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Comparison of the Formulation Requirements of Dosator and Dosing Disc Automatic Capsule Filling Machines

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ABSTRACT The overall objective of this study was to provide 'semi-quantitative' or 'rigorous' definitions of the fluidity, lubricity and compactibility requirements of formulation for representative dosator and dosing disc capsule filling machines. To that end, model formulations were developed for those properties using Carr's compressibility index, ejection force, and plug breaking force at a specified compression force to gauge fluidity, lubricity, and compactibility, respectively. These formulations were each encapsulated on an Hofliger-Karg GKF-400 dosing disc machine and a Zanasi LZ-64 dosator machine. Each machine was instrumented to measure plug compression and ejection forces. The encapsulation process was evaluated for %CV of fill-weight, ejection force, plug breaking force and the dissolution of marker drugs incorporated in the formulations. The f_2 metric was used to compare dissolution profiles. The results suggest: (1) formulations should meet different flow criteria for successful encapsulation on the two machines, (2) a relatively lower level of lubricant may be sufficient for the dosing disc machine, (3) a higher degree of formulation compactibility is needed for the dosator machine, and (4) transferring formulations between these machine types (same class, different subclass per FDA's SUPAC-IR/MR Manufacturing Equipment Addendum) could be challenging. In certain cases dissolution profiles for the same formulation filled on the two machines with equivalent compression force were different based on $f_2 < 50$. Overall, the results of this study suggest a range of formulation characteristics appropriate for transferring formulations between these two types of machines.

KEYWORDS: Capsules, Formulation, Flow, Compactibility, Lubrication, Filling Machines.

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INTRODUCTION A number of studies have been conducted looking at the interplay of various formulation and machine operating variables on specific types of automatic capsule filling machines. Of the 2 most common types of automatic filling machines, dosator machines (eg, MG2, Zanasi, Macofar) and dosing disc machines (eg, Hofliger-Karg [HK], Bosch, and Harro-Hofliger), dosator machines have been studied most extensively. For example, an MG2 machine simulator was employed by Jolliffe and Newton. [1] Cole and May, [2] Small and Augsburger, [3] and Hogan and colleagues [4] are among the many investigators who have reported on research involving Zanasi filling machines. Britten and colleagues [5] conducted research with an apparatus that simulates the action of a Macofar dosator machine. Dosing disc machines used in studies have included HK or Bosch GKF machines. [6-8] However, no systematic study comparing the formulation requirements of dosator and dosing disc machines has been published. Such research would provide critical guidance to formulators concerned with [1] scaling up development batches to larger machines of a different type, [2] making postapproval equipment changes, or [3] developing formulations that would run on either type of equipment.

The objective of this study is thus to provide semiquantitative or rigorous definitions of the fluidity, lubricity, and compactibility requirements of formulations for dosator and dosing disc machines. To that end, sets of model formulations were developed that differed in their degree of fluidity, lubricity, or compactibility. Carr's compressibility index (CI), ejection force, and plug breaking force at a specified compression force were used to gauge fluidity, lubricity, and compactibility, respectively. Each model formulation was encapsulated on an HK GKF-400 dosing disc machine and a Zanasi LZ-64 dosator machine. Both machines were instrumented to monitor plug compression and ejection forces. The encapsulation process was evaluated on percent coefficient of variation (%CV) of fill weight, plug ejection force, plug breaking force, and dissolution of marker drugs incorporated in the test formulations. Encapsulation on the HK was performed at Novartis Pharmaceutical Corporation (East Hanover, NJ).

Table 1. Model flow formulations

Model flow formulation	LBD (g/cc)	TBD (g/cc)	CI	Mean particle size (µm)
Avicel PH 101	0.309	0.488	36.68	50
Avicel PH 102	0.325	0.448	27.45	100
Avicel PH 200	0.329	0.408	19.60	180

Encapsulation on the Zanasi was carried out at the University of Maryland (UM; Baltimore, MD).

MATERIALS AND METHODS

Materials

Anhydrous lactose, USP, direct tableting (dt) grade (Quest International, Hoffmann Estates, IL); ascorbic acid, USP, DC 97 grade (ascorbic acid DC 97; Takeda, USA Inc, Orangeburg, NY); ascorbic acid, USP, Reference Std (USP Convention, Inc, Rockville, MD); microcrystalline cellulose, NF, Avicel PH 101,102, and 200 grades (FMC Corp, Philadelphia, PA) were used in this study. Hydrochloric acid (HCl), reagent grade (JT Baker, Division of Mallinckrodt Baker, Phillipsburg, NJ); hydrochlorothiazide (HCTZ), USP (Lemmon Co, Sellersville, PA); size no. 1 hard gelatin capsules (Capsugel Inc, Greenwood, SC); magnesium stearate, NF (Mallinckrodt Inc, St Louis, MO); and modified starch, Starch 1500 grade (Colorcon, West Point, PA) also were used.

Methods

Development of Model Formulations

Model Flow Formulations

CI was used as the flow criterion for the set of model flow formulations. CI can be calculated from the loose bulk density (LBD) and tapped bulk density (TBD) data using the following equation: [9]

$$CI = \frac{(TBD - LBD)}{TBD} 100 \quad (1)$$

LBD and TBD were estimated by the method described in the USP-NF supplement [10] using a Scott, Schaeffer, and White Paint Pigment Volumeter (Fisher Scientific, Springfield, NJ) that has a fixed volume receptacle of 16.39 cc. LBD was calculated from the weight of the powder and the volume of the receptacle. TBD was determined by using the Stampf Volumeter (J. Engelsman, Ludwigshafen, a Rh; Shandon Southern Instruments, Inc, Sewickley, PA). To measure TBD, a predetermined weight of the material was loosely poured into a 100-mL volumetric cylinder. The volume of the powder was measured after the first 500 drops. The tapping was continued in steps of 100 drops until no further change in volume was observed. The difference in volume reduction noted after the first 500 drops was less than 2% on later drops. TBD was calculated from the weight and the tapped volume of the sample after 500 drops.

The goal was to develop formulations that differed in their fluidity, had similar compactibility and lubricant requirements, and could be processed on the encapsulation equipment. Therefore, the range of CIs selected was such that none of the formulations had either too much or too little fluidity. Several grades of Avicel, differing in particle size and not diluted with any glidants, exhibited a sufficiently broad range of CIs to provide an ideal set of model flow formulations. Since these grades differ in particle size and, thus, specific surface area, their lubricant requirements would be expected to differ slightly. However, microcrystalline cellulose, in general, has an exceptionally low lubrication requirement. No lubricant was added prior to encapsulation. The addition of a lubricant such as magnesium stearate would have altered both the fluidity and compactibility of these materials.

Table 1 lists the LBDs, TBDs, CIs, and mean particle sizes [11] for the set of model flow formulations.

