**Evaluation and study on the adhesion of powder onto punch faces during tablet compaction**

A Thesis

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by

James V Thomas

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**Dedications**

To my beautiful daughter, Abrielle Sarah Thomas

AND

To my loving wife, Nissy Thomas

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## Abstract

**Evaluation and study on the adhesion of powder onto punch faces during tablet compaction**

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Sticking during tablet compaction is an issue that is commonly experienced during tablet manufacturing operations. The term 'Sticking' refers to a phenomenon that results in the adherence of materials onto the punch faces and die wall even after the tooling has left contact with the tablet. The occurrence of sticking during large scale tablet manufacture can produce defective tablets, halt manufacturing operations, and can be very costly. Currently, the mechanisms by which this phenomenon occurs is not clearly understood. However, numerous factors dealing with powder characteristics and instrumentation parameters are reported in literature to affect sticking. Therefore, sticking is a complex multifaceted phenomenon in which multiple factors can simultaneously contribute to the issue.

The aim of the work conducted in this thesis is to study the process of sticking. Ibuprofen was chosen as a model compound in this work as it is widely known to cause this issue. In addition, evaluation of the sticking propensity of Acetylsalicylic Acid (ASA) and of a confidential compound is also presented. A customized punch with a removable punch tip was used to quantify the mass of adhered material on the punch tip during tablet compaction. The effect of particle size on sticking with ibuprofen was evaluated. Formulations containing 30% ibuprofen (AS-IS) and 30% micronized ibuprofen with 0.5% magnesium stearate and 69.5% microcrystalline cellulose were tested.

Results with micronized ibuprofen showed a marked increase in sticking compared to non-micronized ibuprofen. Significant triboelectric charging was observed with micronized

ibuprofen. Analysis of the adhered material on the punch tip by SEM reveals the presence of both heavily deformed particles and minimally deformed fragments that are on the size order of well below 50µm. Triboelectric charging was also demonstrated to occur upon compaction with ASA. Results suggest that that particle size, static charging and fragmentation may play important roles in the mechanism of sticking in ibuprofen formulations. Furthermore, it is observed that sticking in ibuprofen can be influenced by cleaning of punch faces by solvents and by capping defects in tablets.

# CHAPTER 1: INTRODUCTION

## 1.1: Motivation

Sticking during tablet compaction is a phenomenon that results in the adherence of material onto the punch faces and die wall even after the tooling has left contact with the tablet. The initial adherence of material onto the punch faces typically appear as a light dusting of fine powder, or as a fine film coating, or even as islands of adhered material. The quantity of adhered material on the punch faces can accumulate with successive compression cycles. The occurrence of this issue in a tablet formulation not only decreases the image quality of the tablet but can also cascade into a host of other issues such as weight variations in tablet, wasted material, increase in production delays and more importantly can become a very expensive issue.

A tablet formulation, also referred to as a compression blend typically consists of the active pharmaceutical ingredient (API) which is the active drug molecule and other components such as diluents, binders, lubricants and disintegrants. In general, this makes the formulation a multi-component and homogeneously distributed blend designed to produce a quality tablet and provide optimum performance in the human body. A tablet formulation is typically designed during Research and Development (R&D) activities. Sticking of formulations are not always evident during small scale operations in R&D. Often times, the existence of this issue in a formulation may only be discovered during large scale manufacturing at which point there is little that can be done regarding the composition of the formulation to mitigate the issue. Therefore, sticking can bring large scale manufacturing campaigns to a halt. Currently, sticking is not well understood and there is a great unmet need to develop techniques to properly select the best powder attributes that would minimize or eliminate this issue.

Sticking is a multi-faceted phenomenon because there are numerous factors that can simultaneously contribute to the issue. Sticking has been shown to be affected by several factors including compression speed, compression force, lubricant concentration, powder processing conditions, punch surface chemistry, punch surface roughness, punch geometry, moisture and temperature. Currently, there is truly a lack of the fundamental understanding of the mechanisms that lead to sticking.

Materials that exhibit sticking under compaction can have a wide range of behaviors. For example: Sticking in Tartaric acid and Malic acid can be alleviated by increasing the concentration of Magnesium Stearate (MgSt) in formulation however sticking in Mefenamic acid and Ibuprofen worsens with an increase in MgSt content. MgSt is one of the top excipients that is most used in tablet formulations as a lubricant, yet its effect on sticking is not clearly understood. Clearly, there must be various mechanisms by which sticking occurs.

There are several reports in literature on the topic of sticking. However, the mechanisms by which this phenomenon occurs is clearly not understood. By scoping through the vast amount of literature on this topic, one can certainly find clues or factors that are suspect in their involvement with sticking. And these factors can be used as a starting point to formulate well thought out controlled experiments in order to reveal the mechanisms of sticking. Doing so will allow scientists to effectively identify compounds and formulations that would minimize or eliminate sticking. Some of these interesting factors include: electrostatic forces, surface chemistry of crystals and punch faces, fragmentation of powders, formation of liquid capillary bridges, amorphization of powders during compaction, particle size, effect of temperature and low melting compounds, density distribution of compacts, role of lubricants and excipients.

### 1.2: Aims

The overarching goal of this thesis is to provide experimental data and observations, and to study and discuss the mechanism of sticking. First, a literature review on the topic of sticking is presented. Secondly, the studies conducted in this work involving the sticking of various materials is also discussed. Ibuprofen was chosen as a model compound in this work because it is well known to cause sticking and there also exists a vast amount of literature on the study of this material. In addition, studies on the sticking of Acetylsalicylic Acid (ASA) and of a confidential compound are also presented.

### 1.3: Specific Goals

The following is a list of specific goals attempted in the experimental portion of this work.

1. Examine the surface of tablets and punch tips, and document the events that occur at the very onset of sticking and also during its progression.
2. Study the influence of particle size on sticking in Ibuprofen formulations.
3. Evaluate the effect of lubricant type in formulations containing compound X.

## CHAPTER 2: BACKGROUND & LITERATURE REVIEW

Tablets are one of the most popular dosage forms used for drug delivery due to several reasons including the simplicity in manufacturing and competitive production costs. However the manufacturing of tablets is often met with various challenges related to the instrumentation used and the compacting material. Tabletting issues such as picking, sticking, capping and lamination can occur during the compaction process. Tabletting issues can arise due to several factors involving the formulation blend and compaction parameters but often times it's a combination of these factors that contribute to the failure. In some cases, such failure may not be evident during small scale tablet manufacturing and is only realized during large manufacturing campaigns which can result in costly delays, logistical issues with regulatory compliance and stoppage to product delivery. Therefore, this warrants an in-depth understanding of the mechanism of tablet failure in the microstructure of the compact. More importantly, there is a great need for techniques that can assess the propensity of a tablet formulation to undergo such failure prior to large scale manufacturing.

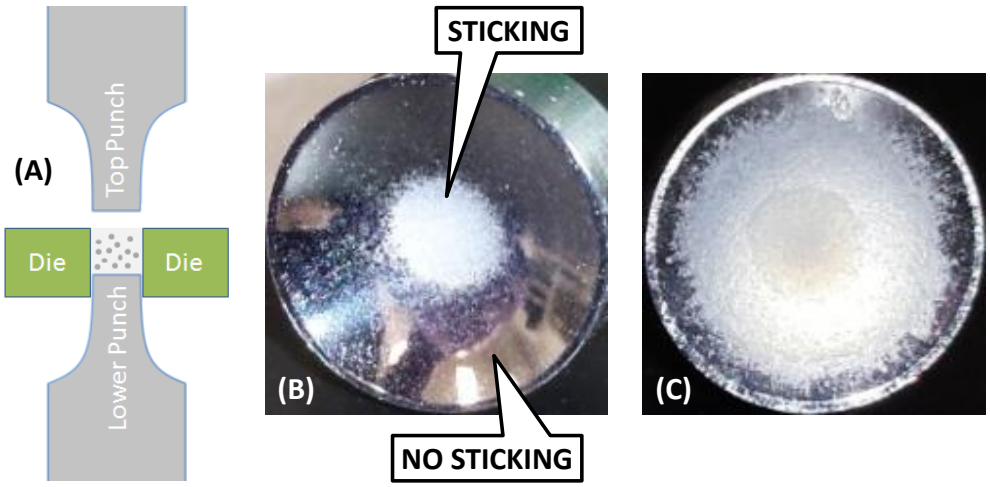



*Figure 1 – (A) Showing a cross-section schematic of tablet compression. (B) Showing the appearance of a punch face affected by sticking after a few compression cycles. (C) Showing the appearance of the punch face after several compression cycles.*

A basic schematic of tablet compression is shown in Figure 1A. During the tablet compression process, the formulation blend is first filled flush into the die. In a typical single ended compaction process, the top punch compresses the powder while the bottom punch remains stationary in the die. After the compression cycle, the top punch retracts and the tablet is ejected upwards by the lower punch. Sticking during tablet compaction is a phenomenon that results in the adherence of material onto the punch faces and die wall even after the tooling has left contact with the tablet. In this process, the material that sticks to the tooling, which should otherwise remain adhered to the tablet, can accumulate on the punch tip and lead to various tabletting issues. An example of sticking on the punch face is shown in Figure 1B and its progression or accumulation of adhered material is shown in Figure 1C.

