesized to have a greater tendency to entrap drug particles than the solid glassy residue that would be expected to remain in SFE-treated capsules at optimal conditions. A decrease in the intimacy of contact between drug particles and the internal surface of the capsules brought about by the removal of the liquid fraction of the lubricant would have the effect of reducing drug retention.

### Effect of SFE on Physical Properties of Capsules

Capsules feature small grooves and protuberances designed to avoid buildup of air pressure when closed and locked. They are believed to facilitate flow of supercritical $CO_2$ into and out of the capsules with no physical damage to the capsules; however, a high rate of pressure buildup can still cause capsules to be crushed or otherwise damaged. Plasticizer-containing capsule lots 5 and 6 are softer than other capsules and are physically sensitive to the high fluid pressures involved in this process when extracted in their assembled state. A slow initial buildup in pressure reduces substantially the tendency of such capsules to be crushed or otherwise damaged by the process. Capsules from lots 1–4 are not damaged by the process.

Supercritical fluid extraction-treated capsules are found to weigh up to 4% less and are more brittle than untreated capsules when measurements are made immediately following SFE; however, they re-equilibrate in a controlled RH environment to nearly their original mass and brittleness at that RH, indicating that changes in mass and brittleness are due to reversible moisture removal by $CO_2$.

### Drug and Carrier Retention and FPM

Table 2 shows the results of Andersen CI tests for drug and carrier retention and FPM yielded by capsules extracted under optimal conditions, i.e., 2 hr of dynamic SFE for open capsules, or 20 pressure variations between 172 and 103 bar with a period of 15 min for assembled capsules (1-E, 2-E-2, 2-E-4, 3-E-2, 4-E, 5-E, and 6-E). Average values along with standard deviations (SD) are shown.

Supercritical fluid extraction-treated capsules retain less drug and carrier than their respective control capsules irrespective of manufacturer and whether the capsules were extracted in the open or assembled state. Standard deviations for retention in SFE-treated capsules are also generally lower than those for control capsules.

Drug retention is generally high and variable ($9.0 \pm 2.2$ μg or $19.7\% \pm 4.8\%$ of total dose) in regular control capsules from manufacturer A (lots 1–3) and low and more reproducible ($3.3 \pm 1.2$ μg or

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***Table 2***

*Drug Retention and FPM (μg/Capsule±Standard Deviation) Yielded by Control Capsules and SFE-Treated Capsules at Optimal Extraction Conditions*

| Capsule Lot | | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| Drug retention | U[a] | 8.1±2.1 | 8.1±1.4 | 10.3±2.3 | 4.9±2.1 | 21.8±1.1 | 21.3±2.0 |
| | E[b] | 4.6±0.8 | E2: 2.3±0.9 E4: 3.1±0.7 | 3.1±1.0 | 4.3±0.5 | 16.4±1.7 | 19.0±1.6 |
| Drug FPM | U | 11.5±2.1 | 14.8±1.5 | 12.2±1.5 | 14.3±1.4 | 7.3±0.4 | 5.6±1.1 |
| | E | 17.7±1.1 | E2: 18.2±1.5 E4: 18.9±0.9 | 17.2±1.8 | 16.6±0.9 | 10.3±1.3 | 9.3±0.6 |
| Carrier retention | U | 237.3±59.3 | 243.1±39.1 | 271.4±49.1 | 450.9±121.7 | 1425.1±88.3 | 1242.6±539.3 |
| | E | 170.1±62.6 | E2: 70.7±28.2 E4: 123.0±24.0 | 112.7±30.8 | 274.5±40.6 | 1205.4±196.5 | 1447.1±86.8 |
| Carrier FPM | U | 168.6±26.5 | 191.0±18.3 | 160.3±23.3 | 299.1±26.0 | 216.7±17.1 | —[d] |
| | E | 292.4±36.8 | 271.7±53.2 299.0±17.0 | 215.4±26.3 | 285.0±6.5 | 269.9±7.3 | 224.9±9.2 |
| Non-respirable drug | U | 26.4 | 23.1 | 23.5 | 26.8 | 16.9 | 19.1 |
| | E | 23.7 | 25.5 24.0 | 25.7 | 25.1 | 19.3 | 17.7 |
| DR/(CR+DR)×100 (%)[c] | U | 3.30 | 3.22 | 3.66 | 1.07 | 1.51 | 1.68 |
| | E | 2.63 | 3.15 2.46 | 2.67 | 1.54 | 1.34 | 1.30 |

[a]U: Untreated (control) capsules.
[b]E: Extracted capsules.
[c]DR/(CR+DR): Drug retention/(carrier retention+drug retention).
[d]No carrier was detected.

