Estimation of Capping Incidence by Indentation Fracture Tests

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ABSTRACT The purpose of this study was to predict the capping tendencies of pharmaceutical powders by creating indentation fracture on compacts. Three sets of binary mixtures containing different concentrations of each ingredient were used in the study. The binary mixtures were chosen to represent plastic-plastic, plastic-brittle, and brittle-brittle combination of materials. The mixtures were tableted at different pressures and speeds on Prester®, a tablet press simulator. These mixtures were also compacted on the Instron® Universal Testing Machine 4502. Static indentation tests were done on these compacts at different depths until surface cracking and chipping were observed. The extent of surface cracking and chipping was observed from light microscope and scanning electron microscope images. A rank order correlation was observed between lamination susceptibility and the depth at which indentation failure occurred. It was concluded that indentation fracture tests could provide a useful estimate of lamination properties of pharmaceutical powders.

Key Words: Indentation Fracture, Capping.

INTRODUCTION

Lamination or capping of tablets as they emerge from the die or during physical testing is one of the possible mechanical failures in tableting. The problem can be alleviated in certain cases by altering the tableting conditions. Reducing compression pressure and reducing decompression speed, within practical limits, may help in overcoming capping or lamination; however, this is not a universal solution. Increasing the binder or moisture content may be another option. The dose may not allow the increase in binder content above a certain level, and increasing the moisture content may cause stability problems. In most cases,

granulation of the drug substance may be the most viable option.

A few theories have been proposed to understand the causes for capping and lamination. One such theory is that of air being trapped in the tablet under pressure (1, 2). After the upper punch starts receding, the entrapped air tries to escape, thereby causing the tablet to cap. This theory is difficult to accept as a universal explanation for capping or lamination because some formulations cap or laminate even at low press speeds. At low speeds, there is sufficient time for the air to escape during compression. In addition, micronized phenazone compressed in a helium atmosphere has been shown to cap (3). Using helium provides an atmosphere similar to air, with the difference being that the smaller helium atoms escape after compression resulting in little entrapment within the tablet. The inert nature of helium also ensures that there is no adsorption on the solid particles. Mann et al (4) suggested that the capping pressure is related to the amount of air present in the granule bed prior to compression. On removal of this entrapped air, capping was reduced but the formulations still laminated. It was concluded that entrapped air may be responsible for capping but it does not affect lamination. Other theories attribute lamination and capping to the deformation characteristics of materials (2, 5-8). Train (9) proposed that lamination was the result of radial elastic recovery during ejection. The top of the compact recovers while the bottom is still in the die, causing the top layer to laminate. The widely accepted theory for lamination (3, 10) attributes capping to the residual die-wall pressure, which causes internal shear stresses in the tablet. The stresses cause initiation and propagation of cracks, which result in

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lamination or capping. The propagation of cracks could be prevented by plastic relaxation of shear stresses. In other words, materials having sufficient plasticity may not be susceptible to lamination.

The objective of this study was to provide a testing procedure or technique that would predict the tendency of a powder or a mixture to laminate. The technique used to predict lamination or capping of a material should be able to measure its plasticity and relate it to its ability to prevent crack propagation.

One of the techniques used to measure plasticity of materials or compacts is indentation hardness measurement. Indentation hardness measurements have a wide application in the pharmaceutical industry. Work hardening of materials has been studied from indentation hardness measurements (11). Hardness measurement by the impact method (12) has been used to determine the physical integrity of tablets by distinguishing between brittle and ductile failure (13). Tablet bonding has been studied using hardness measurements (14, 15). Indentation hardness measurement has been demonstrated to be a useful tool in predicting the shear modulus of pharmaceutical materials (16); however, it has not been an intention in the pharmaceutical field to use the indentation test as a tool to create and propagate cracks in a compact.

In a typical indentation hardness measurement done in our laboratory, the indenter penetrates into the compact surface to a depth of 0.30 mm. What would happen if the indenter were pushed further into the compact? How deep can the indenter be pushed before the compact fails? When the compact does fail, is there a specific pattern in which the compact surface breaks? Can any information be obtained from such crack patterns? At what indentation depths do these cracks originate?

