DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(20), 3151-3173 (1994)

FORMULATION AND COMPACTION OF MICROSPHERES

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ABSTRACT

The factors affecting the tabletability of formulations containing uncoated and/or coated microspheres were discussed by presenting a case study. The size and shape, as well as surface properties of microspherical particles, the type and amount of coating agent, selection of the external additives, and the rate and magnitude of the pressure applied were found to be the most critical factors to be considered in order to obtain and maintain the desired drug release properties of the microspheres. It was found that microcrystalline cellulose was needed in order to produce satisfactory beads in terms of size, shape and surface characteristics. The microsphere formulations, which were found to be highly sensitive to lubrication, were more compressible than their powder forms, but produced much weaker tablets. When coated with Surelease®, increasing the amount of coating on the pellets reduced the tensile strength of their compacts. Compaction of the microspheres at high velocities resulted in a decrease in the tensile strength values and an increase in the volumetric strain recovery values. Dissoultion studies revealed that, regardless of the amount of coating applied, the coated microspheres lost their sustained release properties during compaction.

INTRODUCTION

The design and development of multi-unit dosage formulations (containing microspheres) in the form of compressed tablets, rather than hard gelatin capsules, are becoming increasingly important. Hard gelatin capsules are very elegant dosage forms, but have the disadvantages of higher production cost, lower production rate and tampering potential (Tylenol® and Sudafed-12hour®) when compared to compressed tablets.

When sustained release tablets containing coated or uncoated microspheres are manufactured, it is often desirable to produce compacts that disintegrate into many sub-units soon after ingestion to attain more uniform concentrations of active substances in the body. It is needless to emphasize the fact that the coated microspheres in the formulation must withstand the process of compaction without being damaged, since, for example, the existence of a crack in the coating may have undesirable effects on the drug release properties of that sub-unit. The manufacturing method of microspheres, the type and amount of coating agent, the size of the spheres, selection of the external additives, and the rate and magnitude of the pressure applied must be carefully considered to maintain the desired drug release properties. To prevent undesirable drug release properties of such dosage forms, formulation scientists must also have a comprehensive knowledge of how that formulation will behave during tableting, as well as of how the other materials and/or process-related parameters will affect the performance of that formulation as a drug delivery system.

The aim of this article is, by presenting a case study, to discuss some of the factors influencing the tabletability of the coated and uncoated pellets that are the main components of the multi-unit dosage forms. In this article (and in the literature), the terms pellet, bead, microsphere, and millisphere are used interchangeably.

Concept of compaction:

The physics of compaction of powders have been examined by several workers in the fields of pharmaceutics and metallurgy (1-5). The principal physico-mechanical process involved in the compaction of particulate matter can be summarized as follows:

Initially, the particles undergo a rearrangement stage in which they flow with respect to each other until a 'closer packing' arrangement is achieved. At this stage, as the upper punch penetrates into the die containing the powder bed, there are essentially only points of contact between the particles. Utilizing the punches, application of an external force to the bed results in forces being transmitted through these inter-particulate points of contact, where the stress is developed, and where local deformation of the material occurs. The deformation will feature either one or a combination of the following: elastic, plastic, and/or brittle fragmentation. The type of deformation depends upon the rate and magnitude of the applied force as well as the duration of the locally induced stresses and physical properties of the material.

When the particles are in sufficiently close proximity they can become permanently bonded to each other by several mechanisms. The simplest type of bonding is termed 'mechanical interlocking' which is facilitated by irregular particle shape and surface roughness. Particles can also bond as a result of a phase transition at the points of contact where the magnitude of the pressure is tremendously high, and the temperature at those points may reach the melting points of the materials to liquefy the solid particles. Another mechanism of bonding is termed 'inter-molecular forces' which encompasses three known types of molecular bonding: van der Waals forces, hydrogen bonding, and ionic bonding.

Instrumented single-station presses (6), multi-station presses (7), and during the last two decades, isolated punch-die assemblies and Integrated Compaction Research Systems (ICRS), so called 'compaction simulators' (8), have been widely used in compaction studies. Numerous methods have been proposed to characterize the compaction process (9).

Compaction studies on the microspheres:

There is only a small amount of research (10-19) and review (20) articles available on the compaction characteristics of microspheres.

Juslin and others (10), on their study of the feasibility of achieving controlled release of a drug from compacts of coated spheres, observed that the drug release rate from

phenazone spheres, which were coated with acrylate plastic mixed with different additives, increased with the initial increase in the applied pressure. This was attributed to the cracks in the coat that formed during compaction. However, the authors claimed that further increases in pressure again retarded the release profile, possibly due to the closer inter-particulate contacts within the tablet which partly compensated for the leaks in the pellet coats.