Model Lubricity Formulations

Ejection force was used as a measure of lubricity when developing the set of model lubricity formulations. Formulators commonly regard lactose, the most widely used filler in hard gelatin capsule formulations, to have a greater lubrication requirement than microcrystalline cellulose or Starch 1500. [3] Since the level of magnesium stearate was reported to have little or no effect on the compactibility of lactose plugs formed in a dosator machine (based on plug breaking force measurements), [12] blends of anhydrous lactose, dt grade, and magnesium stearate were used to create the model lubricity formulations. The blends were mixed for 5 minutes. A 0.47-L twin-shell blender (Patterson Kelly Co Inc, E Stoudsburg, PA) was used and the batch size was 100 g. Plugs of capsule size no. 1 were made by using special tooling on a physical testing machine, Instron® 4502 (Instron Corp, Canton, MA), fitted with a 500-N load cell. Three plugs were made from each blend. The plugs weighed 300 mg and were compressed to the same length at a compression force of 200 ± 10 N. To confirm the lack of influence of magnesium stearate concentration on compactibility, the plug breaking forces were measured by using the same machine fitted with a 10-N load cell in a manner similar to that described by Davar and colleagues. [13] **Table 2** lists

Table 2. Model lubricity formulations

Model lubricity formulation	Ejection force* (N)	Plug breaking force* (N)
AL +0.125% mg st	58.1 (4.45)	0.53 (0.029)
AL +0.25% mg st	32.7 (3.02)	0.44 (0.010)
AL +0.5% mg st	21.6 (1.49)	NA
AL +1% mg st	16.9 (0.95)	0.46 (0.042)
AL +1% mg st (20-minute lubrication time)	13.2 (0.38)	0.32 (0.053)

AL indicates anhydrous lactose; mg st, magnesium stearate; and NA, not available.
Numbers in parentheses are SDs.
Plugs were made at a compression force of 200 ± 10 N.

Table 3. Model compactibility formulations

Ascorbic acid DC 97:Avicel PH 200	Plug breaking force (N)
100:0	Did not form an intact plug
80:20	0.32 (0.047)
65:35	0.44 (0.117)
50:50	0.57 (0.047)
35:65	1.07 (0.045)
20:80	1.17 (0.044)
0:100	1.64 (0.063)

Plug weight was 250 mg. Plugs were compressed at 200 N.
Numbers in parentheses are SDs.

the set of model lubricity formulations selected, the ejection forces, and the plug breaking forces. The ejection force was relatively high at the 0.125% level of magnesium stearate. That formulation later was eliminated from further investigation, as the goal was to run only formulations that would process reasonably well on the filling machines. To examine the effect of lubricant blend time at the 1% level of magnesium stearate, a 20-g sample was taken out after 5 minutes of blending and the mixture was blended for an additional 15 minutes. Blending for 20 minutes reduced both the ejection force and the compactibility of the formulation compared to 5 minutes of blending. The fluidity of the model lubricity formulations was similar, with CIs in the range of 30 to 32.

Model Compactibility Formulations

The breaking force of plugs compressed to 200 N was used as a measure of compactibility for the set of model compactibility formulations. Three different sets of binary mixtures, in ratios of 100:0, 80:20, 65:35, 50:50, 35:65, 20:80, and 0:100 were investigated: anhydrous lactose:Avicel PH 200, anhydrous lactose:Starch 1500, and ascorbic acid DC 97:Avicel PH 200.

All binary mixtures were 100 g in batch size and initially were blended in a 0.47-L twin-shell blender (Patterson Kelly Co Inc) for 5 minutes. Magnesium stearate (0.5%) was then added to each mixture, and the mixture was blended for 2 additional minutes. Plugs of capsule size no. 1 were made for each mixture in a manner similar to that described for the lubricity formulations. Three plugs were made for each mixture and their breaking forces were measured. Their compactibility profiles are presented in **Figure 1** . The binary mixtures of ascorbic acid DC 97 and Avicel PH 200 gave a suitably broad range of plug strengths and hence were chosen as the set of model compactibility formulations. These formulations exhibited a range of CIs from 12 to 20, indicating excellent to good fluidity. It was assumed that the ejection forces would differ only slightly from formulation to formulation depending on the ratio of ascorbic acid DC 97 to Avicel PH 200 in the formulation. **Table 3** lists the set of model compactibility formulations.

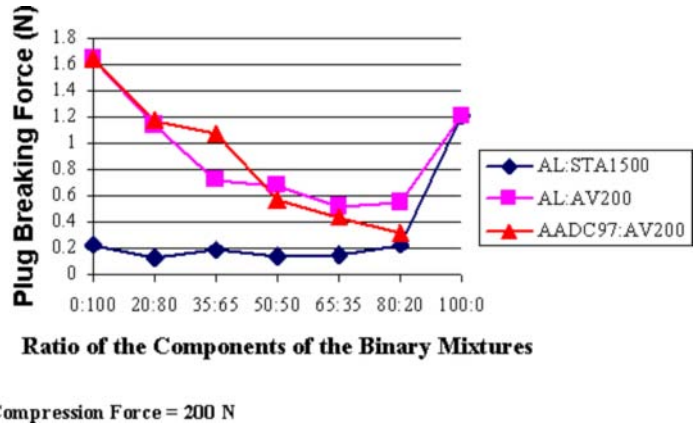

Figure 1. Compactibility profiles of the binary mixtures.

Table 4. Model formulations used in this study

Type of model formulation, code	Formulation components
Model flow formulation, F1	Avicel PH 101
Model flow formulation, F2	Avicel PH 102
Model flow formulation, F2	Avicel PH 200
Model lubricity formulation, L1	Anhydrous lactose +0.25% mg st
Model lubricity formulation, L2	Anhydrous lactose +0.5% mg st
Model lubricity formulation, L3	Anhydrous lactose +1% mg st
Model compactibility formulation, C1	Ascorbic acid DC 97:Avicel PH 200 (100:0) + 0.5% mg st
Model compactibility formulation, C2	Ascorbic acid DC 97:Avicel PH 200 (80:20) + 0.5% mg st
Model compactibility formulation, C3	Ascorbic acid DC 97:Avicel PH 200 (50:50) + 0.5% mg st
Model compactibility formulation, C4	Ascorbic acid DC 97:Avicel PH 200 (20:80) + 0.5% mg st
Model compactibility formulation, C5	Ascorbic acid DC 97:Avicel PH 200 (0:100) + 0.5% mg st

Mg st indicates magnesium stearate.

Instrumentation of Capsule Filling Machines

HK GKF-400

An HK GKF-400 (GKF machines are now manufactured by Bosch Packaging, Machinery Division, Piscataway, NJ) encapsulator located at Novartis Pharmaceutical Corporation was used in this study. The machine was instrumented by the Metropolitan Computing Corporation (West Orange, NJ) as described by Davar and colleagues, [14] and provided with digitized data acquisition.

Zanasi LZ-64

A previously instrumented Zanasi LZ-64 (IMA North America Inc, Fairfield, CT) was reinstrumented in a manner similar to that described by Small [14] and Botzolakis, [15] except that the data acquisition process was completely digitized. The necessary hardware and software for data acquisition were acquired from National Instruments (Austin, TX). The strain gauges and all other accessories used for installing strain gauges on the Zanasi LZ-64 size no. 1 piston were acquired from Micro-Measurements Division, Vishay Measurements Group Inc (Raleigh, NC).

Encapsulation of Model Formulations

The model formulations that were encapsulated on the instrumented HK GKF-400 and Zanasi LZ-64 are presented in **Table 4** . All formulations were filled into size no. 1 capsules. A 4-kg batch was prepared for each model formulation.

Blending

When required, blending was carried out using a 15.2-L twin-shell blender (Patterson Kelly Co Inc). The blend times and procedures were the same as previously described, except in the case of the lubricity formulations in which 4% of a model low-solubility drug, HCTZ, was incorporated. The model drug was included to study the possible impact of magnesium stearate concentration on dissolution and any differences in mixing during encapsulation that may exist between the 2 machine types. First, HCTZ was blended with anhydrous lactose for 5 minutes. The mixture thus formed was blended for 2 more minutes after the addition of magnesium stearate. The lubricant blend time was intentionally reduced from 5 minutes (used in developing the set of model lubricity formulations) to 2 minutes, to avoid possible overshearing of magnesium stearate in the larger batch.