The initial adherence of material onto the punch faces can appear as a light dusting of fine powder or as a fine film coating. The quantity of adhered material on the punch faces can accumulate with successive compression cycles. It is possible for chunks of accumulated material to come loose off the punch faces during compaction process and again continue to re-accumulate. The accumulation of material on the punch faces will constantly change the geometric profile of the compressing surface which can subsequently change the geometry of the final tablet. Sticking in tablet compaction is a complex phenomenon that can be contributed by one or many of several factors. Some factors are observed to correlate with the occurrence of sticking while others are observed to have a direct impact. Several techniques are also reported in literature that attempt to either predict, detect, quantify or somehow correlate with sticking.

### 2.1: Scrapper force measurements

The measurement of scrapper force (SCR) is reported by many authors in literature as a factor that is somehow related to sticking (2,4,24,26,27,39,55,56). This type of measurement is

also referred to as sweep-off or take-off force and is the force required to push the tablet off the bottom punch face after ejection. The measurement of scrapper force is not an accurate measurement of the shear force between the tablet and the bottom punch face. If the punch face is not absolutely flat surface then the punch geometry would influence the measured scrapper force as shown schematically in Figure 2A. Compressed material can partially extrude into the tolerance cavity between the punch and the die. If the extruded lip of material still exists after ejection, then the lip will have to fracture in order to push the tablet off the punch face, see Figure 2B. The force required to fracture the lip can contribute to the measured scrape off force. Moreover, the speed of the die table and the mass of the tablet would have to be considered in order to account for the momentum for the tablet as it hits the scrapper bar.

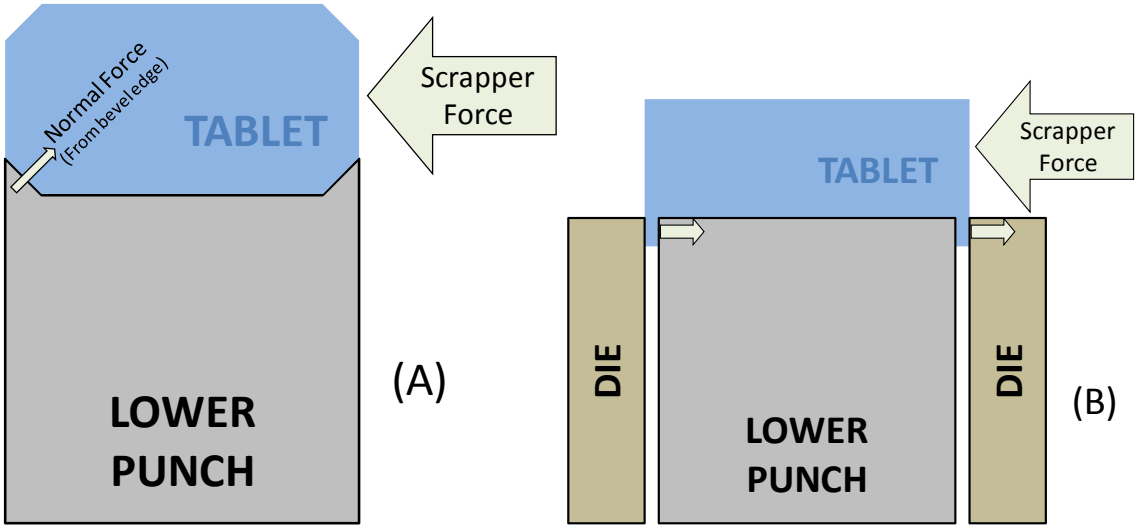



*Figure 2 – Schematic drawings illustrating factors that can affect scrapper force measurements. (A) The bevel edge of the punch tip contributes to the scrapper force measurement. (B) Compressed material can be partially extruded into the tolerance space between the punch and the die. Extruded material will fracture as tablet is pushed off the punch face. The force required to cause this fracture will contribute to the scrapper force measurement.*

Although the scrapper force is related to the force of adhesion between the bottom punch and the tablet, this measurement does not necessarily indicate or quantify sticking. Various parameters can influence the force of adhesion between the tablet and the punch face which can

be detected by scrapper force measurements. In contrast, increasing adhesion forces have been shown to not result in sticking in sorbitol formulations (21). Both positive correlations and the lack thereof between SCR and sticking have been reported in literature. Danjo et al (2) studied the effects of moisture on sticking by measuring the scrapper force. In their study, granules containing Lactose and PVP K30 were dried to various moisture levels and compressed at different pressures. Their results showed that SCR increases as the moisture content in the granules increases to approximately 3% (w/w). Scrapper force is reported to decreases at moisture levels higher than 3%. SCR is also reported to increase with compression pressure at all tested moisture content levels (up to 6%).

Tablet surface roughness (TSR) measurements were also reported to correlate with SCR. Sticking typically results in a rough surface texture of the tablet which would otherwise appear smooth and reflective. Sticking in some formulations can result in a gradual increase in TSR while others may show variations in TSR. Therefore the measurement of surface roughness offer some reliability in at least detecting the presence of sticking and in some cases can be used to qualitatively measure the intensity of sticking (20). The results presented by Danjo et al (2) show a positive correlation between SCR and sticking.

Kakimi et al. (4) also reports positive correlation between SCR and sticking in granulated blends composed of n-Butyl p-hydroxybenzoate, lactose, aerosil and Hydroxypropylcellulose. The authors reported that SCR increased as compression velocity and binder concentration increased. SCR was also reported to decrease with increasing compression pressure. Tablet surface roughness (TSR) measurements were also reported to correlate with SCR. The authors state that the SCR and TSR measurements agreed with visual observations of sticking.

Saniocki et al (56) demonstrated that take-off forces do not correlate with the phenomenon of sticking in Ibuprofen formulations. The authors used 10mm flat faced punches to make tablets on a rotary press. A force feeder was used to fill the die due to the poor flow of the ibuprofen blends tested. The blends consisted of either Ludipress or Microcelac as binding agents and magnesium stearate as lubricant. Ludipress is a combination of lactose and Polyvinylpyrrolidone (PVP) while Microcelac is a combination of lactose and microcrystalline cellulose (MCC). Blends consisting of 50%, 70% and 90% ibuprofen were tested in their study. Sticking was quantified after producing 25 tablets of 300mg quantity compacted to a break strength of approximately 0.85Mpa.

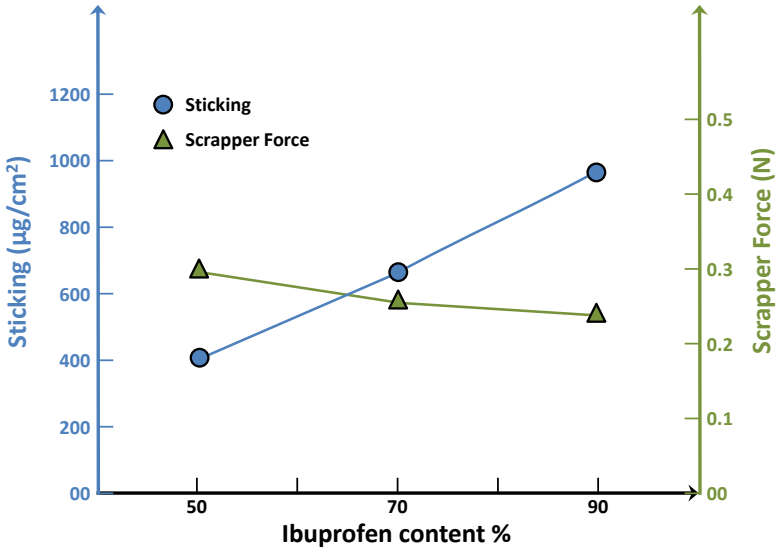



*Figure 3 – Schematic representation of the results reported by Saniocki et al (56). Showing the measurement of adhered weight on punch tip and scrapper force as a function of ibuprofen content.*

The intensity of sticking on the lower punch face was quantified by High Performance Liquid Chromatography (HPLC) and UV-Visible spectroscopy. In this technique, the material adhered to the punch tip is removed and dissolved in a solvent (methanol in this case). The solution is then passed through a chromatography column in which the various dissolved

components elute at different rates. Thus the eluting components including the analyte (ibuprofen in this case) is separated in time and passed through a UV-Visible light spectrophotometer. The magnitude of absorbance of the analyte at a specific wavelength is used to quantify the amount of analyte in the test solution. The authors state that prior experiments were conducted to ensure that the quantification of adhered Ibuprofen by HPLC was representative of the weight of the material adhered to the punch tip.

The flow properties of the ibuprofen blends were tested by a funnel-flow flowability tester. The powder flow of the tested blends are reported to worsen as the concentration of ibuprofen increases. The authors also report that sticking increases with the concentration of ibuprofen in blend and decreases with increasing compression force. However, the scrape-off forces measured did not increase with increasing ibuprofen content. A schematic representation of the results produced by Saniocki et al is shown in Figure 3. Interestingly, the authors note that results from other studies conducted showed sticking to occur only in center of the punch surfaces for formulation containing less than 50% ibuprofen. In addition they state that blends with 50% ibuprofen or greater showed complete layering of punch surfaces. The results presented by Saniocki et al clearly indicates that scrape-off force measurements are not reliable for the purpose of assessing sticking. A similar outcome regarding the lack of correlation between scrape-off force and sticking is reported by Simmons and Gierer (34). Throughout reported literature, there is much discrepancy in the use of scrape-off force measurements to assess sticking such that this technique is rather best avoided for this purpose.