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7.2%±2.6%) in corresponding SFE-treated capsules. Fine particle mass is also low and less consistent in control regular capsules (13.3±2.1 μg or 28.9%±4.6%) than in corresponding SFE-treated capsules (18.0±1.5 μg or 39.1%±3.2%). Retention and FPM yielded by SFE-treated capsules are similar to those obtained by washing capsules with organic solvents. The process is also easily scalable. Capsules extracted at pilot scale (lot 1) behave similarly to those extracted at laboratory scale.

Carrier retention in regular capsules from manufacturer A is less reproducible and 40–350% higher than in their corresponding SFE-treated capsules. It is found that as much as 11.2% of total carrier mass may be retained in a control capsule. Residual carrier in an SFE-treated capsule is always less than 5.9%. Average carrier FPM yielded by control capsules is, on average, 30–70% lower than that yielded by SFE-treated capsules; however, FPM in control and SFE-treated capsules varies in similar and relatively narrow ranges, 2.1–5.9% and 2.5–6.1% of total carrier mass, respectively. The similarity of carrier FPM yielded by control and SFE-treated capsules is desirable because it is preferred that the amount of carrier inhaled not be affected significantly by lubricant removal.

Of all control capsules, lot 4 exhibits the best combination of average drug retention and FPM. Supercritical fluid extraction-treated capsules from lot 4 exhibit similarly low but more reproducible drug retention, substantially lower and more reproducible carrier retention, and significantly higher and more reproducible FPM than regular capsules from lot 4. There is little difference among SFE-treated capsule lots 1–4. Hence, regular capsules from either manufacturer can be treated by SFE to produce capsules that consistently yield low drug retention and high FPM. The reasons for the observed superiority of control capsules from manufacturer B are apparent in SEM images which are discussed in a later section of this paper.

Plasticizer-containing capsules (lots 5 and 6) exhibit the highest retention and the lowest FPM in both their control as well as their extracted state. Retention is at least twice as high as in other lots. Unexpectedly, they benefit only marginally from the SFE process. Scanning electron micrographs of these capsules are used to explain these findings.

For lots 1–3, Table 2 also shows the fractional content of drug in the retained powder [DR/(CR+DR)×100]. It is always higher than in the original formulation (0.84%), indicating that the drug substance is preferentially retained in the capsule. Both extracted and untreated capsules from lots 1–3 appear to have a high selectivity for the drug substance, the untreated capsules being more selective. On the other hand, untreated capsules from lot 4 appear to have little selectivity towards the drug substance, even less than in their extracted state. Lots 5 and 6 exhibit a higher selectivity, but substantially lower than that exhibited by lots 1–3. These results are confirmed using SEM images of untreated and extracted capsules discussed in a later section of this report.

Drug retention and FPM data for CI tests are combined in Fig. 2. Fine particle mass decreases nearly linearly with increasing retention. Linear regression of these data shows that approximately 60% of unretained drug translates into FPM. Nearly 70% translates into FPM if only lots 1–4 are considered. Treatment of capsules by SFE brings about a large reduction in retention and enhancement in its reproducibility as well as a substantially higher and more reproducible FPM, as evidenced by the narrow distribution of the large open symbols representing regular capsules extracted at optimal conditions. Capsules treated at sub-optimal conditions exhibit a wide distribution in drug retention. This suggests that virtually all soluble lubricant needs to be removed to produce capsules that consistently yield low drug retention. Retention in plasticizer-containing capsules, represented by the small symbols, is consistently higher than in other capsules.

Table 2 also shows the non-respirable mass (NRM) of drug calculated as 46 μg−retention−FPM. This is the mass of drug in the pre-separator, stages 0 and 1, the inhalator device, and other powder flow lines. It is not necessarily of any particular particle size distribution (PSD). The NRM is nearly constant for SFE-treated regular capsule lots 1–4 (24.8±0.9 μg). This is expected since both retention and FPM are reproducible for these lots. It is interesting to note, however, that despite the variability of drug retention and FPM yielded by untreated capsules, their NRM (24.9±1.9 μg) is nearly equal and only slightly more variable that that yielded by SFE-treated capsules. This explains why most of the unretained drug (70%) ends up as FPM. As can be expected, the NRM yielded by the highly retentive lots 5 and 6 is lower than that yielded by the other lots.