The urge to investigate indentation hardness measurements beyond the normal depths (0.30 mm) was the result of discontinuities seen in the displacement versus time profiles of ibuprofen and naproxen (17). Visual inspection of compacts after indentation revealed that the edges along the dent were not smooth; cracks were seen on the surface of the compact. Generation and propagation of cracks seem to be common features between indentation fracture tests and lamination or capping during tableting; therefore, the hypothesis for the present

work is that indentation tests can be used to predict lamination or capping tendencies of pharmaceutical materials.

MATERIALS AND METHODS

Three families of binary mixtures were used in the study. The mixtures were chosen to represent brittle-brittle, brittle-plastic, and plastic-plastic combinations. Dicalcium phosphate dihydrate (DCP) (Encompress®) from Mendell (Patterson, NY) and acetaminophen powder USP (APAP) from Mallinckrodt (Paris, KY) were the model brittle materials used in this study. Microcrystalline cellulose (MCC) (Avicel® PH 101) from FMC (Newark, DE) and magnesium stearate NF (MS) from Mallinckrodt (Paris, KY) were the model plastic materials used in the study. The mixture compositions are listed in Tables 1 through 3. These compositions were chosen because some of them capped at all tableting conditions under which they were studied, some capped only at high pressure or speed, and some did not cap at all. The powders were mixed in a 2-quart plexiglass V-blender for 10 minutes (32 rpm, 300 g batch size). For mixtures with no internal lubricant, a 2% wt/vol magnesium stearate suspension in acetone was used to lubricate the die before tableting.

Table 1. Composition of DCP-APAP Mixtures

Mixture	DCP (% wt/wt)	APAP (% wt/wt)
1	50	50
2	55	45
3	60	40
4	65	35
5	70	30
6	75	25
7	80	20
8	85	15

DCP indicates dicalcium phosphate dihydrate; APAP, acetaminophen powder USP.

Table 2. Composition of MCC-APAP Mixtures

Mixture	MCC (% wt/wt)	APAP (% wt/wt)
1	10	90
2	15	85
3	20	80
4	25	75
5	30	70
6	35	65
7	40	60

MCC indicates microcrystalline cellulose; APAP, acetaminophen powder USP.

Table 3. Composition of MCC-MS Mixtures

Mixture	MCC (% wt/wt)	MS (% wt/wt)
1	99	1
2	98	2
3	97	3

MCC indicates microcrystalline cellulose; MS, magnesium stearate NF.

Table 4. Lamination or Capping Incidence at Different Tableting Conditions for Dicalcium Phosphate Dihydrate-Acetaminophen Powder USP (DCP-APAP) Mixtures

Mixture Composition (DCP:APAP)	Tableting Speed (rpm) and Pressure (MPa)			
	40, 150	40, 300	100, 150	100, 300
50:50	-*	+†	+	+
55:45	-	+	+	+
60:40	-	-	+	+
65:35	-	-	+	+
70:30	-	-	+	+
75:25	-	-	+	+
80:20	-	-	+	+
85:15	-	-	-	-

*indicates otherwise

†indicates the occurrence of capping

Table 5. Lamination or Capping Incidence at Different Tableting Conditions for Microcrystalline Cellulose-Acetaminophen Powder USP (MCC-APAP) Mixtures

Mixture Composition (MCC:APAP)	Tableting Speed (rpm) and Pressure (MPa)			
	40, 150	40, 300	100, 150	100, 300
25:75	+*	+	+	+
30:70	+	+	+	+
35:65	-†	-	+	+
40:60	-	-	-	-

*indicates the occurrence of capping

†indicates otherwise

Table 6. Lamination or Capping Incidence at Different Tableting Conditions for Microcrystalline Cellulose-Magnesium Stearate NF (MCC-MS) Mixtures

Mixture Composition (MCC:MS)	Tableting Speed (rpm) and Pressure (MPa)			
	40, 150	40, 300	100, 150	100, 300
99:1	-*	-	-	-
98:2	-	-	-	-
97:3	-	-	-	+†

*indicates otherwise

†indicates the occurrence of capping

Figure 1. Schematic illustration of the IUTM assembly for compact formation.

One portion of the mixtures was tableted on Prester® (East Hanover, NJ) (18) (11 mm flat face tooling, 350 mg, simulated Betapress® waveforms, 40 and 100 rpm, 150 and 300 MPa peak compression pressure); 15-20 tablets were made at each tableting condition.