### 2.2: Atomic Force Microscopy

The cohesion of particles and their relation to sticking have been studied by many authors using various microscopic force measurement techniques. A popular instrument for this purpose

is the Atomic Force Microscope (AFM) (1,23,25,35). In this technique, typically the AFM probe is either coated with a substrate or a particle is directly attached to the tip. The coating of the tip is typically done to mimic the metal on the surface of the punch. Several pharmaceutical materials have been used to functionalize AFM tip. Such materials include various lubricants such as MgSt, binders such as MCC and particles of various pharmaceutical drugs.

Bunker et al (1) investigated the adhesion interaction of lactose particles (mounted on AFM probes) on punch faces exhibiting various surface properties. Their study demonstrates that the increase in punch tip surface roughness correlates with the increase in measured adhesion attributed by secondary bonding forces. The authors measured the relative force of adhesion between a lactose particle and two punch faces differing only on surface roughness; Chromium Nitride (CN) and Chromium Nitride + (CN+). The CN punch face was not polished and exhibited a surface roughness of approximately 45nm (RMS) and the polished CN+ punch face exhibited a surface roughness of approximately 35nm (RMS). Surface roughness was determined using AFM. The same lactose particle attached to the AFM probe was used to measure adhesion on both punch faces in a 10x10μm area consisting of 2500 measurements. The force distribution curves generated during the experiment showed very good agreement with a Gaussian distribution. The mean adhesion forces for the CN and CN+ punch faces were 19.2nN and 14.2nN respectively.

Bunker et al also demonstrates that different punch surface materials (chromium nitride, diamond-like carbon, hard chromium) with varying hydrophobic/hydrophilic character exhibit different adhesion behaviors at varying levels of relative humidity (RH). In this case, the same particle probe was used to test the effect of RH on all punch types. An interesting result from their experiments is that lactose shows sensitivity to humidity which affects its adhesion to metal surfaces, see Figure 4. Adhesion force measurements between lactose and the different punch faces were made by cycling the relative humidity (RH): from 10% to 30% to 60% to 30% to 10%.

With the chromium nitride punch face, a sharp increase in adhesion force is observed between the range of 30% to 60% RH. The authors attribute this phenomenon to the sudden formation of capillary bridges. The effect is reversible as evidenced by the decrease in adhesion when the RH is brought back down to 10%. Both hard chromium and diamond like carbon show higher adhesion forces. The authors suggest that capillary forces may be present even at low RH. The authors also point out that the increase in adhesion with the diamond like carbon punch face appears to be irreversible within the 30 minute equilibration time allowed at each RH step. The results presented by Bunker et al (1) are interesting because the moisture sorption isotherm for lactose shows poor hygroscopicity with only about 0.5% moisture pickup at 60% RH (17). Nevertheless, their data provides evidence that sticking can be affected by the formation of liquid bridges.

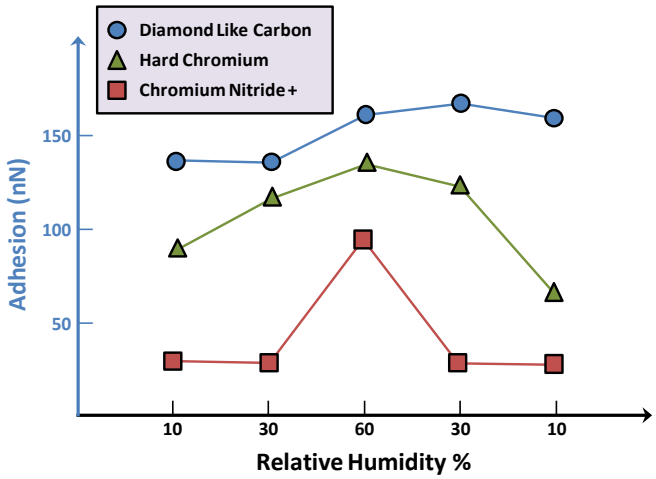



*Figure 4 – Schematic representation of the results reported by Bunker et al (1). Showing the adhesion force measurements of lactose on various punch faces as a function of relative humidity.*

Wang et al (23) also conducted AFM studies on the adhesion forces between the surfaces of iron and 3 profen molecules: ketoprofen, ibuprofen, flurbiprofen. In their work, silicon nitride AFM tips were sputter coated with 20nm thick iron layer. Flat surfaces of the profen compounds were made by melting compound on glass cover slips and recrystallizing by seeding them with crystals. The authors hypothesized that Molecular Modeling would help predict adhesion

behavior. Intramolecular interaction energies between profen molecules and metal surfaces were calculated using molecular modeling software, Cerius2. The interaction energies of the profen molecules were calculated at 8 different orientations against a simulated crystal surface of iron. Their results showed that the calculated profen-iron interaction energy ranked highest for Ketoprofen, lower for Ibuprofen, and lowest for Furbiprofen. The adhesion forces between profen molecules and iron as measured by AFM is also reported to follow the same trend. Microscopic force measurement techniques and crystal surface energetics can certainly be useful in studying adhesion forces, however the problem of sticking is a multi-faceted one. For instance, sticking can be influenced by poor powder flow, the interaction between different components in a compression blend, tooling geometry, particle size, moisture and many more.

Lubricants are generally thought to alleviate sticking issues and the most popular lubricant used in tablet formulations is magnesium stearate (MgSt). Therefore it is important to study the mechanism by which this material affects sticking. AFM studies conducted by Weber et al (25) showed that MgSt adheres to steel more strongly than to Microcrystalline Cellulose (MCC) or to itself. The authors suggested that the increased adhesion of MgSt to steel is responsible for its lubrication function and thus the prevention of sticking of other excipients. However, the mechanism by which MgSt affects sticking is not clear. For example, as MgSt concentration increases, lactose formulations show less sticking (20) but Ibuprofen formulations show increased sticking (6,10).

Typically with formulations known to exhibit sticking, the major component that makes up the bulk of the material adhered to the punch tip is the active drug. Neilly et al (8) investigated sticking of a formulation containing MCC, colloidal silicon dioxide, sodium croscarmellose, MgSt and a confidential drug. Both the tablet and punch faces were examined using a Scanning Electron Microscope (SEM) and Energy Dispersive Spectroscopy (EDS). Their results showed that the major

component adhering to the punch face is the confidential drug. A low level of colloidal silicon dioxide was detected on the punch face while levels of MCC and MgSt were not detected. Their data indicates that MCC and MgSt do not make up any significant fraction of the composition of material adhered to the punch tip.

AFM studies on sticking inherently have its own limitations. For example, in the particle probe technique, the geometry of the particle attached to the probe is not controlled and can affect adhesion force measurements. The electrostatic interactions between the particle and substrate may be difficult to control. The scanning image area with AFM is small and may not provide adhesion force data that is representative of the entire punch face. In addition, AFM techniques do not consider the deformation of particles and the changes in contact area which also affects sticking. Sticking by large is a phenomenon manifested by several variables and AFM techniques can only study a small part of this problem.

### 2.3: Punch surface

Sticking is often shown to be affected by the surface attributes of punch faces. Factors such as punch surface chemistry and surface roughness are often reported in literature to affect sticking. The punch surface chemistry can exhibit various attributes related to sticking such as hydrophobicity (1) and molecular interactions with formulation components (23). The surface roughness of the punch face has also been shown to affect sticking.

Roberts et al (9) studied the effect of punch surface roughness (SR) and compaction force on the sticking behavior of ibuprofen-lactose formulations. The authors tested with three flat faced punches: a chromium-coated punch (low-SR), a new non-coated punch (medium-SR) and an old non-coated punch (high-SR). Sticking was measured by quantifying the amount of

Ibuprofen adhered to the punch tip by liquid chromatography. The results from the study are shown in Figure 5. The authors report that as compression force increases, the new non-coated punch (medium-SR) showed an increase in sticking while the chromium coated punch (low-SR) showed a decrease in sticking. However, the old non-coated punch (high-SR) showed an overall low level of sticking and was not sensitive to compression force. All punches tested are reported to show an increase in sticking as the concentration of ibuprofen in formulation increased. The authors suggest that the enhanced sticking of the chromium coated (low-SR) punch over the new non-coated (medium-SR) punch may be due to the effect of static charging between particles and the difference in punch face material. Although triboelectric charging can contribute to sticking, other factors may also need to be considered. For example, the differences in punch surface chemistry, roughness and hydrophobicity can affect its interaction with particles.