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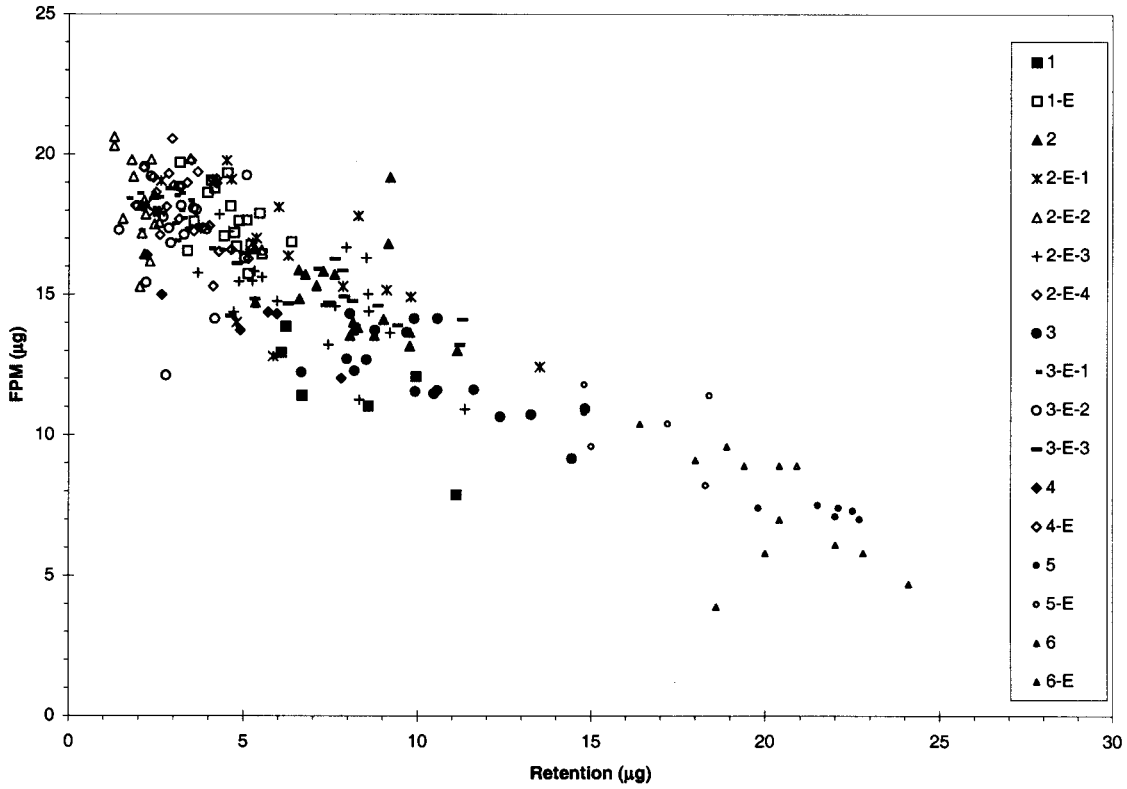


**Figure 2.** Correlation of FPM with drug retention yielded by regular capsules.

## SEM of Capsule Internal Surfaces

Figures 3 and 4 are SEM images of the internal surface of a control capsule and an SFE-treated capsule from manufacturer B (lot 4), respectively. Figure 3 shows that lubricant is distributed evenly throughout the capsule surface as a thin layer with no visible droplets or liquid material. Figure 4 shows that SFE-treated capsules exhibit dry surfaces, where peaks and valleys on the gelatin surface become visible as a result of lubricant removal. Because of these heterogeneities, it may not be possible to produce retention-free capsules, irrespective of extraction conditions.

High-performance liquid chromatography analysis of the lubricant using a Zorbax SB-phenyl column and a 70:30 (v/v) acetonitrile/0.1% phosphoric acid mobile phase indicates that it consists of a wide variety of compounds, including saturated fatty acids, unsaturated fatty acids, and phosphatidylcholine-related materials. The residue appears to contain fewer, but many, of the compounds present in untreated capsules.