The other portion of the mixtures was used for the indentation tests. Flat cylindrical compacts were made on the Instron® Universal testing machine 4502 (IUTM)(Canton, MA). A schematic illustration of the IUTM assembly is shown in Figure 1. The die rests on a flat base and is held in position by the die collar. A load cell of 10 kN capacity is mounted on the IUTM. A flat punch, 11 mm in diameter, is attached to the load cell. The load cell monitors the force during the compression cycle. The die used is vertically split, which aids compact removal after compaction. The rate of compression and decompression was 5 mm/min with a 10-second dwell time.

Compacts with minimum porosity were desired. Elastic recovery after decompression increases the porosity of the compact. Also, there is a limitation of 10 kN on the load the crosshead of the IUTM can support in the compression mode. These factors, coupled with poor compressibility of certain mixtures used in the study, resulted in a solid fraction of 78% to 79% being used in all the studies. The compacts were not removed from the die before the indentation tests

were done; consequently, only axial relaxation of the compact was allowed. The indentation tests were done in about 15 minutes (± 5) after the completion of the compression cycle.

Indentation tests were carried out under a quasistatic condition. The IUTM was used with a few modifications from the setting for compact formation. The punch used in this case was the indenter, which has a diameter of 1.76 mm. A 500 N load cell was used for improved sensitivity. The minimum indentation depth was 0.30 mm and the maximum indentation depth was 0.90 mm or until there was chipping on the tablet surface, whichever occurred first. The rate of indentation was 0.05 mm/min. A 10-minute dwell time was employed at the maximum indentation depth.

Scanning electron microscope (SEM) and light microscope (LM) images of the compacts around the indentation were taken to observe surface cracks and chipping, respectively. Compacts made of DCP-APAP mixtures could not be removed from the die; therefore, the indentation depths at which surface cracks begin to appear could not be recorded. However, the indentation depths at which the surface began to chip off have been recorded.

RESULTS

In this study, capping was categorized as a binary event; a mixture was characterized to have a capping tendency when at least 1 of the tablets capped. The tableting conditions under which capping was observed for the different mixtures are shown in Tables 4 through 6.

LM and SEM of compacts with the indentation are shown in Figures 2 through 14. LM can detect tablet failure only when there is chipping of a surface layer. On the other hand, SEMs can detect failure at an earlier stage, when cracks begin to originate. As noted earlier, the DCP-APAP tablets could not be studied under a microscope because they could not be removed from the die successfully.

The minimum indentation depth for all tablets was 0.30 mm. For MCC-APAP mixtures, compacts containing 25% wt/wt MCC chip at 0.30 mm indentation; therefore, its SEM was not taken. For other mixtures, SEMs at various indentation depths were taken. The SEMs shown include the depth at which cracks originate and the more pronounced

cracks at further depths. The depths at which cracks begin to appear and the depths at which the tablet surface chips off are recorded in Tables 7-9. There is a rank order relation between the depth at which cracks begin to originate and incidence of capping.

Figure 2. LM of 25:75 MCC:APAP. The tablet surface chips off at 0.30 mm indentation depth.

Figure 3. LM of 30:70 MCC:APAP. No visible damage is evident at the tablet surface at 0.65 mm indentation depth. Tablet surface chips off at 0.70 indentation depth, which seems to be the cut-off point.

Surface chipping around the indentation

Indentation, with no evidence of chipping

Figure 5. LM of 35:65 MCC:APAP. There is no sign of failure up to 0.80 mm indentation, but the surface chips off at 0.85 mm indentation.

Figure 4. SEM of 30:70 MCC:APAP. There is no visible crack at 0.30 mm; the crack begins to appear at 0.50 mm and is more pronounced at 0.60 mm.

Cracks originate around the indentation at 60 mm

Cracks deepen around the indentation at 0.75 mm

Indentation, with no evidence of chipping

Figure 7. LM of 40:60 MCC:APAP at 0.95 mm indentation depth. There is no visible damage to the surface. Deeper indentation was not done as end effects may affect the test.

Figure 6. SEM of 35:65 MCC:APAP. There is no significant damage to the surface at 0.30 mm indentation depth. Cracks begin to appear at 0.60 mm indentation and are more pronounced at 0.75 mm.

Figure 8. (left) SEM of 40:60 MCC:APAP. There is no significant damage to the tablet surface at 0.30 mm indentation depth. At 0.70 mm indentation depth, surface cracks begin to appear. More pronounced cracks are seen at 0.90 mm indentation depth.