Encapsulation on HK GKF-400

A dosing disc of 15 mm thickness was selected for all formulations. All 5 tamps were used for the model flow formulations, but only the first 4 tamps were used for the model lubricity and compactibility formulations. It was observed that the dosing disc cavities were completely filled after the first 4 tamps at the selected compression settings of approximately 100 and 200 N (adjusted on all 5 stations), while filling the model flow formulations. The powder bed height was kept constant at 35 mm, and the machine was operated at 50 strokes/min.

Encapsulation on Zanasi LZ-64

The formulations were filled first on the HK encapsulator. To achieve similar fill weights for each model formulation on the Zanasi filling machine, piston heights had to be adjusted for different formulations. All formulations were run at compression forces of approximately 100 and 200 N. The powder bed height was kept constant at 50 mm and the machine was operated to fill approximately 38 capsules/min (using just 1 dosator).

Evaluation of the Encapsulation Process

Fill-Weight Variation
Filled capsules were weighed using a Mettler® balance (model AC 100; Mettler Instrument Corp, Hightstown, NJ), and a sample of 20 readings was used for calculating the average, SD, and %CV of fill weight. The empty hard gelatin capsule shells weighed 75 ± 1 mg.

Plug Breaking Force
Plug collection under the ejection station on both the Zanasi and the HK machines was facilitated by switching off the flow of capsules from the magazine to the bushings. For the plugs made on the HK, breaking force was measured on an Instron physical testing machine, as described by Davar and colleagues. [13] For the plugs made on the Zanasi, breaking force was measured using the tester previously constructed at UM and described by Shah et al. [6] Ten readings were averaged for each run. Although the principle of operation (3-point flexure) was the same for both testers, they employed different transducer types (strain gauge load cell for the Instron tester vs piezoelectric load cell for the UM tester). They also differed in the rate of movement of the blunt-edge blade used to break the plugs (0.55 mm/sec on the Instron tester vs 1.1 mm/sec on the UM tester). These differences may affect the absolute values of plug strengths recorded, but relative comparisons can be made for tests performed on the same tester.

Ejection Force
The instrumentation on both machines made possible the monitoring of ejection forces. Ten readings were averaged in each case.

Dissolution of Model Drugs
HCTZ and ascorbic acid were used as the marker drugs in the model lubricity and compactibility formulations, respectively. Dissolution of these marker drugs was carried out using the USP dissolution apparatus 2 (VanKel VK 6010; Vankel Industries Inc, Edison, NJ) at 50 rpm. The dissolution medium, 0.1 N HCl, was maintained at 37oC. A Beckman DU640 UV-VIS spectrophotometer (Beckman Industries Inc, Irvine, CA) was used to measure the absorbances. Samples at higher concentrations of ascorbic acid were diluted with the medium before measuring absorbances.
Parameters for HCTZ were the following: the dissolution medium was 900 mL 0.1 N HCl; sampling time points were 2, 4 ,6, 8, 10, 15, 30, 45, 55, and 60 minutes; and the absorbance wavelength was 272 nm. Parameters for ascorbic acid were the following: the dissolution medium was 1000 mL 0.1 N HCl; sampling time points were 3, 5, 7, 10, 15, 30, 45, and 60 minutes; and the absorbance wavelength was 245 nm.

f_2 Test
FDA's [Food and Drug Administration] guidance on scale up and post approval changes for immediate release oral solid dosage forms [SUPAC-IR] [16] recommends a metric that can be used to compare dissolution profiles of different formulations. This metric, f_2, is called the similarity factor and is defined by the following equation:

$$f_2 = 50 \log\{[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} x100\} \quad (2)$$

where Rt is the percentage dissolved at each time point for the reference formulation and Tt is the percentage dissolved at each time point for the test formulation. This method of comparing dissolution profiles was introduced by Moore and Flanner. [17] The similarity factor is 100 when the test and reference profiles are identical and approaches 0 as the dissimilarity increases. An f_2 value between 50 and 100 suggests that 2 dissolution profiles are similar and indicates a point-to-point difference of 10% or less. The dissolution profiles for the marker drugs used in the model formulations, HCTZ and ascorbic acid, were compared using this metric.

Particle Size Analysis
Particle size analysis was performed on the model compactibility formulations using a sonic sifter (Allen-Bradley Sonic Sifter; Fisher Scientific). The sieves (ATM Corp, Milwaukee, WI) used included nos. 30 (590 mm), 60 (250 mm), 80 (177 mm), 120 (125 mm), 170 (88 mm), and 200 (74 mm). A 5-g sample was sieved for 5 minutes at a pulse rate setting of 5 and an intensity setting of 5. The amount retained on each sieve was recorded. The cumulative percent oversize was estimated for each formulation.

RESULTS AND DISCUSSION

Flow Formulations

The ejection force, fill weight, and %CV of fill weight for the model flow formulations are tabulated in **Tables 5(a)** and **(b)** . Fill weights varied for different grades of Avicel compressed to similar compression forces, obviously due to differences in the particle size and bulk density of the different grades. The piston heights were adjusted on the Zanasi to provide fill weights similar to those observed with the HK machine. For the least free-flowing grade of Avicel, PH 101, a piston height of 20 mm had to be employed to achieve fill weights similar to those obtained on the HK encapsulator using a 15-mm dosing disc. The HK encapsulator is thus potentially more efficient than the Zanasi at filling relatively bulky materials such as Avicel PH 101.

Table 5(a). Ejection force and fill weight for the model flow formulations encapsulated on HK GKF-400

Model flow formulation		F1 (Avicel PH 101)		F2 (Avicel PH 102)		F3 (Avicel PH 200)	
Compression force	Statistical parameter	Ejection force (N)	Fill weight (mg)	Ejection force (N)	Fill weight (mg)	Ejection force (N)	Fill weight (mg)
Low (100 N)	Average	18.1	242.4	14.9	228.7	12.9	186.9
	SD	2.1	3.3	1.4	4.6	0.4	8.4
	%CV	11.60	1.34	9.4	2.00	3.10	4.49
High (200 N)	Average	26.2	263.9	21.6	249.1	17.1	223.3
	SD	1.9	6.3	0.7	4.1	0.7	4.1
	%CV	7.25	2.37	3.24	1.64	4.09	1.84

The sample size was 10 for ejection force and 20 for fill weight.

Table 5(b). Ejection force and fill weight for the model flow formulations encapsulated on Zanasi LZ-64

Model flow formulation		F1 (Avicel PH 101) *		F2 (Avicel PH 102) †		F3 (Avicel PH 200) ‡	
Compression force	Statistical parameter	Ejection force (N)	Fill weight (mg)	Ejection force (N)	Fill weight (mg)	Ejection force (N)	Fill weight (mg)
Low (100 N)	Average	42.1	273.7	28.1	243.7	20.0	213.5
	SD	5.5	6.7	1.4	8.1	1.2	8.8
	%CV	13.08	2.45	4.97	3.31	5.83	4.13
High (200 N)	Average	53.6	279.7	50.9	251.8	40.0	226.7
	SD	3.7	4.4	3.3	7.1	1.3	7.8
	%CV	2.27	1.59	6.46	2.84	3.10	3.39

The sample size was 10 for ejection force and 20 for fill weight.
*Piston height was set at 20 mm.
†Piston height was set at 19 mm.
‡Piston height was set at 17 mm.