Figures 5 and 6 show similar micrographs for regular capsules from manufacturer A. In this case the internal surface of control capsules appears to be covered with droplets of different sizes (0.5–2.5 µm) and different contact angles with the gelatin surface. Supercritical fluid extraction-treated capsules do not show any of the fluid lubricant material. Although it exhibits larger valleys, the internal surface of the extracted capsule is similar to that of the extracted capsule from manufacturer B, which explains why retention properties of extracted capsules from both manufacturers are similar. Hence, the difference in retention between control capsules from both manufacturers appears to be due to the use of a less-adhesive, better-wetting, or more solid-like lubricant by manufacturer B.

Figures 7 and 8 show SEM images of plasticizer-containing capsules. Uniformly distributed droplets of diameter roughly 5–30 µm and 5–15 µm are observed in control capsules and SFE-treated capsules, respectively. The presence of droplets on SFE-treated capsules explains why retention in such capsules is still high. Droplets in SFE-treated

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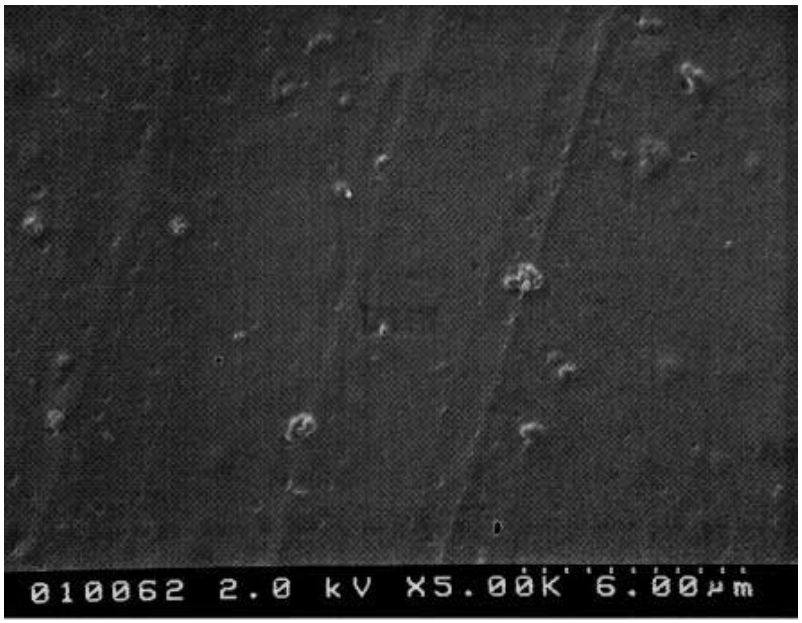