Badwan and others (11) reported an increase in the drug release profile of sulphamethoxazole beads when compacted into a tablet.

Bodmeier and Chen (12), who compacted the biodegradable spheres prepared from polylactides, observed that the energy imparted during compaction caused fusion of the low molecular weight polylactide particles resulting in transparent pellets with no visible particle boundaries.

In a compaction study on microcapsules (125-250μm) containing phenylpropanolamine-resin complexes (13), it was found that the time required for 50% drug release (T50%) from the compacts of microcapsules with various external diluents was affected by the magnitude of the pressure, the quantity of microcapsules, and the type of external additive. The drug release rate from the microcapsule compacts increased with an increase in the magnitude of the pressure, suggesting that the diffusion retarding membrane was ruptured during compaction. An increased percentage of microcapsules also caused a decrease in the T50%. None of the external additives used, including microcrystalline cellulose, spray-dried lactose, and dextrates, was able to retain the retarded drug release from the microcapsules. However, formulations containing microcrystalline cellulose as the diluent were found to be least influenced by the pressure effects and capable of accepting larger quantities of microcapsules.

Millili and Schwartz (14) reported that the strength and physical properties of microspheres containing microcrystalline cellulose were affected by the granulating solvent. In their work, water granulated microcrystalline cellulose pellets were found to be strong, hard, and uniform in shape, whereas the 95/5 ethanol/water granulating

solvent resulted in microspheres with lower strength and a less uniform shape. On the other hand, the former pellets exhibited poorer compactability than the latter ones. This was attributed to the weak bonding of the 95% ethanol granulated pellets which ruptured upon compaction, exposing more smooth surface to surface contacts for bonding. The water granulated pellets resisted rupturing due to their high bond strength and allowed less surface to surface contacts for bonding to occur, thus producing weaker tablets.

Béchard and Leroux investigated (15) the effect of compaction on the drug release from the compacts of varying mesh cuts of coated microspheres containing chlorpheniramine maleate. In their study, microspheres were coated with Aquacoat®, and mesh cuts of 20/30 (590-840μm), 30/40 (420-590μm) or 40/60 (250-420μm) were compacted with external additives of microcrystalline cellulose, dicalcium phosphate anhydrous or compressible sugar. The workers reported that massive film fracture occurred at high pressures regardless of the microsphere particle size or the external additives used, and total loss of the controlled release was observed. They pointed out that smaller particles appeared to be more fragile than larger ones. This was attributed to the differences in film thickness, which was found to be 15μm for the 40/60 mesh microspheres, as opposed to 20-25μm for the 20/30 and 30/40 mesh pellets. However, the formulations containing the smallest size spheres were found to be more compatible, in terms of particle size, with direct compression excipients.

Maganti (16) and Maganti and Çelik (17) observed significant changes between the compaction properties of the powder and pellet forms of the same formulations. In their study, the powder formulations deformed plastically and produced strong compacts, whereas their pellet forms exhibited elastic deformation and brittle fragmentation which resulted in compacts of lower tensile strength. Later, they reported that the addition of Surelease® as a coating material altered the deformation characteristics of uncoated pellets by introducing plasto-elastic properties into their previously brittle and elastic nature (18).

Flament and others (19) investigated the drug release properties of tablets containing 50% Eudragit coated microspheres (consisting of 75% theophylline and 25% excipient) and 50% placebo granules (consisting of 50% microcrystalline cellulose and 50% corn

starch). When comparing the drug release properties of the tablets and uncompacted coated pellets, they observed an increased dissolution rate from the tablets, and this was found to be due to the deformation of the coating during compaction.

FORMULATION CONCERNS

When a multi-unit dosage form containing coated and/or uncoated microspheres is to be developed in the form of a tablet, the following factors must be considered in order to produce tablets with the desired drug release properties: the selection of the internal and external additives; the size and shape, as well as surface properties of the microspherical particles; the type and amount of coating agent; and the rate and magnitude of the applied pressure.