Figure 2 compares the %CVs of fill weight for the model flow formulations encapsulated on both the HK and the Zanasi machines at low and high compression settings (approximately 100 and 200 N). For the Zanasi machine, the %CV of fill weight was observed to increase as the formulation CI decreased (from Avicel PH 101 to Avicel PH 200). Lower CIs are associated with less cohesiveness and greater fluidity, properties that may make more difficult the quantitative pickup and transfer of plugs. A similar trend was seen on the HK encapsulator at the 100-N compression setting. At 200 N, lower %CVs are associated with the more free-flowing formulations, but there seems to be a shallow minimum between the best-flowing (Avicel PH 200) and the worst-flowing (Avicel PH 101) formulations for Avicel PH 102. Whether this behavior at higher compression force on the HK is an anomaly or could be attributed to the mechanics of operation of the machine is unclear.

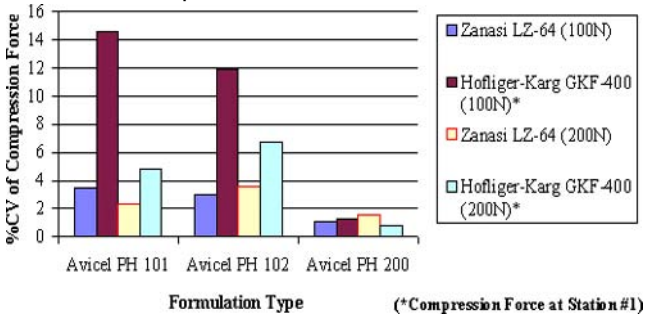

Figure 3. Comparison of %CV of compression force for model flow formulations.

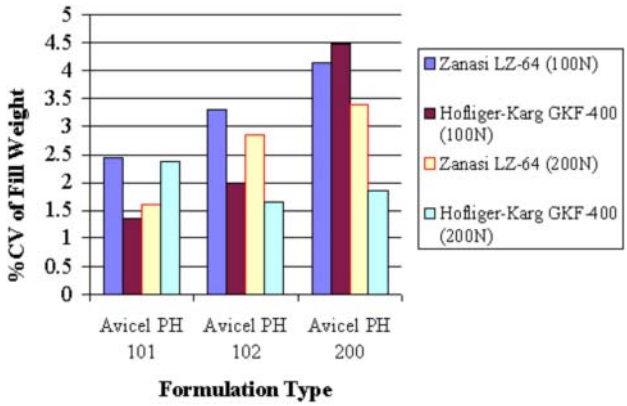

Figure 2. Comparison of %CV of fill weight for model flow formulations.

Figure 3 compares the %CVs of the compression force recorded for the model flow formulations encapsulated on both the HK (compression force recorded at station no. 1) and the Zanasi machines at both low and high compression settings. There is a greater %CV of compression force recorded for the more poorly flowing formulations on the HK encapsulator at tamping station no. 1. Shah and colleagues [6] made a similar observation and attributed this phenomenon to powder building up at station no. 5 and the ejection station upon rotation of the dosing disc, as well as to not having enough fluidity to distribute evenly to tamping station no. 1. This phenomenon did not affect fill weights.

In general, ejection forces increased as the particle size of the model flow formulations decreased (**Table 5** ; particle size of PH101<PH102<PH200). This observation most likely reflects the greater specific surface area and number of contact points the smaller particle size grades make with the dosing tube or dosing disc cavity surface. For both machines, ejection force also increased as the compression force employed increased, confirming previous observations. [3] It is interesting that the ejection forces recorded at equivalent compression forces for these unlubricated fillers were higher on the Zanasi machine than on the HK machine. For some of the comparisons, fill weights were slightly higher on the Zanasi machine, which suggests that those plugs were slightly longer and thus would present greater frictional resistance to ejection. However, higher ejection forces were also observed when fill weights were closely matched. Materials that can be run without lubricants often owe their low-lubricant requirement to postcompression elastic recovery that serves to reduce residual radial forces and probably reduces adhesion to confining walls. Britten and colleagues [5] discussed this phenomenon in the context of Starch 1500. On the basis of measurements made on an instrumented Macofar dosator machine simulator, Britten and colleagues [5] found for Starch 1500 plugs, which exhibit considerable elastic recovery, that residual radial pressure was lower than that for lactose and that the ejection pressures were undetectable. Microcrystalline cellulose, used as the model flow material, also exhibits substantial postcompression elastic recovery, [18] which at least in part accounts for this material's ability to be run without lubricant. However, in the present study, it is hypothesized that the gradual buildup of plugs in segments in the multiple-tamping process of the HK machine may allow for more complete postcompression elastic recovery, and hence lower ejection forces, than occurs on the Zanasi machine.

Lubricity Formulations

The ejection force, fill weight, plug breaking force, and %CV of fill weight estimated for the model lubricity formulations appear in **Tables 6(a)** and **(b)** for the HK GKF-400 and the Zanasi LZ-64, respectively.

Table 6(a). Ejection force, fill weight, and plug breaking force recorded for the model lubricity formulations encapsulated on HK GKF-400

Model lubricity formulation		Formula L1			Formula L2			Formula L3		
Compression force	Statistical parameter	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)
Low (100 N)	Average	4.2	383.9	0.84	3.6	385.2	0.72	4.7	394.6	0.97
	SD	1.5	6.2	0.30	1.5	3.8	0.14	0.7	3.3	0.22
	%CV	35.71	1.61	35.99	27.78	0.98	19.91	14.89	0.84	22.49
High (200 N)	Average	5.8	392.7	1.42	6.5	400.2	1.34	6.1	404.6	1.51
	SD	1.9	5.7	0.37	1.5	3.5	0.21	0.6	2.4	0.19
	%CV	32.76	1.46	26.33	23.08	0.89	15.5	9.84	0.58	12.81

The sample size was 10 for ejection force, 20 for fill weight, and 6 for plug breaking force.
Refer to Table 4 for the formula codes for model lubricity formulations.

Table 6(b). Ejection force, fill weight, and plug breaking force recorded for the model lubricity formulations encapsulated on Zanasi LZ-64

Model lubricity formulation		Formula L1			Formula L2			Formula L3		
Compression force	Statistical parameter	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)
Low (100 N)	Average	14.4	395.1	0.30	11.5	397.3	0.41	8.9	392.6	0.26
	SD	2.8	2.8	0.06	0.3	3.0	0.08	0.8	8.6	0.11
	%CV	2.53	0.7	20.13	2.75	0.74	19.20	8.48	2.19	43.54
High (200 N)	Average	37.7	402.8	1.69	30.6	404.6	1.12	21.2	413.5	1.13
	SD	2.9	4.4	0.26	0.7	3.0	0.15	0.7	10.8	0.21
	%CV	7.67	1.08	15.23	2.28	0.74	12.76	3.23	2.6	18.75

The sample size was 10 for ejection force, 20 for fill weight, and 6 for plug breaking force.
Refer to Table 4 for the formula codes for model lubricity formulations.