**Figure 3.** Scanning electron micrograph of a control capsule from manufacturer B.

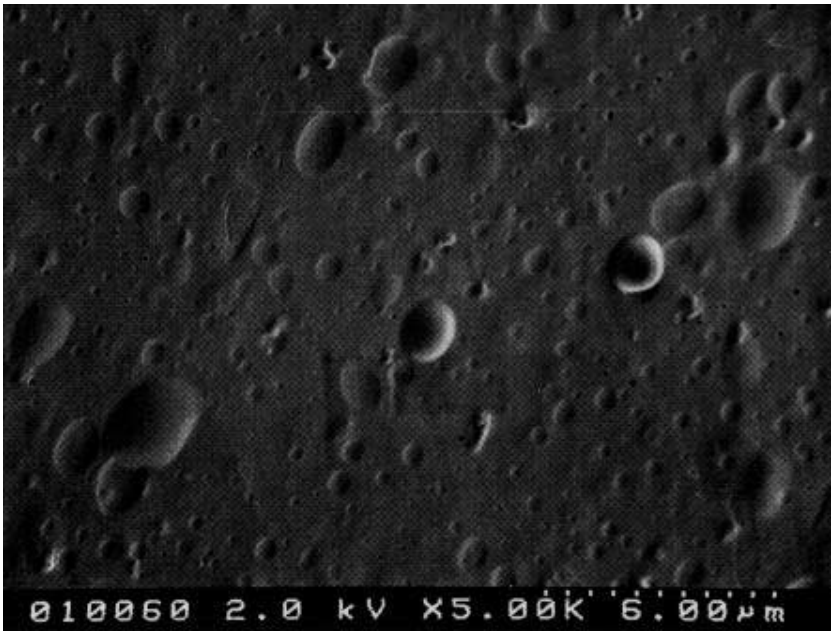


**Figure 4.** Scanning electron micrograph of an SFE-treated capsule from manufacturer B.

capsules are slightly smaller than in control capsules, which explains the lower powder retention in SFE-treated capsules, but still large enough to lodge small drug particles and numerous enough to possibly also act as physical barriers to aerodynamic flow of the powder out of a capsule during inhalation. The extraction process uncovered a gelatin surface strewn with material that appears connected to the droplets.

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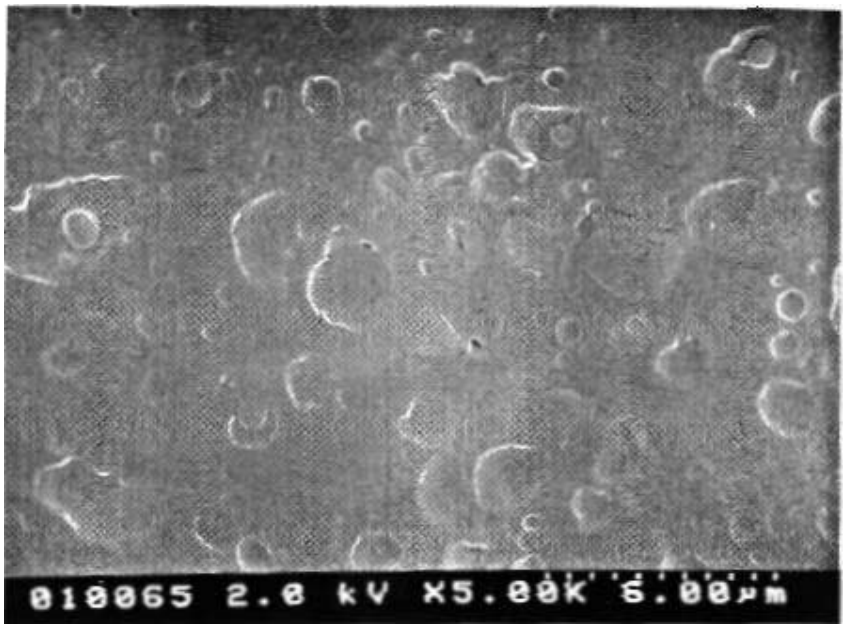


**Figure 5.** Scanning electron micrograph of a control capsule from manufacturer A.

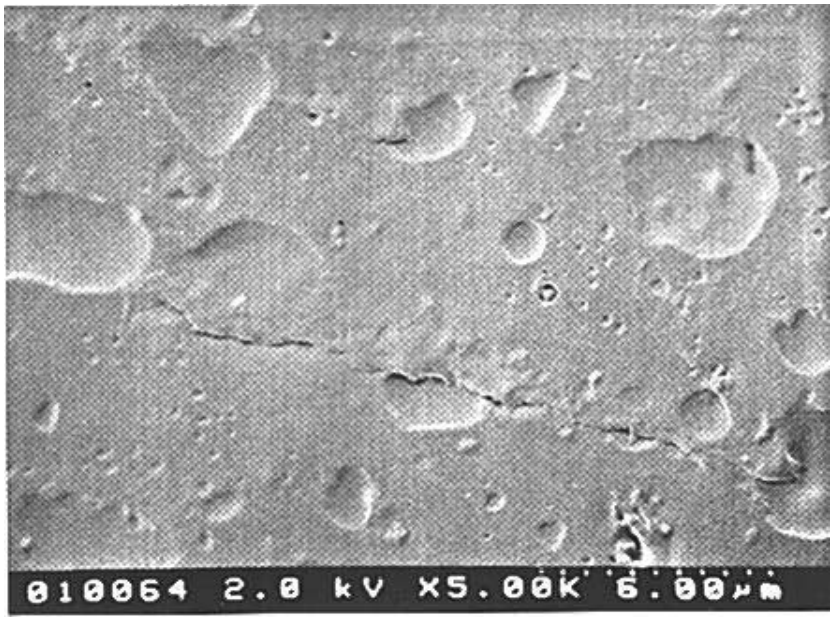


**Figure 6.** Scanning electron micrograph of an SFE-treated capsule from manufacturer A.

Since lubricant has been shown to be extractable with $CO_2$, it can be concluded that the droplets contain insoluble material. Such material was unexpected because only lubricant was applied to the capsule molding pins. The high contact angle exhibited by the near-spherical droplets suggests that the material has a high surface tension. The plasticizer used by manufacturer A is indeed a high molecular weight polar substance with higher surface tension than the lubricant and little