It is convenient to briefly present the materials used and the methods employed in the case study before discussing the above factors influencing the tabletability of the coated and uncoated microspheres, although, this was previously reported elsewhere (16-18). The materials used were microcrystalline cellulose (Emcocel 50M, E. Mendell Co.), lactose (Fast-Flo, Foremost Whey Products), dicalcium phosphate dihydrate (Emcompress, E. Mendell Co.) and propranolol HCl (Byron Chemicals). The microspheres contained microcrystalline cellulose alone, (F-0), or were made of one of two formulations (F-I and F-II). One formulation, F-I, consisted of 80% w/w microcrystalline cellulose, 10% w/w propranolol HCl and 10% w/w lactose while the other formulation, F-II, contained 80% w/w microcrystalline cellulose, 10% w/w propranolol HCl and 10% w/w dicalcium phosphate dihydrate. Pregelatinized starch (Starch 1500), soy polysaccharide (Emcosoy, E. Mendell Co.), and magnesium stearate (Fisher Scientific) were used as the external additives. Surelease (Colorcon Inc.), an aqueous coating material, was used to coat the microspheres at three different levels (10% w/w; 15% w/w ; and 20% w/w).

A Glatt rotor granulator (GPCG-1Kg, Glatt Air Techniques, Inc) was used to produce uncoated and coated microspheres. Compaction tests were performed using an Integrated Compaction Research System (ICRS, Mand Testing Ltd.) fitted with 10.3 mm diameter,

flat-faced, round BB tooling. Each test was performed on an amount of material corresponding to a pre-determined constant absolute volume of 0.2 cm^3. The punch displacement profiles were double-ended with constant velocities of 1mm/s and 100 mm/s per punch up to the maximum applied pressure which varied from one material to another in order to produce compacts at a pre-determined final porosity of $3 \pm 0.3\%$ within the die.

Internal additives and the particle characteristics of the microspheres:

The size, shape, and surface properties of microspherical particles differ when compared to their powder form. In the case of mixtures, the percentage of each component can also have an effect on the shape and surface characteristics of the resulting microspheres. As can be seen from Table 1, pellets made from 30% microcrystalline cellulose and 70% dicalcium phosphate or from 30% microcrystalline cellulose and 70% hydrous lactose possessed an irregular shape and a rough surface, whereas, the pellets made from the powder formulation consisting of 90% microcrystalline cellulose and 10% dicalcium phosphate or 90% microcrystalline cellulose and 10% hydrous lactose were almost spherical in shape and had a smoother surface. From these findings, the inclusion of microcrystalline cellulose at relatively high concentrations is recommended in order to produce microspheres with satisfactory shape and surface properties.

There are many process-related factors which play a significant role during pelletization and affect the characteristics of the resulting microspheres, for instance, the particle size distribution. Careful control of the end point during pelletization is essential in order to obtain a reproducible particle size distribution from batch to batch (16). It is important to achieve a narrow particle size distribution (Table 2) and acceptable size (Table 3) of the beads. This will ensure a minimum variation in the coating thickness throughout the batch of microspheres, and hence, a uniform release from the beads within a batch. A wider range of particle size distribution may cause a nonuniform fluidization pattern, an important coating process variable in a rotor granulator, as well as segregation during compaction and variation in the content uniformity of the resulting product.

Any change in size, shape, or surface properties of microspherical particles when compared to their powder form may also alter their deformation mechanisms. For

Table 1

Morphological characteristics of the microspheres made from different proportions of fillers (After Reference 16)

Formulations				
MCC/DPD: microcrystalline cellulose : dicalcium phosphate dihydrate				
MCC/HL : microcrystalline cellulose : hydrous lactose				
MCC/FFL : microcrystalline cellulose : Fast-flo lactose				
	30:70	**50:50**	**70:30**	**90:10**
MCC/DPD	irregular shape rough surface	irregular shape rough surface	oval shape less rough surface	spherical and oval shape smooth surface
MCC/HL	irregular shape rough surface	irregular shape rough surface	oval and spherical less rough surface	mostly spherical smooth surface
MCC/FFL			oval and spherical less rough surface	mostly spherical smooth surface

example, microcrystalline cellulose, which deforms primarily by plastic deformation, can produce pellets that exhibit elastic and/or brittle fragmentation (17). Any 'undesirable' change in the mechanism of compaction may cause a reduction in the mechanical strength of the ejected compacts and/or can alter the drug release characteristics.

External additives:

The selection of external additives is of importance in the design of multi-unit tablets since these additives are expected to prevent the incidence of film cracking in the coated sub-units. Their compatibility with the sub-units, in terms of particle size, is also very

Table 2

Typical particle size distribution of uncoated microspheres produced

Mesh Number	Size of Opening (μm)	Frequency (%)
18	1000	2.14
20	840	42.86
25	695	32.14
30	595	17.86
35	500	5.00

Table 3

The geometric mean diameter of the microcrystalline cellulose (MCC), dicalcium phosphate dihydrate (DPD), and Fast-Flo lactose (FFL) powders and uncoated and Surelease® coated F-I and F-II microspheres.