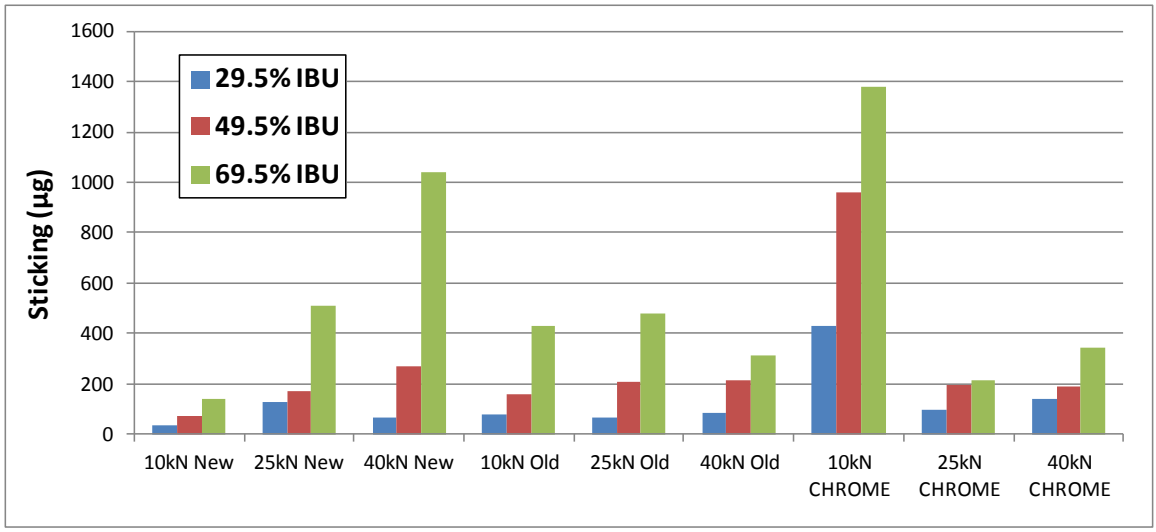



*Figure 5 – Schematic representation of results reported by Roberts et al (9). Showing the effect of three types of punches, ibuprofen content and compression force on sticking.*

The un-coated punches used in the study are reported to not exhibit electrostatic interaction between powder and punch. The authors suggest that the low level of sticking observed using the old punches maybe due to the surface imperfections that leads to reduced attractive forces between the tablet and the punch. However this explanation is not sufficient for

why the old punch exhibited a relatively low level of sticking. Old punches typically exhibit corrosion on the punch surface that can be attributed to various reasons. For example, corrosion of punches have been demonstrated to occur with the use of materials containing hydrochloride salts (85). Currently it is not well understood if corrosion plays a part in sticking. The increase in surface roughness and surface asperities have been suggested to increase the force of adhesion by some authors while others claim the opposite. Bunker et al (1) conducted AFM studies and demonstrated that an increase in punch surface roughness increased adhesion of lactose particles and suggested that this was due to the increase in surface asperities that effectively increases the number of surface contacts and thus contact area.

In contrast, Lam and Newton (51) studied the adhesion of lactose and starch on steel surfaces and reported that the asperities on the surface of large particles due to the presence of fine particles on their surfaces reduces to force of adhesion. The authors suggested that fine particles on the surface of large particles serve as asperities that separate the body of the large particle from the steel surface thus reducing that contribution of van der walls forces. Similar results were presented by Otsuka et al (79) where the addition of sub-micron sized silicic particles on starch significantly reduced its adhesive force onto a glass substrate. A similar train of thought may be applied to the asperities on the punch face which effectively separates the particle from the body of the punch thus reducing van der walls interactions. Definitely, punch surface roughness affects sticking and is demonstrated by many researchers. However, exactly how surface roughness affects sticking is not well understood. Perhaps one would need to consider both the size and spatial distribution of the punch face asperities and also the size of the particles and their asperities.

Schumann and Searle (62) reports that un-coated and chromium coated punches showed similar and considerable sticking and that the chromium coating of punch tips did not offer any

significant advantage in overcoming sticking. The authors investigated the effect of various punch surfaces and punch surface conditioning on granulated blends of a confidential drug. Tablets were compressed using flat faced punches (with lettering and bisect line) for about 10 minutes on a 16 station rotary tablet press at a rate of 40000 tablets per hour. Sticking was measured qualitatively by using a simple ranking system based on visual observations. In their study, high compression forces were used initially which was gradually reduced to achieve a target tablet hardness. Of the three punch surfaces tested: un-coated, chromium coated and Chromium Nitride Ion Bombarded (CNIB); the CNIB punch showed a significant reduction in sticking. SEM analyses revealed that the chromium coated punch exhibited a smooth surface, the un-coated punch exhibited pitted regions on the order of 1-2µm in diameter and the CNIB punch exhibited several evenly distributed pitted regions on the order of 10-50µm in diameter. The authors suggested that the increase in sticking of the smooth chromium coated punch may be due to suction generated at the tablet-punch interface as the punch is removed away from the tablet and that the pitted regions of the CNIB punch may serve as regions that break the suction causing less sticking.

This explanation is highly questionable because it indirectly suggests that suction is the mechanism by which sticking occurs on the un-coated and chromium coated punches. At a rate of 40000 tablets per hour with 16 stations, the die table will complete one revolution in approximately 1.44 seconds. Assuming that about 35% of this time is spent in just the compression-ejection process, then each tablet is produced in approximately 0.5 sec. Suction may result if the upper punch was retracting so fast that a vacuum is pulled in the die. However, with a compression cycle lasting approximately for 0.5 sec, any type of suction would be improbable. Moreover, air is continually evacuating from the powder bed as the upper punch plunges into the die. At maximum compression, there would exist compressed air in the compact that would

continue to evacuate. Suction at the punch-tablet interface would again be improbable under these conditions.

### 2.4: Tablet surface

Another popular technique used to assess sticking is by measuring the tablet surface roughness. This is because the area on the tablet face affected by sticking would exhibit higher surface roughness compared to regions that are not affected. Toyoshima et al (20) used tablet surface roughness measurements to study tablet sticking on a set of formulations containing lactose and another set containing a confidential drug. The effect of lubricant content, mixing times and compaction pressure on surface roughness were investigated. Roughness measurements where made with a surface analyzer (Surfcom 700B). Tablets were compacted using a concave punch on a single punch machine at a rate for 15 tablets per minute for up to a maximum of 2000 tablets. The surface roughness of the tablets were measured intermittently throughout the study. The authors plotted the measured surface roughness values against the number of compression cycles as shown in Figure 6 in order to generate a regression line. The authors used the slope of the regression line as a parameter to evaluate sticking tendency. This 'sticking parameter' is considered as a measure of the intensity of sticking for a given formulation. Correlation coefficients of regression lines were either close to or above 0.9 in all experiments.

Their results for the lactose formulations show that the log of the sticking parameter decreases linearly as lubricant content increases as shown in Figure 6. The slope of the linear relationship was comparable for the various lactose formulations except for the manually hand-blended formulation which showed variable results. Their results also show that the sticking parameter decreases with increasing compression pressure. For formulations mixed using a blender, the change in blending time from 10 to 30 minutes showed little effect on the sticking

parameter. The sticking parameter for lactose formulations are also reported to show a deviation from linearity and plateaus beyond a certain concentration of MgSt. The authors state that the deviation of data points from the linear trend indicates a critical concentration of MgSt in the formulation related to sticking.

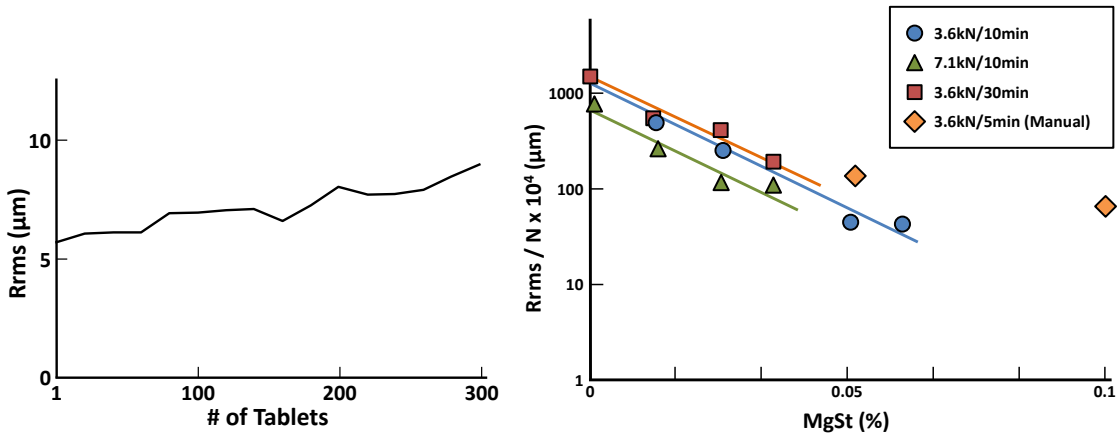



*Figure 6 – Schematic representation of the results reported by Toyoshima et al (20). Left: plot showing the change in tablet surface roughness vs. tablet number. The slope of a regression line of the curve is termed the sticking parameter. Right: plot showing change in sticking parameter vs. lubricant (magnesium stearate) content for lactose formulations at varying blending times and compaction forces.*

The formulations containing confidential drug are also reported to show same trends in that the sticking parameter decreases with increasing compression force and lubricant content. The data presented by Toyoshima et al (20) demonstrates that tablet surface roughness can be used to assess the sticking propensity of formulations. However, this method may only work if the sticking process is gradual in which there is a slow formation of a film on the punch face. It is important to point out that tablet surface roughness will not continue to increase infinitely with the progression of sticking. If sticking occurred in a cyclic manner such that large chunks of material are removed from the tablet face or material from the punch face is removed by the tablet then surface roughness measurements may not properly assess sticking propensity. Toyoshima et al (20) states that there is a critical concentration of MgSt related to sticking. It is

important to note that increasing the concentration of MgSt may reduce sticking but can also reduce the inter-particle cohesion in the compact.