In general, ejection forces increased with the compression force employed. When encapsulating the model lubricity formulations on the Zanasi machine, it was observed that the ejection forces generally decreased with an increase in the concentration of magnesium stearate (**Figure 4**). When encapsulating the same formulations on the HK machine, we observed that the ejection forces were not significantly influenced by the amount of magnesium stearate in the formulation. This finding could be attributed to the fact that the HK encapsulator employs a screw-fed hopper, the mixing action of which may cause sufficient coating of particles with magnesium stearate to compensate for differences in concentration. A related observation was made by Ullah and colleagues. [19] When transferring a formulation originally developed on a Zanasi machine to an HK GKF-1500, they found dissolution to be slower from the capsules filled on the HK machine. They proposed that shearing of the laminar magnesium stearate during the tamping step caused excessive coating of the formulation with the hydrophobic lubricant. They concluded that the problem could be overcome by reducing the initial level of lubricant from 1% to 0.3%. It is interesting that overmixing of magnesium stearate in the hopper of an MG2 dosator machine in which a rotating blade continuously mixes the powder also has been reported [20] ; the dissolution of 3 drugs (with 1% magnesium stearate) was reduced after 30 minutes of running the machine. The mixing or shearing sensitivity of magnesium stearate has been discussed. [21-23]

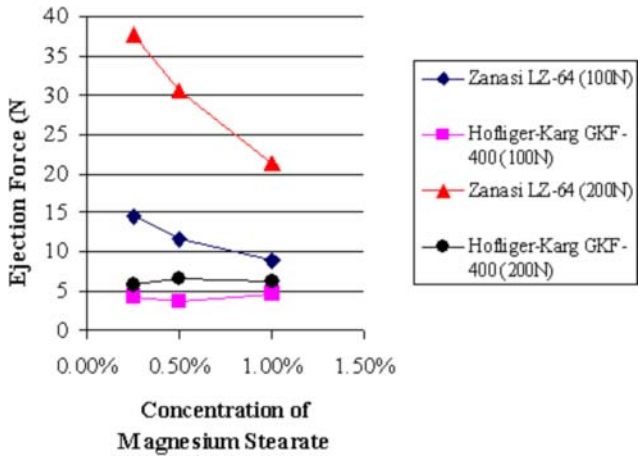

Figure 4. Comparison of ejection force for model lubricity formulations.

The absolute value of ejection force was generally higher on the Zanasi machine than on the HK machine for the same formulation. As discussed previously, materials that exhibit substantial elastic behavior may recover differently in the 2 machines, thereby leading to greater ejection forces in the dosator machine. While it is conceivable that such a theory could apply to the lactose-based model lubricity formulations, lactose exhibits substantially less elastic recovery than Starch 1500 [5] and a substantially higher lubricant requirement than either Starch 1500 [3,5] or microcrystalline cellulose. [3] Clearly, any possible greater powder shearing in the dosing disc machine, as suggested by Ullah and colleagues, [19] would tend to increase the lubricant efficiency in that machine, thereby leading to easier ejection.

Similar fill weights were attained on the Zanasi and HK machines, but a piston height of 18 mm had to be used on the Zanasi as compared to the dosing disc height of 15 mm used on the H&K. As noted previously, the multiple-tamp principle appears to be more efficient at densification than the single tamp of the dosator mechanism.

Compactibility Formulations

The ejection force, fill weight, plug breaking force, and %CV of fill weight estimated from encapsulation of the model compactibility formulations are tabulated in **Tables 7(a)** and **(b)** for the HK GKF-400 and the Zanasi LZ-64, respectively.

Table 7(a). Ejection force, fill weight, and plug breaking force for the model compactibility formulations encapsulated on HK GKF-400

Model compactibility formulation		Formula C1			Formula C2			Formula C3		
Compression force	Statistical parameter	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)
Low (100 N)	Average	< 2	380.5	0.46	2.8	360.1	< 0.1	4.1	314.6	< 0.1
	SD	-	16.6	0.14	1.8	16.2	-	0.1	13.2	-
	%CV	-	4.36	29.95	16.98	4.48	-	2.44	4.12	-
High (200 N)	Average	5.2	411.7	0.78	5.3	384.2	0.21	6.2	341.15	0.17
	SD	1.7	16.4	0.18	0.9	15.8	0.1	0.69	6.51	0.05
	%CV	32.69	3.99	23.32	16.98	4.12	47.06	11.13	1.91	27.09

Model compactibility formulation		Formula C4			Formula C5		
Compression force	Statistical parameter	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)
Low (100 N)	Average	2.5	274.0	< 0.1	4.1	256.25	0.25
	SD	0.05	10.7	-	1.3	7.1	0.06
	%CV	2.0	3.89	-	31.71	2.75	25.23
High (200 N)	Average	6.1	304.4	0.37	8.8	279.4	0.63
	SD	0.7	8.1	0.07	0.78	7.0	0.07
	%CV	11.48	2.66	19.28	2.50	2.50	11.51

The sample size was 10 for ejection force, 20 for fill weight, and 6 for plug breaking force.
Refer to Table 4 for the formula codes for model compactibility formulations.

Table 7(b). Ejection force, fill weight, and plug breaking force for the model compactibility formulations encapsulated on Zanasi LZ-64

Model compactibility formulation		Formula C1			Formula C2			Formula C3		
Compression force	Statistical parameter	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)
Low (100 N)	Average	4.4	366.1	0.25	6.0	341.9	< 0.1	6.6	301.9	< 0.1
	SD	0.4	20.6	0.05	0.6	5.3	-	0.4	3.60	-
	%CV	9.75	5.62	20.00	10.54	1.54	-	6.38	1.18	-
High (200 N)	Average	22.2	397.4	0.96	9.1	365.3	0.44	8.9	322.3	0.34
	SD	2.5	22.1	0.19	0.7	5.4	0.10	0.6	3.69	0.07
	%CV	11.4	5.55	19.9	7.42	1.49	21.84	6.69	1.14	22.01

Model compactibility formulation		Formula C4			Formula C5		
Compression force	Statistical parameter	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)	Ejection force (N)	Fill weight (mg)	Plug breaking force (N)
Low (100 N)	Average	8.1	268.4	0.19	9.8	253.0	0.15
	SD	0.2	2.8	0.04	0.6	2.6	0.05
	%CV	2.88	1.05	22.15	6.25	1.02	33.33
High (200 N)	Average	11.8	278.8	0.57	14.9	275.6	0.47
	SD	0.5	3.6	0.11	0.9	3.0	0.19
	%CV	3.82	1.28	19.63	6.10	1.10	40.01

The sample size was 10 for ejection force, 20 for fill weight, and 6 for plug breaking force.
Refer to Table 4 for the formula codes for model compactibility formulations.
Piston height was set at 22 mm for all formulations.

Table 8. CIs for the model compactibility formulations

Model compactibility formulation	LBD (g/cc)	TBD (g/cc)	CI	%CV of fill weights*
C1	0.669	0.757	11.64	3.99
C2	0.595	0.696	14.57	4.12
C3	0.506	0.621	18.49	1.91
C4	0.437	0.541	19.20	2.66
C5	0.396	0.499	20.60	2.50

*At compression force of 200 N.

The %CV of fill weight was comparatively low whenever a model compactibility formulation filled on the Zanasi machine included Avicel PH 200 in the formulation, regardless of the amount present (**Figure 5**). This observation could be attributed to the cohesive and compressible nature (ie, compactibility) of microcrystalline cellulose that should contribute to the formation of a stable arch at the dosator open orifice [24] and the formation of mechanically strong plugs. In the Zanasi machine, where the bottom end of the plug is unsupported during plug transfer, formulation compactibility and the formation of stable arches are critical to quantitative plug transfer. When encapsulating model compactibility formulation C1 (containing no Avicel PH 200) on the Zanasi machine, it appeared that a portion of the bottom end of the plug was separating. In most cases, the lower ends of these plugs gave the appearance of having been chipped. The observed high %CV of fill weight is likely attributable at least in part to this phenomenon.