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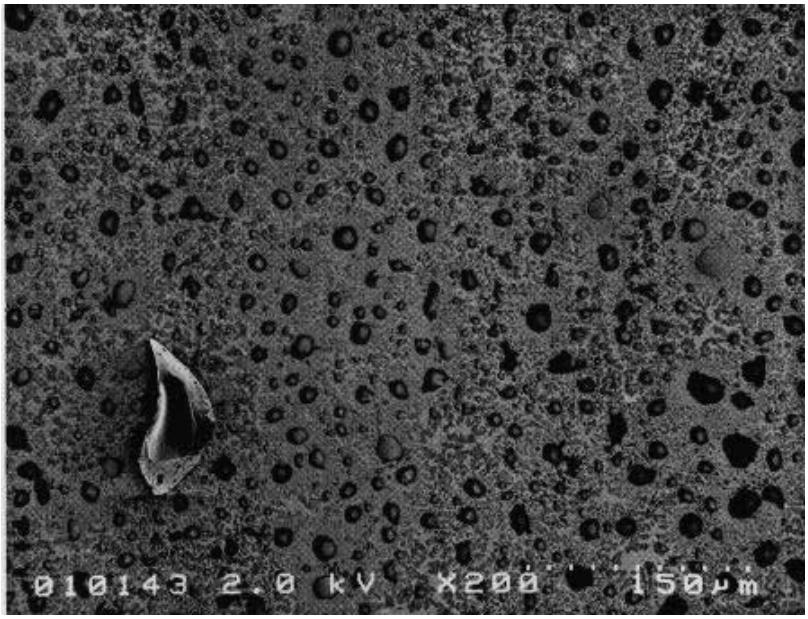


**Figure 7.** Scanning electron micrograph of a plasticizer-containing control capsule.

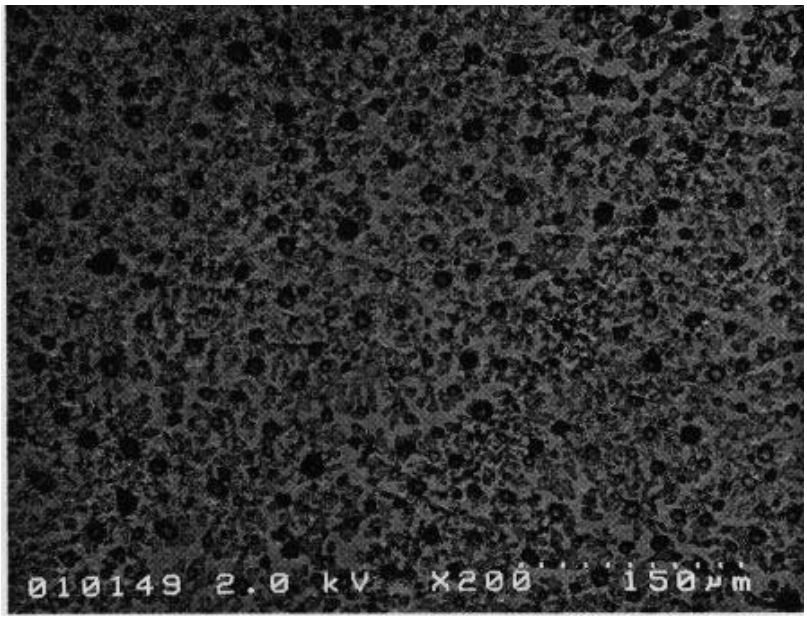


**Figure 8.** Scanning electron micrograph of an SFE-treated plasticizer-containing capsule.

solubility in $CO_2$. Because plasticizer is not observed on the external surface of the capsule, this suggests that the gelatin material became supersaturated with plasticizer during the drying step of the capsule manufacturing process, and plasticizer precipitated on the internal surface of the capsule which is in contact with the relatively cool molding pins.