	Geometric Mean Diameter (μm)				
	MCC	**FFL**	**DCP**	**F-I**	**F-II**
powder	60	70	50	-	-
uncoated microspheres	650	-	-	650	650
10% coated	-	-	-	690	700
15% coated	-	-	-	720	720
20% coated	-	-	-	750	740

critical since a non-uniform size distribution can cause segregation, resulting in many tableting problems, such as, weight variation and poor content uniformity. In order to assess the effect of the external additives on the compaction mechanism of microspheres, the pellets were compacted with a number of additives including soy polysaccharide, microcrystalline cellulose, and pregelatinized starch. It was shown in that work that the presence of external additives resulted in an increase in the pressures required to obtain the same porosities within the die, and this effect was found to be dependent on the nature and the amount of excipients added (Table 4). The external additives, being small and irregular particles, when added to the pellets, increased the duration of the particle rearrangement stage during compaction, and possibly, introduced new bonding sites. Microspheres containing microcrystalline cellulose were found to be more compressible, and produced stronger compacts than the pellets containing pregelatinized starch or soy polysaccharide as external additives. In fact, the addition of soy polysaccharide to the microspheres actually reduced the strength of the resulting compacts.

In order to minimize the occurrence of problems due to a non-uniform size distribution, placebo microspheres or granules, with good 'compaction' and 'cushioning' properties, can also be used as diluents if the size of the active microspheres is much larger than that of the external powder additives. If a formulation scientist were to choose this method, the strength of the placebo microspheres should be determined carefully. In order to provide a good cushioning effect, the strength of the placebo spheres should be less than that of the coated active beads so that they will not damage the film layer of the active beads during compaction. In fact, they should only be strong enough to withstand the processes up to the compaction stage and be easily broken apart when pressure is applied during compaction. The manufacturing method of the placebo and active spheres is also a critical factor. If the active beads are manufactured using an extrusion/spheronization method, which usually produces spheres with high densities, then it would be more beneficial to prepare the placebo beads using a rotor granulator, which can produce spheres with low densities. Of course, regardless of the manufacturing method chosen, the placebo beads should possess good compaction properties in order to produce tablets with acceptable strength.

Table 4

Comparison of the maximum pressures required to produce compacts (from F-I microspheres with external additives) at a 3% in-die porosity and tensile strength values of their compacts.

external additives and their percentage concentration (w/w)	Maximum Applied Pressure (MPa)	Tensile Strength (MPa)
F-I without external additive	169	0.56
10% microcrystalline cellulose	203	1.61
20% microcrystalline cellulose	228	2.18
10% pregelatinized starch	256	chipped
20% pregelatinized starch	277	chipped
10% soy polysaccharide	220	0.47
20% soy polysaccharide	239	0.45
10% soy polysaccharide and 0.5% magnesium stearate	198	0.00

Another technique for preventing the problems associated with segregation is to produce microspheres of smaller sizes. At present, the technology is available to manufacture coated sub 100μm microspheres. Small-size active sub-units also improve the content uniformity of low dose drugs. However, the surface area to be coated will increase as the size of the microspheres decreases. Any problems or advantages associated with the increased amount of surface area to be coated must also be considered carefully.

Lubrication:

Since the surface area of the spherical particles will be minimum as compared to the other shapes, microspherical formulations may require only a very small amount of

lubricant. Therefore, the amount of, and mixing time with, the lubricant must also be carefully considered. The data showing the effects of lubrication on the mechanical strength of the tablets containing microspheres are presented later in this report.

Type and amount of coating:

It is important that the coated sub-units in the formulation be able to withstand the process of compaction without being damaged. The type and amount of coating agent, as well as the size of the sub-units, the selection of the external additives, the rate and magnitude of the applied pressure, and the residual porosity of the resulting tablets are among the most critical factors to be considered in order to maintain the desired drug release properties of that sub-unit.

Maganti and Çelik (18) observed that the radial tensile strength values of the compacts of uncoated microspheres were less than those of the Surelease® coated pellets (Table 5). However, further increase in the amount of coating caused a reduction in the strength of the compacts. This was attributed to the adhesive binding properties of Surelease®. The increase in the tensile strength of the compacts with the addition of a small amount (10%) of Surelease® as a coating agent to the microspheres was presumed to cause the development of some binder-binder and binder-substrate bonds in addition to the substrate-substrate bonds between the fragmented neighboring microspheres. On the other hand, further increases in the amount of coating caused an increase in the overall binder concentration and in the relative ratio of binder-binder bonds to substrate-binder bonds, thereby producing compacts with lower radial tensile strength values due to the lack of cohesive properties of Surelease®. From this, it is evident that the addition of a coating material can alter the deformation characteristics of uncoated pellets by introducing plasto-elastic properties into their previously brittle and elastic nature.