### 2.5: Punch force measurements

A popular category of methods cited in literature deals with the measurement of punch forces to understand sticking. This includes the measurement of forces required to pull the top or bottom punch off of the tablet surface, compression or ejection forces and slipping force which is the force required to rotate the punch off the tablet face as the tablet that remains stationary in the die.

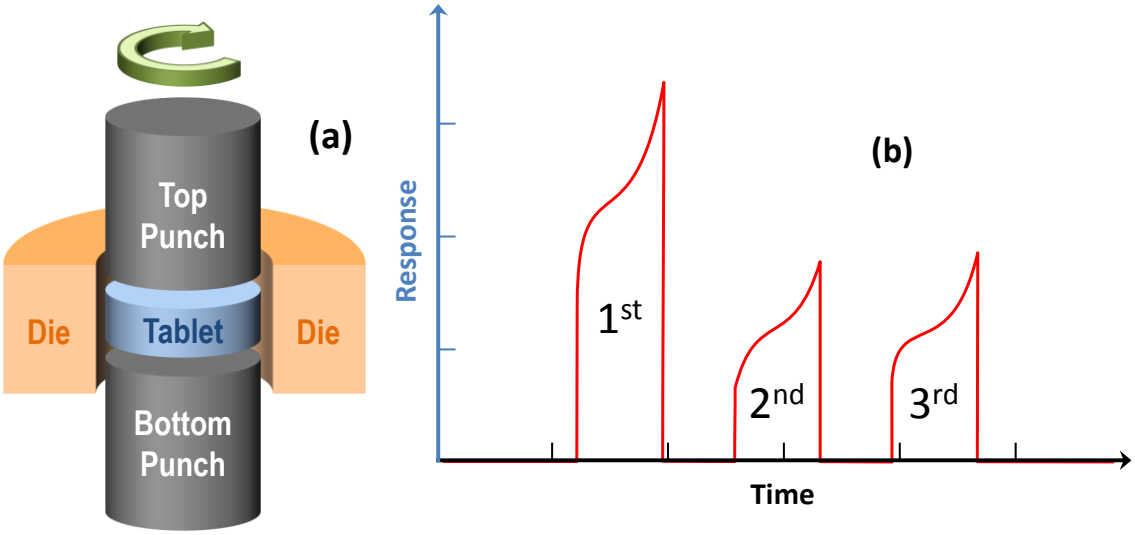



*Figure 7 – (a) A simplified schematic illustrating the technique of slipping force measurement described by Shunichi and Koichi (18). (b) Schematic representation of the slipping force measurements recorded by an oscilloscope.*

Shunichi et al (7,18,19) describes the use of an apparatus and a specialized punch-split-die assembly capable of measuring the slipping force. In this technique, the force required to rotate the top punch on the tablet surface is termed the 'Slipping Force'. The measurement is conducted at the end of the compaction process while the top punch remains in contact with the tablet in the die. The upper punch is rotated on the tablet surface as the tablet remains fixed in

the die, see illustration in Figure 7a. An external normal force is not applied to the top punch during the slipping force measurement. The upper and lower punches were also instrumented with strain gauges to measure vertical forces. Once a tablet is formed, slipping force measurements are conducted in triplicate. The authors proposed that if sticking had not occurred, then there would be no variation in the slipping force between the three measurements. However in the presence of sticking, there would exist a measurable variation in the slipping force as illustrated in Figure 7b.

The authors evaluated several materials and proposed a generalized set of criteria that would indicate a high probability of sticking. The authors concluded that when sticking is evident, the compression force on the upper punch and ejection force of the lower punch are generally high. The authors also conclude that when sticking is evident, the force transmitted to the lower punch during compression would be significantly lower relative to the force applied by the upper punch and that the slipping force measurements would exhibit large variations. Thus, the larger the variation is the larger the magnitude of sticking. The slipping force measurement cannot be a reliable technique to indicate or quantify sticking. For example, it is possible to have a situation where tablets made from two different formulations to exhibit two different magnitudes of adhesive force to the punch face. And it is also possible that when the punches leave contact from the tablet after the compression cycle that sticking never occurs in either formulation. An example of such a material is Sorbitol. Sorbitol formulations can exhibit high adhesion forces at the tablet-punch interface and yet show absolutely no sticking (21). The variation in adhesive forces may be interpreted from the slipping force measurements however this does not necessarily indicate or quantify sticking. A major discrepancy in literature involving the research of sticking is in fact the incorrect use of the term ‘Sticking’. The term ‘Sticking’ in tablet compaction does not mean the adhesion of tablets to the punch face. ‘Sticking’ is a term used to describe a specific type of

tabletting issue in which material from the tablet face is actually removed and remains adhered to the punch faces even after the tablet has terminated any physical contact with the punch faces.

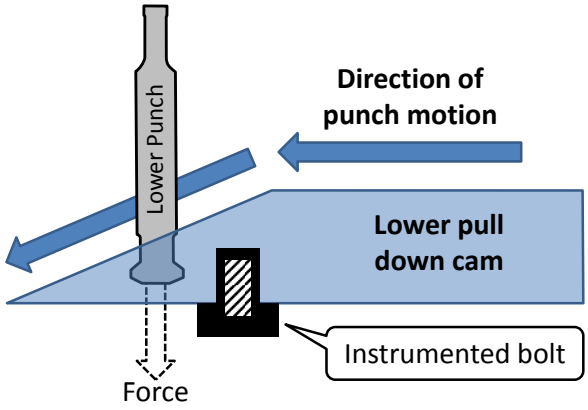



*Figure 8 – Schematic illustration of the instrumented lower pull down cam reported by Goodhart et al (3). An instrumented bolt fastened to the lower cam measures the force required to the pull the lower punch down as it travels the guide track of the cam.*

Goodhart et al (3) describes the development of a system capable of measuring forces experienced by the lower punch in the die as it is pulled down by the lower cam on the tablet press, see Figure 8. This was achieved by fitting a strain gauge into a bolt that is used to hold the lower punch pull-down cam in place. Granulated formulations containing mannitol with various types of lubricants (magnesium, calcium and zinc stearates) at concentrations of 0.5% and 1.5% were studied. Flat faced bevel edged punches with 5/8$^{th}$ in diameter was used produce tablets on a rotary press. In addition, two methods of lubricant mixing was performed: dry mixing of powders with lubricant and spraying of lubricant suspension (in isopropanol) over powder bed.

Their results show that the lower punch pull-down forces were in general lower for formulations dry-mixed with lubricant than for those sprayed with a lubricant suspension. The pull-down forces on average were higher for formulations with 0.5% lubricant than those with 1.5%. With the dry-mixing method of lubrication, stearates of calcium and magnesium showed lower pull-down forces than zinc stearate. The authors also state that punches giving a pull-down force response were visually observed to show material either adhering to the punch, die or both

and those that did not give a response showed no adherence of material. The researchers suggest that the sticking of material on to punch faces would results in higher pull-down forces.

The pull-down force of the lower punch interpreted from the strains experienced by a bolt holding the pull-down cam cannot be a reliable method of detecting or measuring sticking. For one, the bottom punch is not in contact with a tablet when it is being pulled down by the lower cam because the tablet is ejected prior to this event. The pull-down force measurement is therefore primarily affected by the friction between the punch - die wall interface. Inferring about sticking from this type of measurement therefore cannot be reliable.

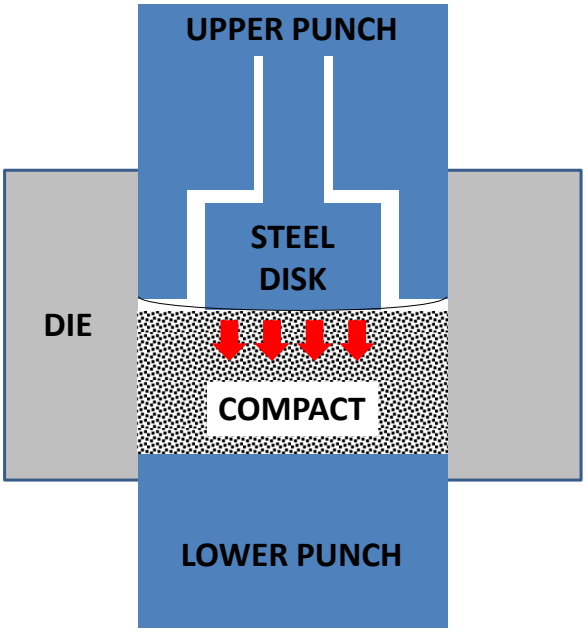



*Figure 9 – Schematic illustration of an instrumented upper punch reported by Waimer et al (21). The tip of the punch contains a steel membrane. A steel disk inside the punch body is fixed on to the membrane and is connected to a strain gauge.*

Waimer et al (21) discusses the development of a modified upper punch capable of measuring the force of adhesion between the upper punch and the surface of the tablet, see Figure 9. Their unique design made it possible to detect forces in the range of 1 to 250N. The authors studied the adhesion of sorbitol, microencapsulated acetylsalicylic acid (ASA) and starch

1500. The authors chose sorbitol as a model compound due to its known hygroscopic behavior and strong binding to punch faces. Sorbitol containing 1% moisture and varying levels of MgSt was compacted and their results show that the force of adhesion increases with increasing compression forces. The authors attributed this result to the increase in true contact area between the tablet and punch face. Increasing lubricant content in sorbitol from 0.25% to 1% shows a clear reduction in adhesion forces. The authors also state that no sticking was observed on the punch faces despite the high adhesion forces.