The low selectivity of untreated capsules from lot 4 for retaining the drug substance, shown

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in Table 2, appears to be due to the smooth, unretentive material on its internal surfaces. The slightly higher selectivity of these capsules in their extracted state appears to be due to the small peaks and valleys observed on their surfaces. The high selectivity of untreated lots 1–3 for retaining the drug substance, which has a lower particle size than the carrier, appears to be due to the presence of droplets where small drug substance particles are more effectively retained than larger carrier particles. The still high selectivity of extracted capsules from lots 1–3 for the drug substance appears to be related to the size of the peaks and valleys on the gelatin surface. The valleys appear to be large enough to retain the smallest particles. Capsules from lots 5 and 6 are highly retentive and would be expected to retain all powder that comes in contact with their surfaces; this may explain why they exhibit much less selectivity towards the drug substance than lots 1–3.

### Effect of Lubricant Content on Drug Retention

Assuming that the lubricant spreads uniformly as a thin film over a perfectly smooth gelatin surface, with a density of lubricant of 0.8 g/mL and a capsule surface area of 2.0 $cm^2$, an increase in lubricant content from 1 to the maximum observed level of 40 μg would amount to a change in lubricant thickness from 0.006 to 0.25 μm. If it is assumed that the lubricant is spread over a smooth gelatin surface as spherical droplets 2 μm apart, droplet diameter will vary in the range of 0.4–2 μm. Actual lubricant thickness may therefore be roughly somewhere within the range of 0.006–2 μm. The upper end of this range is close to the average size of drug particles.

Figure 9 shows the effect of lubricant content on drug retention in five regular capsule lots from manufacturer A. The data point (1.75, 8.15) is for capsules from lot 2. Within region I, small amounts of lubricant affect adhesion significantly. The maximum retention of about 15 μg is taken from results shown in Fig. 2 for regular capsules from lot 3. There is a shortage of data for an accurate profile, but the profile in regions I and II is qualitatively drawn based on the observation from Fig. 2 that regular capsules from this lot retain the most drug of all regular capsules (10.3 μg), and that retention characteristics of capsules from lot 3-E-1 (2.9 μg), which were extracted at sub-optimal conditions, are similar to those of capsules treated at optimal conditions. Lubricant in regular capsules from this lot is therefore rapidly removed by supercritical $CO_2$, suggesting that such capsules contain the smallest amount of lubricant and that regular capsules with the lowest lubricant content may exhibit the highest retention. Such rapid removal is not observed with lot 2-E-1 (5.8 μg), suggesting that capsules from this lot contain more lubricant than those from lot 3. A high retention was also exhibited by capsules from lots 2-E-3 (6.8 μg) and 3-E-3 (7.4 μg). This indicates that conventional SFE of assembled capsules is strongly

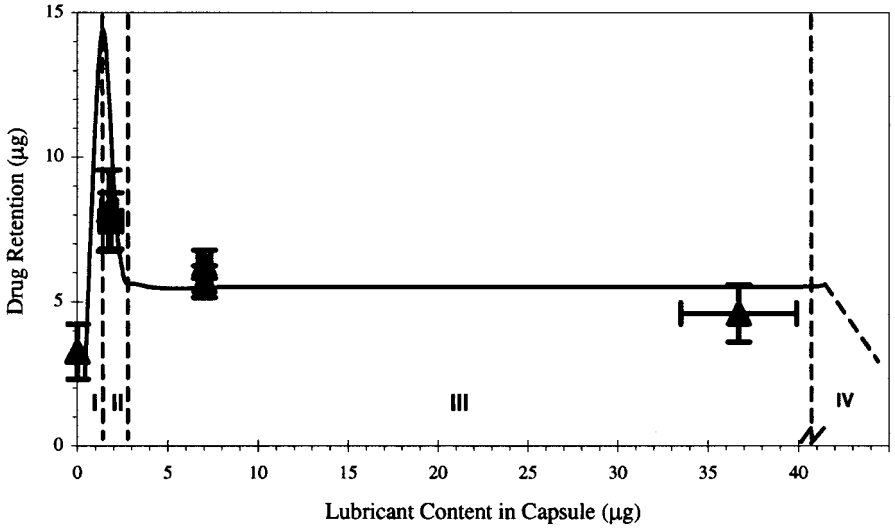


**Figure 9.** Effect of capsule lubricant content on drug retention.

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diffusion-limited and is inefficient at treating assembled capsules irrespective of lubricant content.