The dissolution studies (10-19) revealed that, regardless of the amount of coating applied, the sustained release properties of the coated microspheres diminished on application of compaction pressure. This can be attributed mainly to the formation of cracks within the coating and to the fragmentary/elastic nature of the pellets (16-18).

Table 5

Comparison of the tensile strength values of tablets made from the F-II powders and their uncoated and Surelease® coated microspheres compacted at different punch velocities

		Tensile strength (MPa)	
		Punch velocity = 1 mm/sec	Punch velocity = 100 mm/sec
compacts of powder formulation		9.9	8.3
microsphere compacts	uncoated	0.5	0.5
	10% coated	2.1	1.7
	15% coated	1.8	1.4
	20% coated	1.1	0.8

Compaction:

The rate and magnitude of the applied pressure:

As mentioned, the rate and magnitude of the applied pressure are important factors to be considered in order to maintain the desired drug release properties of sub-units. As can be seen from Table 5, a decrease was evident in the consolidation of Surelease® coated pellets as the rate of load application increased. The optimization method reported previously (18) showed that the dependency on the rate of load application was a function of the amount of coating added to the microspheres. Pellets with increasing amounts of coating exhibited more time dependancy. As mentioned above, regardless of the amount of coating applied, the coated pellets lost their sustained release properties when compacted into tablets.

Compaction behavior of powders, uncoated and coated microspheres:

The measurement of the porosity changes during compaction is a method used to determine the 'compressibility' of a powder bed, i.e. the degree of volume reduction due

to an applied pressure. The following equation can be used for percentage porosity determination:

$$\in(\%) = 100 \cdot [1 - (V_t / V_c)] \quad (1)$$

where V_t is the specific solid volume, i.e. 'true volume' of the material and V_c is the compact volume at a given pressure.

Upon compaction, the microspheres usually require lower pressures than their powder form to obtain the same residual porosities. As can be seen from Figure 1, microcrystalline cellulose powder, F-0, exhibited a higher initial porosity change at low pressures than that of its uncoated microspheres. This could be attributed to the higher initial porosity of the powder which required low pressures to undergo repacking, whereas the microspheres exhibited a shorter particle rearrangement stage and proceeded to the subsequent steps of compaction more rapidly (17-18). The differences between the magnitude of the pressure applied to the powder and microsphere forms to achieve the same porosities increased as the minimum porosity was approached. However, the powder produced stronger compacts than the pellets (Table 6), suggesting that the ability of a material to be reduced in volume when compressed does not ensure the formation of a strong compact, and that percentage porosity profiles are not suitable for determining the consolidation ability of a material which can probably be predicted better by the use of energy involved during compaction. The total work of compaction (TWC) can be calculated using the following equation, in which the contributions of the upper and lower punches were estimated separately (8):

$$TWC = \int_{X=0}^{X_{max(up)}} F_{up} \cdot dX_{up} + \int_{X=0}^{X_{max(lp)}} F_{lp} \cdot dX_{lp} \quad (2)$$

where, F_{up} and F_{lp} are the forces on the upper and lower punches respectively; X_{up} and X_{lp} are the contributions of the upper and lower punches, respectively, to the decrease in the distance between them; $X = 0$ is the point where the porosity

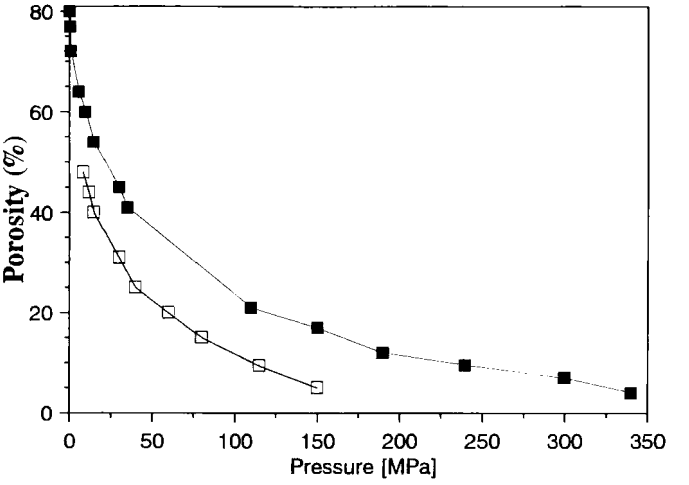

FIGURE 1. Porosity vs pressure plots for the compacts of the powder (■) and microsphere (□) forms of F-0 formulation.

corresponds to the initial porosity and maximum applied load is attained at $X_{max(up)}$ and $X_{max(lp)}$.