Surface chipping around the indentation at 0.80 mm

Cracks originate around the indentation at 0.70 mm

Indentation, with no evidence of chipping at 0.70 mm

Cracks deepen around the indentation at 0.90 mm

Figure 9. LM of 97:3 MCC:MS. The surface chips off at 0.80 mm indentation depth; there is no sign of cracking on the surface at 0.70 mm indentation.

Cracks originate around the indentation at 0.70 mm

Surface chips off at 0.80 mm indentation

Surface chipping around the indenter at 0.90 mm

Indentation, with no evidence of chipping or cracking

Figure 11. LM of 98:2 MCC:MS. The surface chips off at 0.90 mm indentation depth; there is no sign of cracking on the surface at 0.80 mm indentation.

Figure 10. SEM of 97:3 MCC:MS. There is no crack around the indenter at 0.60 mm indentation depth. Cracking begins at 0.70 mm indentation depth and tablet surface chips off at 0.80 mm indentation depth.

Cracks originate around the indenter at 0.70 mm

Cracks deepen and cause chipping around the indenter at 0.90 mm

Indentation, with no evidence of chipping or cracks

Figure 13. LM of 99:1 MCC:MS. There are no cracks on the surface at the deepest indentation point (0.90 mm) studied.

Table 7. Correlation between Indentation Failure and Capping Incidence, Dicalcium phosphate (DCP):Acetaminophen Powder USP (APAP)

DCP:APAP (% wt/wt)	Indentation Depth (mm) at Which Surface Chips Off	Capping Incidence (as Observed on Prester)
50:50	0.30	+*
55:45	0.30	+
60:40	0.30	capping at high pressure
65:35	0.50	capping at high pressure
70:30	0.50	capping at high pressure
75:25	0.60	capping at high pressure
80:20	0.60	-†
85:15	0.80	-

*indicates capping at all tableting conditions studied

†indicates no incidence of capping in any tableting conditions studied

Table 8. Correlation between Indentation Failure and Capping Incidence, Microcrystalline Cellulose (MCC):Acetaminophen Powder USP (APAP)

MCC:APAP (% wt/wt)	Indentation Depth (mm) at Which Cracks Originate	Indentation Depth (mm) at Which Surface Chips Off	Capping Incidence (as Observed on Prester)
25:75	not done	0.30	+*
30:70	0.50	0.70	+
35:65	0.60	0.85	capping at high speeds
40:60	0.70	not done	-†

*indicates capping at all tableting conditions studied

†indicates no incidence of capping in any tableting conditions studied

Figure 12. SEM of 98:2 MCC:MS. There is no crack around the indenter at 0.60 mm indentation depth. Cracking begins at 0.70 mm indentation depth and tablet surface chips off at 0.90 mm indentation depth.

Table 9. Correlation between Indentation Failure and Capping Incidence, Microcrystalline Cellulose (MCC):Magnesium Stearate (MS)

MCC:MS (% wt/wt)	Indentation Depth (mm) at Which Cracks Originate	Indentation Depth (mm) at Which Surface Chips Off	Capping Incidence (as Observed on Prester)
97:3	not done	0.80	capping at high speed and high pressure
98:2	0.70	0.90	-*
99:1	0.70	no chipping	-

*indicates no incidence of capping in any tableting conditions studied

DISCUSSION

There are 2 different theories proposed in the literature explaining the origin of cracks and their propagation in brittle materials.

According to the "elastic failure model" (19), radial and lateral cracks and permanent impressions can be generated by elastic failure. Plastic deformation is not necessary to explain the indentation damage of elastic, brittle materials; however, for 2 reasons, this model may not truly represent the stress states within the compacts studied here.

The strain rate of the indenter in the elastic failure model was as high as 231 m/s. This is an extremely dynamic event when compared to the strain rate used in the static indentation hardness tests (5 mm/min). Whereas brittle failure may be the primary or only mechanism of deformation at high strain rates, plastic deformation is more likely at lower strain rates.

The elastic failure model was proposed for brittle materials like ceramics; however, most pharmaceutical materials are plastic or viscoelastic. APAP is a brittle material but its plasticity is more than that of ceramic or glass; therefore, a model that explains indentation damage without plastic deformation may not be appropriate for all pharmaceutical materials.