The profile in Fig. 9 is at least partially inspired by Zimon (10), who investigated the adhesion of 40–60 μm glass beads on an oily surface. In Zimon's study, regions I and II form one region where adhesion simply increases with increasing oil content until it reaches the plateau delimiting a constant retention region. In our case, drug particles are smaller (typically $<5$ μm) and the increase in retention depicted in region I may be explained by the observed heterogeneities on the gelatin internal surface in the form of microscopic peaks and valleys, in addition to the lubricant, that could enhance entrapment of particles when lubricant thickness is small enough for particles to contact and lodge within these heterogeneities. This effect subsides in region II where an increase in lubricant content or thickness reduces the degree of contact between the particles and these heterogeneities.

Within region III, most particles do not contact surface heterogeneities. An equilibrium between inertial and gravitational forces that tend to immerse particles in the liquid, and the resistance of the lubricant layer that tends to keep particles from sinking deeper into the lubricant, is established. Particles will sink to only a certain depth irrespective of lubricant thickness. Observed differences in retention in region III are not statistically significant. Retention is therefore nearly constant in this region.

The exact lubricant content at which region III ends and region IV starts is not known. In this latter region the lubricant layer is thick enough to flow and may be detached along with the particle during inhalation, thereby reducing retention (10). Lubricant thickness in the present capsules appears to be too small for such flow to take place. An important conclusion from Fig. 9 is that nearly all the retentive fraction of the lubricant has to be removed in order to ascertain that drug retention is minimized.

## CONCLUSIONS

Capsule mold lubricant affects drug retention even when present in very small amounts. A novel method that involves the use of supercritical $CO_2$ as a solvent was developed to allow for lubricant removal from assembled capsule shells. It is remarkable that relatively fragile assembled capsules can be subjected to high supercritical pressures without incurring any physical damage. The method was successfully tested at laboratory and pilot scales. Supercritical fluid extraction of capsules provides a means to remove the lubricant material and leave dry and less retentive lubricant residue on the capsule internal surface. All regular gelatin capsules can be treated by SFE to produce capsules that yield consistently low drug retention and consistently high FPM. Supercritical $CO_2$-insoluble plasticizer material on the internal surfaces of capsules from lots 5 and 6 is determined to be responsible for high drug retention.

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## REFERENCES

1. Ganderton, D.; Kassem, N.M. Dry Powder Inhalers. Adv. Pharm. Sci. **1991**, *6*, 165–191.
2. Brown, S. Boehringer Ingelheim Pharmaceuticals, Inc., Unpublished Results, 1994.
3. Clark, A.R.; Gonda, I. Method for Treating Capsules Used for Drug Storage. U.S. Patent 5,641,510, 1997.
4. Horhota, S.T.; Saim, S. Supercritical Fluid Extraction of Mould Lubricant from Hard Shell Capsules. U.S. Patent 6,228,394.
5. McHugh, M.; Krukonis, V. *Supercritical Fluid Extraction*, *Principles and Practice*, 2nd Ed.; Butterworth-Heinemann: Boston, 1993.
6. Broadhead, J.; Edmond Rouan, S.K.; Rhodes, C.T. Dry Powder Inhalers: Evaluation of Testing Methodology and Effect of Inhaler Design. Pharm. Acta Helv. **1995**, *70*, 125–131.
7. Witek, T.J.; Ghafouri, M.; Horhota, S.T. An Approach to the Clinical Relevance of Pharmaceutical Specifications of Aerosol Delivery. Poster Presentation, American Thoracic Society Meeting, Chicago, IL, May 1998.
8. Horhota, S.T.; Saim, S. Method for Extraction and Reaction Using Supercritical Fluids. U.S. Patent 6,294,194.
9. Saim, S.; Horhota, S.T. Pressure-Swing SFE of Soluble Material from Closed and Nearly-Closed Vessels, Manuscript in Preparation, 2001.
10. Zimon, A.D. *Adhesion of Dust and Powder*, 2nd Ed.; Consultants Bureau: New York; 264.

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