Çelik and Marshall (8) observed that the rank order of total energy involved during compaction of the powders and the tensile strength values of their compacts were similar. This opinion is also supported with the findings of the present case study (Figure 2 and Table 6). The TWC and strength values of the compacts of microcrystalline cellulose pellets were both significantly less than those of the powder form, suggesting that the degree of bonding of this material was considerably affected by the changes in its shape, size and also possibly by the reduction in the number of its potential bonding sites that occur due to the pelletization process. The pellets, which were large and spherical in shape, as compared to the small, irregular powder particles, had a low surface to volume ratio, and this might have resulted in a decreased area of contact between the particles as they consolidated.

When the percentage porosity, TWC and tensile strength values of the powder and microsphere forms of microcrystalline cellulose are compared (Figures 1, 2 and Table

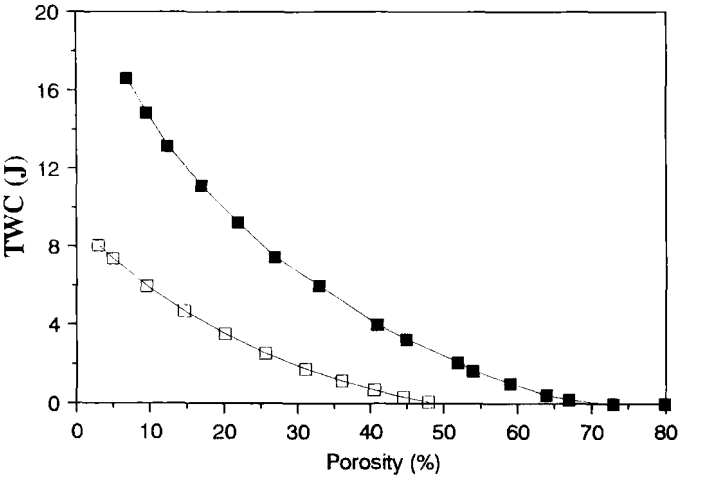

FIGURE 2. Total work of compaction vs pressure plots for the compacts of the powder (■) and microsphere (□) forms of F-0 formulation.

Table 6

Comparison of the maximum pressures required to produce compacts (from F-0, F-I, F-II powders and their microspheres) at a 3% in-die porosity and tensile strength values of their compacts.

Formulation		Pressure (MPa)	Tensile Strength (MPa)
F-0	powders	348	10.70
F-0	microspheres	165	0.52
F-I	powders	431	8.89
F-I	microspheres	169	0.56
F-I	microspheres (lubricated)	138	"-"
F-II	powders	418	8.28
F-II	microspheres	177	0.54
F-II	microspheres (lubricated)	129	"-"

6), it is evident that the beads of this material required less pressure and less energy, and formed weaker tablets than its powder form when compacted to the same residual in-die porosity. This observation is also valid for the compacts of the powder form of the other formulations (F-I and F-II) and their uncoated spheres (16). This is further support for a good correlation between the tensile strength and the work of compaction, not between the tensile strength and percentage porosity.

Using the Heckel equation (21,22), Maganti and Çelik (17,18) compared the yield pressure values of the compacts of F-0 powder and pellets as well as the uncoated and coated pellet formulations. They observed that these values (which can be calculated from the reciprocal of the slopes of the linear regions of the Heckel plots) differed for the powder and pellet forms suggesting that changing the shape, size, or surface properties of microcrystalline cellulose particles may have affected the compaction properties (such as degree of bonding) of this material.

Maganti and Çelik (17) modified the commonly used percentage axial elastic recovery method in order to take into account the radial expansion, which was later termed

Volumetric Strain Recovery (VSR) by Çelik and Okutgen (23) as follows:

$$VSR\ (\%) = 100 * [(D_e^2 H_e - D_u^2 H_c)/(D_u^2 H_c)] \quad (3)$$

where H_u, H_e, D_u and D_e are the thicknesses (H) and diameters (D) of the compacts on unloading in the die, and after ejection, respectively. It was observed that the compacts of microspheres had higher VSR values than those made from the corresponding powder formulations (17). A large decrease in the mechanical strength of the compacts of the pellets suggested that many of the bonds formed during compaction did not survive the unloading and ejection phases.