The "elastic-plastic model" (20) explains the entire process in a manner that is more convincing for pharmaceutical materials. The assumptions and theories underlying this model are described here briefly. During the indentation process, it is not possible to visually examine the stress patterns as

Figure 14. SEM of 99:1 MCC:MS. There is no crack around the indenter at 0.70 mm indentation depth. Cracking begins at 0.80 mm indentation depth; the crack is more pronounced at 0.90 mm indentation depth.

they develop within the compact; therefore, the explanation given in this section is the most likely one to describe the indentation event. The following explanation for the origin and propagation of cracks is valid only where Poisson's ratio, ν , is below 0.5. When ν is above 0.5, the test material is highly ductile. For highly ductile materials, tensile components of the principal stresses disappear, thereby precluding the possibility of initiating a brittle crack.

There exist compressive, shear, hydrostatic, and tensile stresses in the compact undergoing indentation. The tensile component of the stress is responsible for the initiation of a brittle crack. Once a crack is initiated, it will tend to propagate in a direction perpendicular to the major tensile stress components (21); therefore, a crack developed beneath the indenter during loading will progress further down axially. This direction is perpendicular to the tensile stresses, which act radially. The progression of cracks sideways is restricted by the compressive components of the principal stresses. The propagation of the lateral cracks during decompression relieves the wall stresses.

Initial loading produces a zone of irreversible plastic deformation about the contact point. At some critical indenter load, a crack suddenly initiates below the contact point. This is called a median vent. It is possible that several median vents could originate at the same time. Increasing the load further by pushing the indenter deeper into the compact causes stable extension of the median vent. The median vents close but they do not heal completely when the indenter unloads. Just before the unloading phase, the compact is under residual tensile stresses, in addition to the compressive stress. This causes cracks to develop sideways and lateral vents to appear. As the indenter unloads, lateral vents continue to extend. The rate of growth of lateral vents depends on the rate of unloading. If the material does not have sufficient plasticity, the lateral vents grow fast enough to reach the tablet surface. This causes chipping on the tablet surface.

The indentation depths at which median vents begin to appear depend on the strength of the material. It is a flaw in the compact induced by deformation by the indenter that causes the development of the

median vents. The extents to which the lateral vents develop and spread are a function of the deformation nature of the material. Plastic materials have the ability to curb the growth of lateral cracks; therefore, materials with higher strength and plasticity have a better chance of preventing the initiation and propagation of cracks. This criterion is the same as that required for prevention of capping or lamination; therefore it is not surprising to see a correlation between the failure of a compact in an indentation test and susceptibility of the same material to cap or laminate in a tablet press.

The critical concentrations of APAP in DCP+APAP and MCC+APAP mixtures at which capping begins to occur may correspond to the percolation threshold of APAP. As explained by the percolation theory (22), at low concentrations of APAP, capping may occur as finite clusters in the infinite clusters of DCP and MCC, respectively. The critical concentration of APAP at which capping is observed in each of these 2 systems of binary mixtures may be the point where APAP may begin to percolate throughout the system. However, percolation theory may not be able to explain the critical capping concentration MS in MCC+MS mixtures. There is no evidence in the literature wherein a material could cross the percolation threshold at a concentration as low as 3%. MS has a low shear strength and is a laminar lubricant; therefore, it may be able to spread throughout the system and interfere with MCC-MCC bonding.

CONCLUSIONS

Static indentation tests that create cracks on the tablet surface at 0.50 mm indentation depth or lower indicate susceptibility of the material to laminate. If there are no cracks up to 0.70 mm indentation depth, there is little risk of capping. If cracks begin to develop between 0.50 and 0.70 mm indentation depth, the material has to be treated with caution. The material may cap under extreme tableting conditions, which may be at either high pressure or high speed.

The susceptibility or tendency of a new material or mixture to cap can be predicted from the SEMs and LM after the indentation tests. This study could be extended beyond binary mixtures with the inclusion of formulations that have been known to cap or laminate. The crack patterns of these formulations

after indentation tests could serve as standards for capping and laminating materials.

When a new chemical entity is to be evaluated, indentation tests could be carried out on the materials at different indentation depths (depending upon the quantity of material available). A visual observation of the surface cracks and their comparison with established standards may provide a useful estimate of the capping or lamination propensity of the new chemical entity.

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