Pure ASA was compacted at 10kN force for 200 cycles and the results showed that the adhesion forces gradually increase and plateaus after 150 cycles. The authors state that sticking was visually observed during this process which appeared as a thin incomplete film with islands of aggregated particles. Compaction with both pure ASA and that lubricated with 0.5% MgSt showed that adhesion force decreases with increasing compressive force. With lubricated ASA the increase in compressive force showed a steady decrease in adhesion that reached to undetectably low levels. The measured adhesion forces was higher in non-lubricated ASA than lubricated ASA at all tested compression forces. With non-lubricated ASA, the increase in compressive force showed a decline in adhesion force but reached a steady state plateau of measurable adhesion. The authors state that sticking was visually observed to reduce as the measured force of adhesion diminished. The authors also state that sticking with lubricated ASA became visually undetectable with increasing compression force and only became visible at lower compression forces.

Starch 1500 showed very small adhesion forces initially but increased as compression force increased to 30kN. However the measured adhesion force rapidly decreased to undetectable levels when compression force increased to 40kN. The authors state that this effect is caused by the increase in cohesive force in the compact that overcomes the force of adhesion

to the punch face as compression force increases. The authors also state that moistening the punch face caused an excessive increase in sticking with starch 1500.

The results presented by Waimer et al (21) highlight a number of important observations. 1: Higher adhesion forces at the tablet-punch interface does not necessarily indicate or quantify sticking. 2: There is a pressure dependence of sticking and increasing compression force may reduce sticking like in the case of ASA as discussed above. Sticking with increasing compression force on Ibuprofen formulations have been previously reported to increase with an uncoated punch but decrease with a chrome coated punch (9). 3: Moisture can definitely influence sticking and may even affect powders that exhibit poor hygroscopicity. Starch is a hygroscopic material and the formation of capillary bridges between particles and tooling surface can influence sticking. Similar results on the adhesion of potato starch as a function of relative humidity was reported by Shimada et al (17). Lactose on the other hand exhibits poor hygroscopicity yet Bunker et al (1) demonstrated that capillary bridges between lactose and punch face can form between 30% & 60% RH. Moreover, tooling surfaces are often wiped clean using various solvents. It is possible for residual solvent or moisture remaining on the punch tip to initiate sticking.

### 2.6: Moisture and Triboelectric Charging

It is well known that moisture can affect sticking during tablet compaction. Moisture related sticking is attributed by factors such as relative humidity of the operating environment and hygroscopicity or compaction powders. Several pharmaceutical excipients and active ingredients are known to exhibit hygroscopic behavior. Therefore, formulations that contain hygroscopic components or high moisture content can cause sticking mediated by the capillary formation between particles and tooling surfaces. The effect of triboelectric charging of pharmaceutical powders specifically on sticking is not well understood. However the impact of

triboelectric charging of particles on adhesion and powder processing is studied by several researchers and well documented in literature.

Fine powders are known to exhibit an increased sensitivity to charging and can cause them to become cohesive due to inter-particle interactions mediated primarily by Van der Waals and electrostatic forces (73). Thus triboelectric charging can negatively impact powder flow which is a crucial property in several pharmaceutical applications. An extensive review on the topic of triboelectric charging of pharmaceutical materials is provided by Karner and Urbanetz (73). It is widely known that the magnitude of triboelectric charging can be significantly affected by the presence of adsorbed water on particle surfaces and by the relative humidity. The adsorbed water on the surface of powders acts to improve the electrical conductivity of the surface which allows for faster charge neutralization during the separation of contacts. Humidity can affect the electrical conductivity of air which allows for the transfer of charge between surfaces and air.

Shimada et al (17) describes the measurement of inter-particle adhesion forces using a novel device capable of directly separating adhering surfaces. In their technique, particles resting on a substrate are pulled off by a contacting needle to measure the force of adhesion. Their device is capable of measuring forces as low at 2nN. The authors studied the effect of triboelectric charging and moisture on glass beads and particles of various pharmaceutical materials. Their results show that the inter-particle adhesion force of hygroscopic materials such as corn starch and potato starch increase rapidly at high relative humidity due to the formation of capillary bridges. Shimada et al also demonstrated that the specific charge of corn starch, potato starch and lactose particles decrease with increasing relative humidity indicating that triboelectric charging can be affected by humidity especially with moisture sensitive materials.

Their experiments also demonstrate that triboelectric charging and particle shape can have significant effect on adhesion. The authors used glass beads having an average size of ~50µm and The adhesion force measured between a particle of irregular shaped glass and a spherical glass bead (~50µm diameter) was 5 times higher (~162nN) than that between smooth spherical glass beads (~33nN). The authors explain that this effect is due to the accumulation of triboelectric charge on the surface with sharp asperities while the smooth surface allows for the charge to distribute more uniformly. The charging of irregular glass resulted in a force of inter-particle adhesion that was comparable to that of corn starch measured at 50-55% RH (145nN). According to data presented by Shimada et al, the grade of corn starch evaluated in their experiments can absorb approximately 11.2% moisture (w/w) at 50% RH. The data presented by Shimada et al (17) illustrates that powder moisture, humidity, morphology and surface charging can profoundly affect the force of adhesion. Thus adhesion, mediated by capillary and electrostatic forces can certainly affect the behavior of sticking in pharmaceutical powders.

### 2.7: Centrifugal methods

Several authors report the use of centrifugal techniques to measure the adhesion force of particles onto substrates. An early use of such a technique is reported by Krupp (28) where a centrifugal method is devised to measure adhesion of iron particles. In this method iron particles are gently dusted onto an iron substrate that is fixed onto a centrifuge which is spun at increasing speeds. The number of particles remaining on the substrate and their sizes are recorded periodically and compared to the initial time point. The data is used to plot the percent residual remaining vs. the adhesive force derived from the centrifugal velocity. A similar technique was used by Mizes et al (11) to measure the adhesion of toner particles on a flat surface. In this technique, toner particles are adhered to a flat surface which is mounted onto a centrifuge. The

centrifuge it spun at successively increasing speeds and the detachment of particles is monitored using a CCD camera. Similar centrifugal techniques have been adopted to study sticking of pharmaceutical materials onto various substrates and are reported by several authors (11,12,15,28,29,50,51,52,53,67).

Booth and Newton (29) describes the use of a nylon centrifuge tube devised to hold a substrate onto which particles can be deposited. Various substrates including mild steel, stainless steel, brass and PTFE were used to study the adhesion of polyethylene glycol (PEG 4000) and starch 1500. Sieve fractions in the range of 45 to 53μm were deposited onto the various substrates such that particles were separated at least one diameter apart. In one set of experiments, particles were loosely deposited on the substrate without applying force and in another particles were forced onto the substrates by centrifugation. The particles were detached off the substrates by centrifugation at increasing speeds while intermittently monitoring the number of particles remaining adhered. The effect of lubrication and surface roughness of substrates were also investigated. Substrates exhibiting smooth and rough surface profiles were fabricated for each substrate material tested. The effect of lubricant was tested on steel substrates by pre-treating the surfaces with a 5% (w/v) solution of stearic acid.

Their results showed that lubrication significantly reduced adhesion forces for starch 1500 on steel surfaces. Particles that were forced onto the substrates showed significant increases in adhesion forces over those that were loosely deposited. PEG 4000 showed significantly higher adhesion forces over starch 1500 on all substrates after being initially forced on by centrifugation. For particles forced onto steel substrates, starch 1500 showed increased adhesion onto mild steel compared to stainless steel. Starch 1500 also showed increased adhesion to a smooth surface of mild steel compared to a rough surface. The results presented by Booth and Newton demonstrates that lubrication, surface roughness and compressive force affects sticking.

Shimada et al (15) studied the adhesion of fine particles on the surfaces of tablets made of MicroceLac. MicroceLac is a spray dried fused mixture of microcrystalline cellulose and crystalline lactose. The mean particle size [d50] of this powder (MicroceLac® 100) reported on the manufacturer's catalog is 132µm (70). The authors used impact separation and centrifugal force methods to measure the force required to dislodge particles adhering to the surfaces of compacted tablets. In the impact separation method, typically particles adhered to a substrate is dislodged by simply striking the opposite side of the substrate at a given velocity. In their experiment, the particles on the surface of the tablets were dislodged on to a clear container which can be analyzed under a microscope. The size distribution of the dislodged particles ranged from approximately 1 to 50µm and was measured using a microscope with an attached image analyzer. The force, f_50 at which 50% of the particles have been dislodged was calculated to be approximately 107nN. The mean particle size of the dislodged particles at f_50 was 15.8µm.