As mentioned earlier, microspherical formulations may require only a very small amount of lubricant. Therefore, the amount of, and mixing time with, the lubricant must be considered carefully. The data presented in Table 6 show that the strength of the

compacts of the microspheres was completely lost when the microspheres were lubricated with magnesium stearate at 0.5% (w/w) concentration by blending for as short as 30 seconds in a laboratory scale mixer. This decrease in the mechanical strength of the tablets of the lubricated microspheres could also be predicted from the TWC vs percentage porosity plots (Figure 3) in which the energy involved during the densification of the unlubricated microspheres was significantly higher than that of the lubricated ones. This energy contributed to the strength of the tablets of the unlubricated beads. This finding is further supported by the higher amount of power exerted during the compaction of the unlubricated microspheres when compared to those of the lubricated ones (Figure 4). The power consumption was calculated according to the method of Çelik and Marshall (8). They proposed the following equation to calculate the 'Average Power Consumption' (APC) by dividing the cumulative total work of compaction by the corresponding contact time using the equation:

$$APC = \left(\int_{X=0}^{X_{max}} F.\, dX \right) / t \qquad (4)$$

where F is the applied force; X is the decrease in the distance between the upper and lower punches; $X=0$ and X_{max} are the points where percentage porosity is maximum and minimum, respectively; and t is the time during which the powder has been compressed.

When the TWC values of the Surelease® coated F-II microspheres were compared, it was observed that beads with increasing amounts of coating exhibited relatively lower TWC values at corresponding porosities (Figure 5) or at corresponding pressures (16). Similar correlations were also observed regarding the tensile strength values of their ejected compacts (Table 5). Maganti and Çelik (18) observed that the uncoated pellets required higher applied pressures to produce compacts of the same in-die porosities as the coated pellets. They also reported that the maximum applied pressure required to compact the coated pellets to the pre-determined in-die porosity decreased as the amount of coating on the pellets increased, indicating that the pellets coated with higher amounts of coating were more easily compressed. These workers found that both the VSR values and the

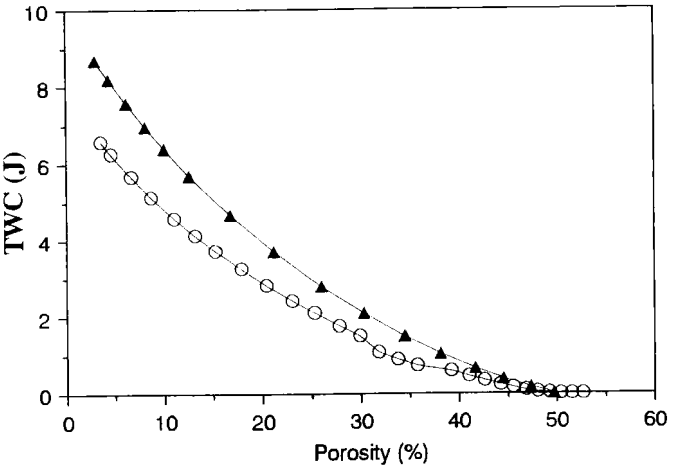

FIGURE 3. Total work of compaction vs porosity plots for the compacts of lubricated (○) and unlubricated (▲) F-I microspheres (uncoated).

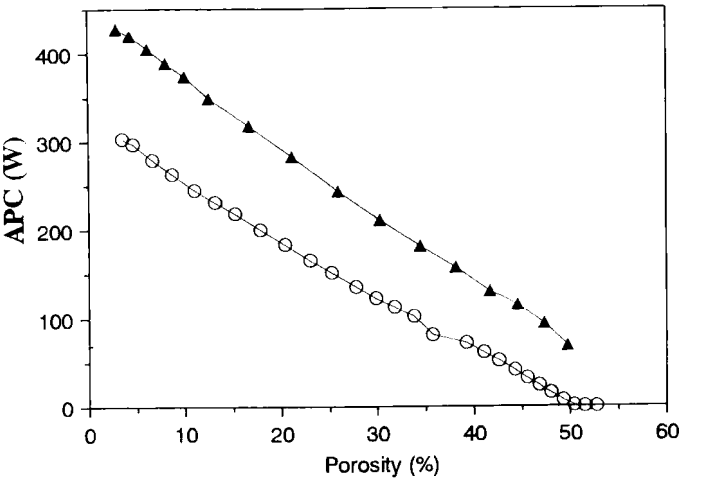

FIGURE 4. Average power consumption vs porosity plots for the compacts of lubricated (○) and unlubricated (▲) F-I microspheres (uncoated).