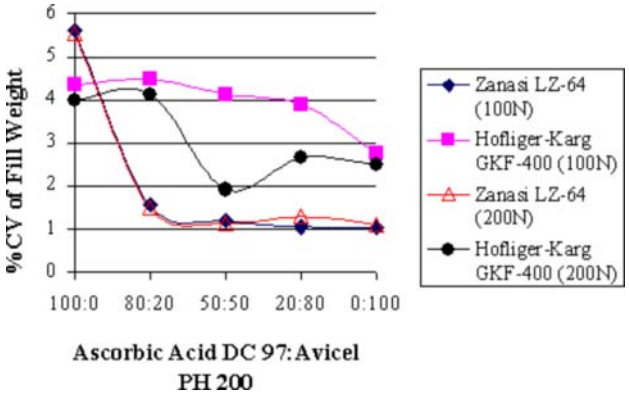

Figure 5. Comparison of %CV of fill weight for model compactibility formulations.

On the HK machine, the %CV of fill weight for the compactibility formulations exhibited a minimum when the compression force used was approximately 200 N. Kurihara and Ichikawa [25] correlated a minimum in %CV of fill weight on an HK encapsulator to differences in the fluidity of the formulations. They observed that whenever the fluidity of the formulation was either above or below an optimum level based on angle of repose or minimum orifice diameter measurements, the %CV of fill weight was higher. CIs were estimated to compare the fluidity of the different model compactibility formulations and are tabulated in **Table 8** . It can be observed that a minimum %CV of fill weight is associated with an intermediate CI value. This observation is consistent with that of Kurihara and Ichikawa [25] and suggests that there is an optimum CI for best weight variation. Therefore, it can be said that neither excessive fluidity nor poor fluidity is desirable when filling formulations on the HK machine.

The pattern of %CV of fill weight for the model compactibility formulations when filled at 100 N cannot be explained by the same rationale. The compression force of 100 N may be too low to form stable powder arches from the mixtures of granular ascorbic acid DC 97 and Avicel PH 200, thus allowing loss of material during the transfer step. Relatively higher %CVs were observed for all formulations containing ascorbic acid DC 97.

A piston height of 22 mm was used on the Zanasi to accommodate fill weights similar to those encapsulated on the HK. The fill weights decreased as the amount of ascorbic acid DC 97 decreased in the formulations (**Tables 7(a)** and **(b)**) because the granular ascorbic acid (DC 97) was denser and more free-flowing than Avicel PH 200.

Even though all model compactibility formulations had the same level of lubricant (0.5%) blended for the same amount of time, ejection forces generally increased as the amount of Avicel PH 200 increased in the formulation. This pattern is attributed to changes in the particle size distribution of the binary mixtures of ascorbic acid DC 97 and Avicel PH 200. The particle size distribution is skewed to the higher end with greater amounts of ascorbic acid DC 97, thus reducing the overall surface area for coverage with the same concentration of lubricant and leading to lower ejection forces. Cumulative percent over-size plots comparing the particle size distributions of the model compactibility blends are shown in **Figure 6** . The absolute values of the ejection forces again were relatively lower when the same formulation was filled on the HK machine. Possible explanations for this phenomenon have been discussed above.

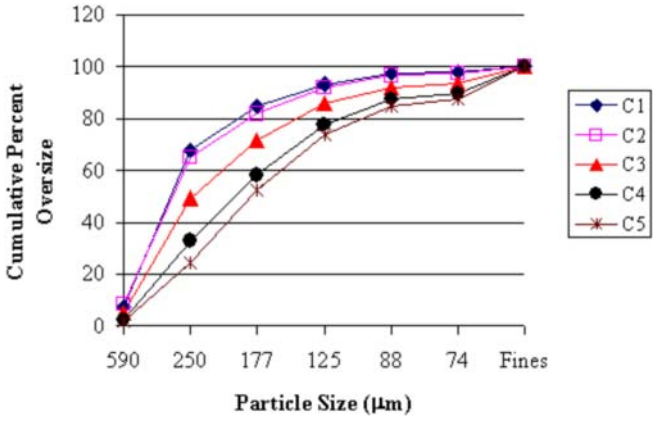

Figure 6. Cumulative percent oversize plots comparing particle size distribution of the model compactibility formulations.

Figures 7(a) and **(b)** compare plug breaking forces for model compactibility formulations encapsulated on the HK and Zanasi, respectively. Whenever the plug breaking force was not measurable (usually < 0.1 N), it was plotted as 0 in these figures.

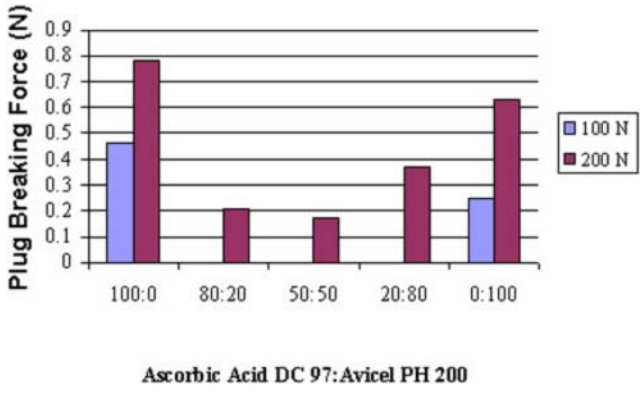

Figure 7(a). Comparison of plug breaking force for model compactibility formulations encapsulated on the HK encapsulator.

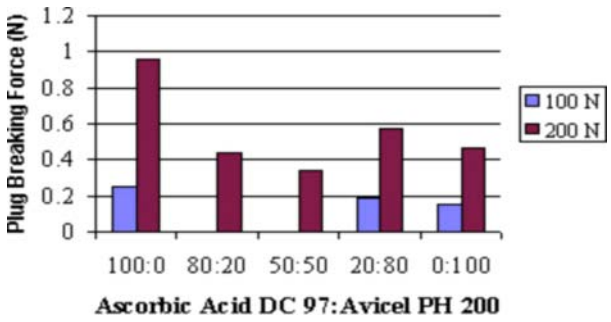

Figure 7(b). Comparison of plug breaking force for model compactibility formulations encapsulated on the Zanasi encapsulator.

In general, plug breaking force increased with compression force proportionately for all formulations regardless of the machine used for encapsulation. The plug breaking force reached a minimum with the 50:50 mix of ascorbic acid DC 97 and Avicel PH 200. Unlike the plugs made on the Instron when developing the model compactibility formulations, the formulation containing ascorbic acid DC 97 without any Avicel PH 200 made plugs of measurable strength in the 2 filling machines. The plugs formed from the model compactibility formulations were stronger when all particles were of the same type. Dilution with a relatively compactible material like Avicel PH 200 often did not result in plugs of measurable strength, especially at a lower compression force. This behavior reflects the significance of interactions between like particles, and hence the minimums seen in **Figures 7(a)** and **(b)** .

In general, plug breaking force increased with compression force. Since plug breaking forces were measured on 2 different testers, the absolute values might be different and may not be able to be compared fairly between the machines. Nevertheless, it is clear from **Tables 6(a)** and **(b)** that the plug breaking forces of the model lubricity formulations were not significantly influenced by the levels of magnesium stearate in the formulations.