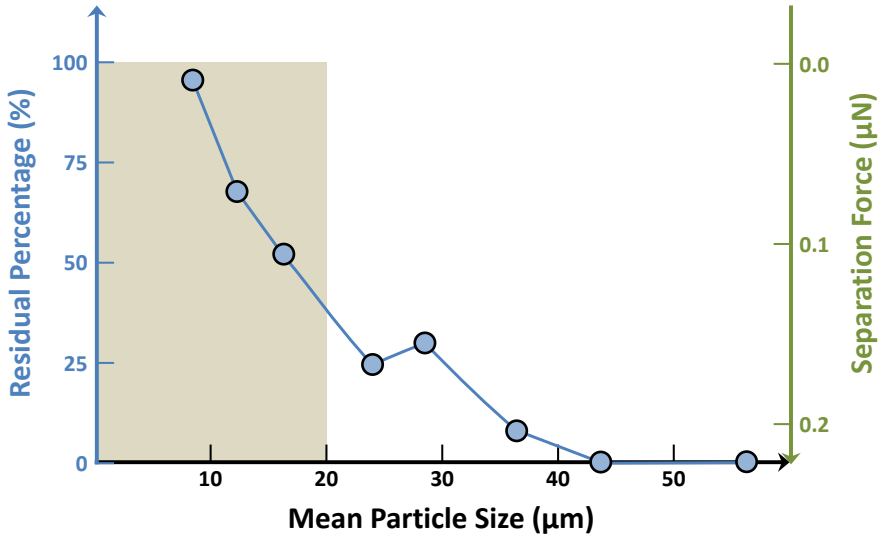



*Figure 10 – Schematic representation of the data reported by Shimada et al (15). Fine particles adhered to the surfaces of tablets are removed by centrifugal and impact separation method. The particles are removed off the tablet surface given sufficient force either by increasing centrifugal or impact velocity. The 'Residual Percent' represents the % number of particles remaining adhered to the tablet surface. The mean particle sizes are observed to be between 5-20µm even when the residual fractions are reduced to ~40%.*

An illustration showing the mean particle sizes of various residual fractions of particles remaining adhered to the tablet is shown in Figure 10. The authors also note that the residual percent of particles decreased rapidly in the size range of 10-20μm indicating the existence of a critical size range with respect to adhesion. Data collected from approximately 3000 tablets show that the mean size of particles adhered to tablet surfaces ranged from 10 to 20μm in diameter. Lactose is an agent known to intensify sticking and was observed by Abdel-Hamid and Betz (54). Fragmentation of particles during powder compaction can result in the generation of fines. The work conducted by Shimada et al (15) demonstrates that there exists a size dependence of particles with respect to adhesion especially in the 5-20μm range. Particle size may become an important parameter to consider especially since many materials that exhibit sticking such as ibuprofen and ASA are also reported to undergo fragmentation under compaction. However it is not clearly understood if and how particle size affects sticking. Centrifugal methods allows for the determination of the statistical distribution of adhesion forces. However, this method does not necessarily quantify sticking due to several reasons. For one, particles undergo significant deformation during compression which is also experienced by the particles sticking to the punch tip. The centrifugal method does not consider several depending factors in sticking including particle deformation, effect of excipients and lubricants, compression force and speed, evolution of tablet microstructure during compaction etc.

### 2.8: Molecular interaction

The surface chemistry of interacting surfaces and their effect on adhesion is purported to be an important factor that contributes to sticking by many authors. Studies that substantiate this claim include AFM force measurements between various metal surfaces and particles, molecular simulations between metal and particle surface and observations of the intensity of sticking on

various types of punch faces. Wakins et al (61) investigated the effect of particle morphology on sticking. In their study, the morphology of Mefenamic acid crystals were modified by solution crystallization in order to produce needle and plate shaped particles. AFM tips coated with oxidized iron was used to measure the relative adhesion forces of the two morphologies. AFM measurements were conducted at 25C and at 35-40% relative humidity. The researchers also used modeling software to predict the composition of exposed surface groups on the various facets of the crystal.

Their results show that the various crystal facets exhibit a different makeup of exposed surface groups such as non-polar hydrocarbon, hydrophilic amine and carbonyl groups. The (100) face of the crystal is relatively hydrophobic and exhibits the largest surface area on the plate morphology. In contrast, the (010) face exhibits the dominant surface area on needles and the (100) face area is relatively small. Powders of Mefenamic acid of both plate and needle morphologies were compacted on a Carver press at 1 ton pressure with a 10 minute dwell time. Needles were visually observed to exhibit higher sticking than plates. Molecular modeling showed that the (100) face is relatively non-polar/hydrophobic consisting of exposed methyl groups attached to internal benzene rings while the (010) face is relatively polar consisting primarily of nitrogen and oxygen atoms. The calculated surface energy of the (100) face (0.045 $kcal \cdot mol^{-1} \cdot Å^2$) is lower than that of the (010) face (0.083 $kcal \cdot mol^{-1} \cdot Å^2$). The pull off force measurements obtained by AFM showed statistically lower adhesion of plates than needles. The authors state that the difference in surface energetics between needles and plates show good correlation with observed sticking.

Although Wakins et al (61) suggests that the surface energetics of the crystal plays an important role in sticking, they did not discuss about the effect of morphology on powder flow, deformation or preferred orientation. Needle morphology is well known to cause poor powder

flow and can result in high friction and variations in the density distribution of the tablets. A particle with needle morphology can fragment into smaller particles with lower aspect ratio. Fragmentation of needles can occur more readily than with plates under a given load and can result in the generation of fine fragmented particles. Fine particles can enter the tolerance space between the wall of the die and the punch tip and can result in an increase in tooling friction. The presence of fine particles in a compression blend can also affect sticking. Both needle and plate morphologies can exhibit preferred orientation when forced against a surface. Although surface energetics of the crystal may contribute to its adhesion onto surfaces, it is important to consider other parameters in order to evaluate their effect on sticking. Sticking is often a multivariate phenomenon and literature cites several factors that contribute to sticking. It is possible that the difference in sticking observed between needles and plates of Mefenamic acid are contributed by other factors in addition to surface energetics.

### 2.9: Weighing methods

A direct way of measuring sticking is by determining the weight of the material adhered to the punch tip. In this technique, typically the tare weight of the clean punch is first recorded. The punch is then weighed intermittently during tablet production after successive compression cycles in order to generate a sticking profile of the formulation. The rate at which the weight of adhered material accumulates can be compared with different formulations in order to assess the propensity of sticking. Many researchers have employed this method to assess the propensity of sticking in various tablet formulations. Sendall and Staniforth (64) studied the sticking propensity of effervescent tablet formulations containing citric acid, tartaric acid, sodium bicarbonate, povidone and marcogol 6000. Formulations were prepared with and without the lubricant, sucrose ester. Tablets were made using 25mm and 12.5mm flat faced punches. The amount of

material adhered to the upper punch face was quantified by weighing the punch before and after compaction cycles. The surface roughness of tablets were measured using an instrument that uses a stylus in contact mode to scan surface contour. Their results show that both the adhered weight on the punch tip and the surface roughness of tablets are high for formulations without lubricant and low for formulations with lubricant. Formulations containing citric acid are reported to exhibits increased sticking over formulations with tartaric acid. The authors also report that the punch weight was observed to fluctuate in a cyclic manner with successive compression cycles. This effect is due to the accumulation of adhered material on the punch tip followed by an abrupt loss of material. Material will again continue to re-accumulate on the punch tip with successive compression cycles. The accumulation and loss of material on the punch tip occurs in a quasi-periodic manner.

Lubricants are often thought to reduce sticking and have been used in formulations successfully. However, not all materials show the same effect. For example, with increasing concentrations of magnesium stearate (MgSt), formulations of tartaric and malic acids are reported to show reduced sticking (5) while formulations of Ibuprofen and Acetyl Salicylic Acid (ASA) are reported to show increased sticking (10,21). Mullarney et al (6) investigated the effect of lubricant and drug content on the sticking propensity of Ibuprofen and mannitol formulations. In their work, a custom punch with a removable punch tip was designed so that the tip alone can be weighed in order to measure the quantity of adhered material. The punch tip used in their study were flat faced and 0.5in in diameter. Tablets were made on a single station automatic press with a shoe feed system and compressed to a target relative density of 0.85. Their results showed that sticking increases with increasing ibuprofen content in blends consisting of MCC and 0.25% MgSt. As the concentration of ibuprofen increased, fluctuations in adhered weight with successive compression cycles increased in magnitude. Interestingly, the photograph included in their paper

of the appearance of the punch tip at the 100th cycle for the 20% ibuprofen blend shows sticking to be pronounced towards the center of the punch tip and for the 40% ibuprofen blend shows sticking to be present on the entire surface of the punch tip. Similar observations of sticking in ibuprofen formulations were reported by Saniocki et al (56).