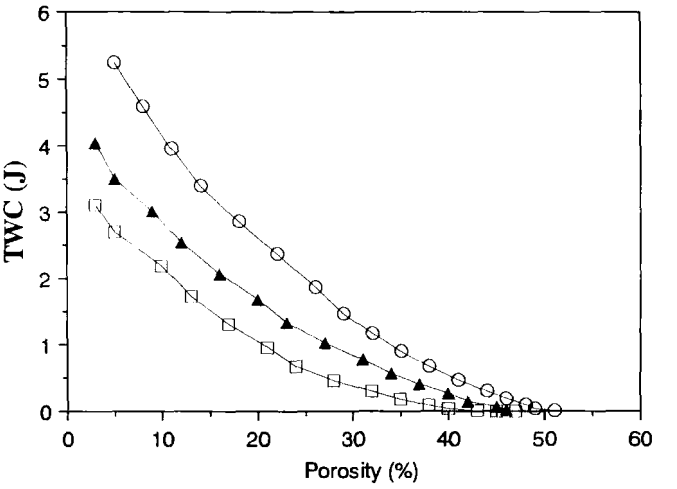

FIGURE 5. Total work of compaction vs porosity plots for the compacts of Surelease® coated F-II microspheres.

Coating levels (w/w): 10% (○) ; 15% (▲) ; and 20% (□)

mechanical strength of the compacts of pellets decreased when the pellets were coated with 10% Surelease®. This was attributed to an increase in the number of bonds between these phases due to the introduction of stronger binder-substrate bonds by Surelease®. However, further increases in the amount of coating (15% and 20%) on the pellets diminished the mechanical strength of the resulting compacts. Although their mechanical strength was relatively higher, the VSR values of these compacts were found to be higher than those of the uncoated pellets. The apparent contrast in the rank order of VSR and mechanical strength values was attributed to the differences in the elastic properties of the uncoated pellets and the film coating.

CONCLUSIONS

When a sustained release formulation containing uncoated or coated microspheres is to be developed in the form of a tablet, several factors must be considered in order to produce tablets with the desired compaction and post-compaction properties.

The selection of external additives is of importance since these additives are expected to prevent the incidence of film cracking in the coated microspheres. Their compatibility with the microspheres in terms of particle size is also very critical since non-uniform size distribution can cause segregation, resulting in many tableting problems such as weight variation, and poor content uniformity. In order to minimize the occurrence of such problems, placebo microspheres, with good 'compaction' and 'cushioning' properties, can be used as diluents if the size of the active microspheres is much larger than that of the external powder additives. Another alternative is to produce beads of smaller sizes. Small size active spheres also improve the content uniformity of low dose drugs. However, the surface area to be coated will increase as the size of the microspheres decreases. Any problems or advantages associated with the increased amount of total coating substrate must also be considered carefully in the multi-unit dosage development.

The size and shape, as well as surface properties, of microspherical particles may differ when compared to their respective powder form. This may also cause a change in their deformation mechanisms. Since the surface area of the spherical particles will be at a minimum as compared to the other shapes, microspherical formulations may require only a very small amount of lubricant. Therefore, the amount of, and mixing time with, the lubricant must also be considered carefully.

It is important that coated microspheres in the formulation must be able to withstand the process of compaction without being damaged. The type and amount of coating agent, size of the spheres, the selection of the external additives, and the rate and magnitude of the applied pressure are the most critical factors to be considered in order to maintain the desired drug release properties of the tablet.

ACKNOWLEDGEMENT

We would like to acknowledge Colorcon Inc. (West Point, PA) and Sandoz Research Institute (East Hanover, NJ) for supporting one of us (L. Maganti) financially, and Glatt Air Techniques (Ramsey, NJ) for providing the rotor-granulator (GPCG).

List of symbols

D_e	compact diameter after ejection
D_u	in-die compact diameter
$\epsilon(\%)$	percentage porosity
F_{lp}	axial force exerted upon the lower punch
F_{up}	axial force exerted by the upper punch
H_e	compact thickness after ejection
H_u	in-die compact thickness on unloading
X	decrease in distance between two punches
X_{lp}	upper punch contribution to the decrease in distance between two punches
X_{up}	upper punch contribution to the decrease in distance between two punches
TWC	total work of compaction
V_c	powder volume on under applied pressure
V_t	the specific solid volume (true volume)
VSR	volumetric strain recovery

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