Comparison of Dissolution Performance

Table 9 lists the times for 60%, 75%, and 85% dissolution of HCTZ from the model lubricity formulations. It can be observed that the time taken for 85% dissolution (t85%) of HCTZ is not significantly influenced by either the compression force used or the amount of lubricant used (up to 0.5%) (**Figure 8**). At the 1%_magnesium stearate level, it was observed that the capsules filled on the Zanasi at 100 N exhibited a shorter t85% of HCTZ than those filled at 200 N. At 100 N, the plugs are possibly sufficiently soft for the dissolution of HCTZ to not be affected significantly by the level of magnesium stearate.

Table 9. Dissolution of HCTZ from model lubricity formulations

Dissolution data from encapsulation on HK GKF-400

Formulation*	Formula L1		Formula L2		Formula L3	
% Mg stearate	0.25	0.25	0.5	0.5	1.0	1.0
Compression force (N)	100	200	100	200	100	200
Statistical parameter	Time in minutes for **60%** dissolution of HCTZ					
Average	4.5	4.9	3.9	4.1	6.9	6.3
SE of mean	0.27	0.23	0.25	0.55	0.34	0.37
Statistical parameter	Time in minutes for **75%** dissolution of HCTZ					
Average	6.6	7.0	5.6	5.9	9.8	9.5
SE of mean	0.24	0.36	0.23	0.90	0.66	0.54
Statistical parameter	Time in minutes for **85%** dissolution of HCTZ					
Average	8.0	8.7	7.3	7.8	16.8	15.0
SE of mean	0.18	0.30	0.29	1.44	1.5	1.29

Dissolution data from encapsulation on Zanasi LZ-64

Formulation*	Formula L1		Formula L2		Formula L3	
% Mg stearate	0.25	0.25	0.5	0.5	1.0	1.0
Compression force (N)	100	200	100	200	100	200
Statistical parameter	Time in minutes for **60%** dissolution of HCTZ					
Average	3.9	4.1	4.5	4.4	4.4	7.1
SE of mean	0.32	0.37	0.43	0.47	0.47	0.79
Statistical parameter	Time in minutes for **75%** dissolution of HCTZ					
Average	6.7	5.3	6.5	6.2	7.0	9.5
SE of mean	0.32	0.32	1.04	0.77	1.01	1.13
Statistical parameter	Time in minutes for **85%** dissolution of HCTZ					
Average	9.8	9.0	9.6	9.8	8.5	14.6
SE of mean	0.16	0.53	1.33	1.58	1.03	1.52

*Refer to Table 4 for the formula codes for model lubricity formulations.

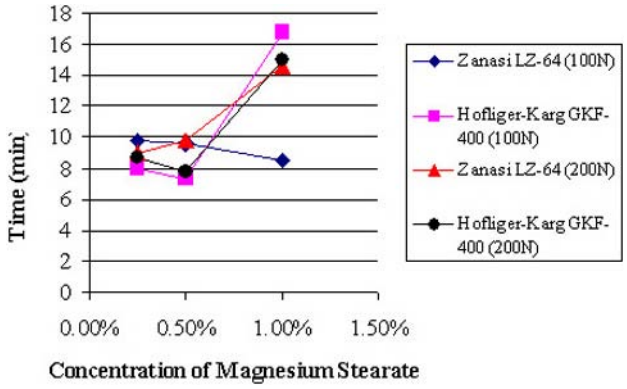

Figure 8. Comparison of t85% of HCTZ from model lubricity formulations.

Unlike for the formulations filled on the Zanasi machine, t85% of HCTZ from capsules filled on the HK machine at both 100 and 200 N were similar at each lubricant concentration. In addition, dissolution from the 1%_magnesium stearate formulation was the slowest among all formulations tested, regardless of the filling machine used. This slower dissolution and lack of influence of compression force on dissolution may be due to the combined effect of a higher 1% concentration and possible greater shearing of the lubricant in the HK machine. The latter may have overwhelmed any effect of compression force.

Table 10 lists the times for 60%, 75%, and 85% dissolution of ascorbic acid from the model compactibility formulations. The dissolution of ascorbic acid was slowest from the formulation that did not contain any Avicel PH 200, as seen in **Figure 9** comparing the t85%s of ascorbic acid from the model compactibility formulations. For those formulations containing Avicel PH 200, the microcrystalline cellulose may be acting as an in-situ disintegrant by promoting liquid uptake and swelling.[26] Also, as the binary mixtures were diluted with Avicel PH 200 (formulations C2, C3, and C4), the plug strength decreased, as discussed previously. This softening of the plugs could promote faster dissolution of ascorbic acid from these formulations. Dissolution of ascorbic acid from C1 appears to be slower when filled on the Zanasi. The plug was formed in multiple stages on the HK, and the plug segments may separate to speed up the initial stages of the dissolution process.

Table 10 Dissolution of ascorbic acid from model compactibility formulations

Dissolution data from encapsulation on HK GKF-400

Formulation*	Formula C1		Formula C2		Formula C3		Formula C4	
AADC97™:Avicel PH 200	100:0	100:0	80:20	80:20	50:50	50:50	20:80	20:80
Compression force (N)	100	200	100	200	100	200	100	200
Statistical parameter	Time in minutes for **60%** dissolution of ascorbic acid							
Average	10.9	16.3	5.4	6.6	3.3	4.1	2.3	2.5
SE of mean	2.50	2.28	0.08	0.43	0.23	0.16	0.11	0.08
Statistical parameter	Time in minutes for **75%** dissolution of ascorbic acid							
Average	16.7	23.4	7.6	9.5	4.3	4.7	3.0	3.4
SE of mean	2.88	2.68	0.85	0.76	0.27	0.18	0.22	0.17
Statistical parameter	Time in minutes for **85%** dissolution of ascorbic acid							
Average	23.8	27.6	9.1	12.1	5.0	5.3	4.1	4.5
SE of mean	2.71	2.9	1.29	1.48	0.30	0.30	0.59	0.34

Dissolution data from encapsulation on Zanasi LZ-64

Formulation*	Formula C1		Formula C2		Formula C3		Formula C4	
AADC97™:Avicel PH 200	100:0	100:0	80:20	80:20	50:50	50:50	20:80	20:80
Compression force (N)	100	200	100	200	100	200	100	200
Statistical parameter	Time in minutes for **60%** dissolution of ascorbic acid							
Average	13.3	22.0	4.4	6.5	4.4	3.6	3.0	3.1
SE of mean	1.36	2.44	0.06	1.34	0.51	0.15	0.13	0.21
Statistical parameter	Time in minutes for **75%** dissolution of ascorbic acid							
Average	21.0	30.4	4.9	7.9	5.1	4.4	3.9	3.8
SE of mean	2.72	2.37	0.05	1.48	0.57	0.11	0.11	0.25
Statistical parameter	Time in minutes for **85%** dissolution of ascorbic acid							
Average	28.8	38.2	5.8	9.1	5.7	5.1	4.4	4.4
SE of mean	3.59	2.23	0.28	1.64	0.76	0.20	0.05	0.20

*Refer to Table 4 for the formula codes for model compactibility formulations.
AADC97 indicates ascorbic acid DC 97. Compactibility formula C5 did not contain any ascorbic acid and therefore, dissolution was not performed.

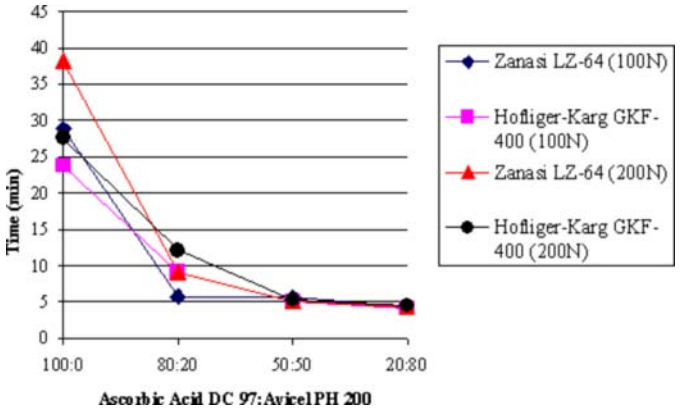

Figure 9. Comparison of t85% of ascorbic acid from model compactibility formulations.

The dissolution profiles of ascorbic acid from capsules filled on both machines were compared using the f_2 test. **Table 11** lists the f_2 values estimated when comparing the ascorbic acid dissolution profiles for the same formulation filled on the 2 machines at the same compression force. There are 2 cases in which the f_2 value was less than 50, suggesting that the dissolution profiles for the same formulation differ on the 2 machines. **Figure 10** displays 1 of these 2 dissolution profiles. Similarly, the dissolution profiles of HCTZ from capsules filled on both machines were compared using the f_2 test (**Table 12**). For 1 set of conditions (Formula L3 at the 100-N compression force), the f_2 value was less than 50, again suggesting that the dissolution profiles for the same formulation differ on the 2 machines. The dissolution profiles are exhibited in **Figure 11** .

Table 11. f_2 Values comparing the dissolution profiles of ascorbic acid from model compactibility formulations

Model compactibility formulation/ Compression force	f_2 Metric
C1/100 N	60.4
C2/100 N	**47.7**
C3/100 N	52.2
C4/100 N	57.1
C1/200 N	**46.0**
C2/200 N	78.4
C3/200 N	69.1
C4/200 N	64.3

f_2 Values less than 50 are boldface.

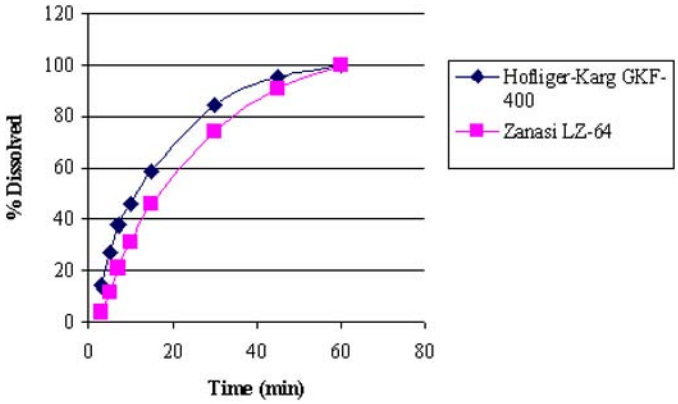

Figure 10. Comparison of ascorbic acid dissolution from model compactibility formulation C1 (0% Avicel PH 200) filled at compression force of 200 N.

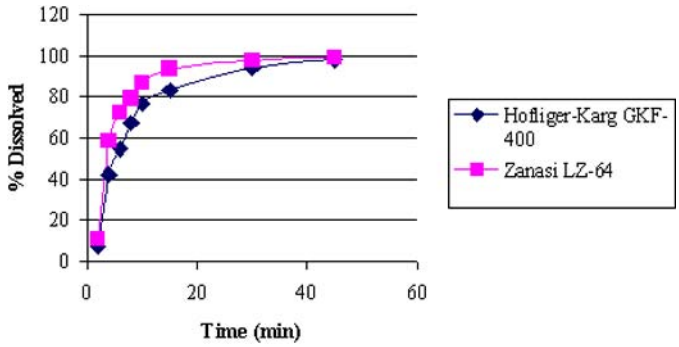

Figure 11. Comparison of HCTZ dissolution from model lubricity formulation L3 filled at compression force of 100 N (1% magnesium stearate).

Table 12. f_2 Values comparing the dissolution profiles of HCTZ from model lubricity formulations

Model lubricity formulation/ Compression force	f_2 Metric
L1/100 N	67.9
L2/100 N	54.9
L3/100 N	**48.0**
L1/200 N	53.2
L2/200 N	62.7
L3/200 N	72.2

f_2 Value less than 50 is boldface.

These differences in dissolution between the 2 machines indicated by the f_2 metric may not signify different product performance in vivo, as discussed by Polli and colleagues. [27] However, such results would suggest the need for a preapproval supplement if these were the outcome of a postapproval change in filling machines. According to the manufacturing equipment addendum to the SUPAC-IR and SUPAC-MR [modified release] guidances, the 2 types of capsule filling machines used in this study are members of the same class of machines but belong to different subclasses. [28] Equipment within the same class and subclass are considered to have the same design and operating principle under SUPAC-IR and SUPAC-MR. Provided certain other conditions are met, a postapproval change of manufacturing equipment between subclasses within the same class of equipment likely would not require a preapproval supplement. But the guidance also states that changes in equipment that are in the same class, but different subclasses, as is the case here, should be considered carefully and evaluated on a case-by-case basis. The SUPAC guidance places the burden on the applicant to provide the scientific data and rationale at the time of change to determine whether a preapproval supplement is justified. These data are subject to FDA review at its discretion.

CONCLUSION The results of this study suggest that an optimal degree of fluidity is required in a formulation for successful encapsulation on either machine. In the present study, a CI value from 20 to 30 is an optimum value based on capsule weight variation. Of the 3 Avicel grades, the medium-flow grade, PH 102, seems to be the most suitable for transferring formulations between these machines.

A relatively lower level of lubricant may be sufficient for encapsulation on the HK machine as compared to the Zanasi, as evidenced by the ejection forces recorded during encapsulation of all model formulations.

The dissolution of the model drug, HCTZ, from capsules filled on the Zanasi machine was more affected by compression force at a higher level of magnesium stearate.

A higher degree of formulation compactibility may be needed for clean processing on the Zanasi machine as compared to the HK. This observation is reflected in the present study by the higher %CV for capsule weight recorded for the model compactibility formulation without Avicel PH 200. In general, higher

compression forces resulted in stronger and more intact plugs on either machine. Higher compression forces may eliminate or reduce inefficient plug transfer.

Transferring formulations between machine types could be challenging in certain situations (eg, when the drug is hydrophobic or dose is very high with very low bulk density). It may be advisable to lower the level of laminar lubricants such as magnesium stearate when transferring formulations originally developed on Zanasi machines to HK machines, regardless of the hydrophobicity of the drug. For the materials and test conditions studied, it appears that the lubricant level could be reduced by as much as 50%.

In general, the multiple-tamping principle of the dosing disc machine may be more efficient in encapsulating a very bulky material into a given size capsule.

The f_2 test comparing the dissolution profiles suggested that in vitro dissolution of the same formulation differed on the 2 machines. Since these machines represent different subclasses, a preapproval supplement may be needed if this result were the outcome of a postapproval change.

In summary, the results of this study reveal important differences in formulation requirements between the Zanasi (dosator) and HK (dosing disc) machines. An understanding of these differences facilitates the design of optimal capsule formulations for such machines and provides guidance on making equipment changes within these types of machines.

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