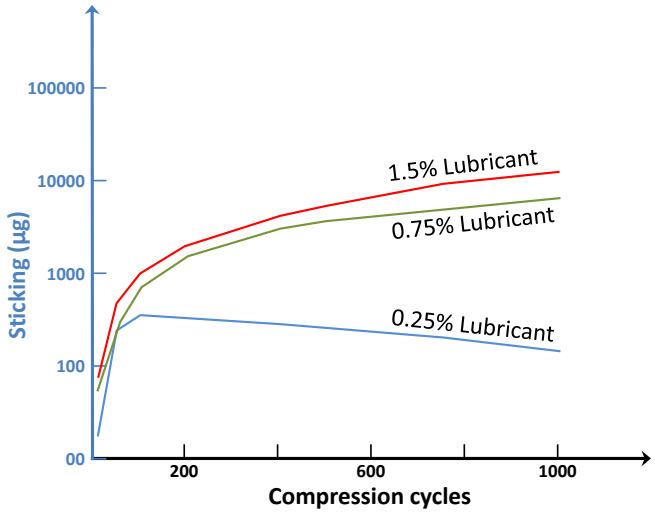



*Figure 11 – Schematic representation of the data reported by Mullarney et al (30). Showing the sticking profile of 20% ibuprofen blends containing MCC and varying levels of MgSt.*

The effect of lubricant concentration in 20% ibuprofen blends was also evaluated. The results show another interesting effect that is the sticking increases with lubricant content, see Figure 11. With 0.25% MgSt, sticking is initially observed to rapidly increase and then gradually decrease with successive compression cycles. However with 0.75% and 1.5% MgSt, sticking is initially observed to rapidly increase and then gradually increase at a slower rate with successive compression cycles. It is not clear why this effect was observed. However it does indicate that the role of MgSt in sticking of ibuprofen is not clearly understood. The effect of lubricant on sticking may also vary depending on the blending conditions of the formulation. In contrast, Mullarney et al also demonstrates that compaction with 50% mannitol blends showed that sticking decreases as the concentration of MgSt increased from 0.25% to 0.75% to 1.5%. The mannitol grade used was spray dried granular powder. The authors also evaluated the sticking propensity of various

grades of mannitol. Their results show that 100% mannitol powder exhibits significantly increased sticking over 100% spray dried granular mannitol.

The results presented by Mullarney et al highlight a number of important observations. Those of particular importance are that regarding the effect of MgSt on sticking in ibuprofen formulations and the effect of powder processing on sticking with mannitol. The powder processing of mannitol by spray drying produces granules that exhibit a reduction in the fraction of fine particles and improves powder flow (75). Mannitol powder is also reported to undergo fragmentation under compaction and the various polymorphs of mannitol exhibit different compression behaviors (71). Is it not clear exactly why spray dried granular mannitol exhibits less sticking than powder mannitol but clues as to why may come from the differences in powder properties.

The removable punch tip method is a fairly quick and easy way to directly quantify sticking. However, it is not clear how reproducible the results are. If sticking in a formulation occurs as a gradual filming-layering process, then the adhered weight on the punch tip may also gradually increase. It is not clear whether repeating the experiment would produce the same result and to what degree of accuracy. If sticking occurs in some cyclic fashion resulting in the accumulation and abrupt loss of adhered material, then this would result in significant variability in data for adhered weight. In such a situation, comparing the propensity of sticking in similar formulations may be difficult unless there are gross differences in adhered weights. Furthermore, if sticking is a slow gradual process, an assessment of sticking propensity may require a substantial quantity of material. For example, approximately 350 grams of material may be required to produce a 1000 tablets weighing 250mg each on a rotary press, assuming that about 100g of material is wasted in various ways such as loose powder on the die tablet and material in the force feeder.

### 2.10: Magnesium Stearate

Magnesium Stearate (MgSt) is a common lubricant added to formulations primarily to improve powder flow during compaction. Typically, tablet formulations are only blended with MgSt for a few minutes. Over blending a formulation with MgSt can effectively reduce the cohesive strength of the tablet compact. Under blending can result in poor distribution uniformity of MgSt throughout the powder bed. An example of this can be found in data reported by Neilly et al (8). The authors conducted elemental analysis on tablet surfaces by Energy Dispersive Spectroscopy (EDS). The pictures presented in their paper show a very fine distribution of MgSt along with the presence of several large chunks on the order of about 20µm. This can typically result from under blending of the formulation. MgSt has been reported to both increase sticking in some formulations while decrease sticking in others.

Roberts et al (10) reported that sticking increases in ibuprofen blends with increasing MgSt content. Here, the researchers evaluated the sticking behavior of ibuprofen formulations consisting of Lactose and varying concentrations of MgSt. The grade of lactose used in their study was Tablettose 80, which consists of agglomerated particles of α-lactose monohydrate. Tablets were compacted using chrome coated and uncoated flat faced punches with a diameter of 12.5mm. Compactions were conducted on single station automated press with a shoe fill system for up to 1 minute at a production rate of 19 tablets per minute. Sticking on the upper punch was characterized by HPLC in which the amount of ibuprofen adhered to the punch face is quantified. Their results show that increasing MgSt content from 0.25% to 2% in ibuprofen formulations causes significantly increased sticking. In contrast, ibuprofen formulations containing 0.5% Aerosil 200 (Colloidal Silica – ~10µm sized particles as reported in manufacture's brochure) showed that sticking was independent of MgSt content (0.25% to 2%) and remained steady at a constant level. Interestingly, the authors report that triboelectric charging of particles were observed on chrome

coated punches and not on the uncoated punches. However sticking with ibuprofen blends occurs for both types of punches. The results presented by Roberts et al (10) clearly demonstrates that increasing MgSt only intensifies sticking in ibuprofen formulations. It is quite evident that the mechanism is by which MgSt affects sticking is not well understood. It is also not clear exactly what role triboelectric charging plays in sticking.

### 2.11: Techniques used to measure sticking

The following contains a tabulated list of various techniques reported in literature that are used to measure sticking. Each technique is categorized by the type of information obtained from the measurement. The four categories assigned are: Quantification (Q), Correlation (C), Detection (D), and Prediction (P). Quantitation refers to the direct measurement of the magnitude of sticking of a powder with successive compression cycles. This type of technique would involve some form of numerical gauging of the quantity of material adhered to the punch tip. Correlation refers to the measurement of parameters that has been shown to correlate with the phenomenon of sticking. This type of measurement is also used to gauge the magnitude of sticking. Detection refers to the qualitative measurement of sticking. This type of technique can be used to detect the occurrence or qualitatively assess sticking. Prediction refers to the indirect assessment of sticking propensity that does not involve any tablet compaction operation.

| **Technique** | **Type** | **Reference** |
|---|---|---|
| AFM | P | 1,23,25,35,72 |
| Air Blasting | P | 30 |
| Centrifugal Method (CFG) | P | 11,12,15,28,29,50,51,52,53,67 |
| Die Wall Pressure | C | 54 |
| Direct Separation | P | 16,17 |
| Ejection Force | C | 24,44 |
| HPLC | Q | 5,9,10,36,39,43,45,47,49,78 |
| Image Analysis | D | 40,44,45,87 |

| Technique | Type | Reference |
|---|---|---|
| Impact Separation (IMP) | P | 12,13,15 |
| Infrared Spectroscopy (IR) | D | 8,32,38,47 |
| Lower punch pressure | C | 7,18,19 |
| Molecular Modeling (MOD) | P | 23,24,41,61,68 |
| Pull-down Force | C | 3 |
| Pull-up Force | C | 4,21,31 |
| Punch Surface Roughness | C | 1,60 |
| Punch Weight | Q | 6,46,64 |
| SEM/EDS | D | 5,8,76 |
| Shear Cone Pull-up | C | 22 |
| Slipping Force | C | 7,18,19 |
| Spring Balance | P | 14 |
| Sweep-off/Scraper/Take-off Force (SCR) | C | 2,4,24,26,27,39,59,55 |
| Tablet Surface Roughness (TSR) | Q,C,D | 4,20,64 |
| Powder Rheometry | C | 37 |
| Thermal Analysis | C | 41 |
| Visual inspection | D | 33,34,42,48,62 |

### 2.12: Parameters reported to affect sticking

The following contains a tabulated list of various parameters reported in literature that are reported to affect sticking.

| Parameter | Material | Reported Result | Technique | Reference |
|---|---|---|---|---|
| Blending time | Lactose | Increasing blending time with lactose formulations did not increase sticking. | TSR | 20 |
| Compression speed | Ibuprofen | Sticking increases with increasing compression speed. | SCR | 59 |
| Compression speed | n-Butyl p-hydroxybenzoate | Sticking increases with increasing compression speed. | SCR, TSR | 4 |
| Compression force | Ibuprofen | Sticking decreases with increasing compression force. | SCR | 59 |
| Compression force | Ibuprofen | Sticking decreases with increasing compression force. | HPLC | 39,56 |
| Compression force | Ibuprofen | As compression force increases, sticking decreases on a Cr-coated punch but increases for an uncoated punch. | HPLC | 9 |
| Compression force | ASA | Sticking observable at low compression force but decreases with increasing compression force. Adhesion force at tablet punch interface decreases with increasing compression force. | Pull-up | 21 |
| Compression force | Sorbitol | Adhesion force at tablet punch interface increases with increasing compression force with no sticking. | Pull-up | 21 |
| Compression force | Lactose | Sticking increases with increasing compression pressure in wet granulated lactose-PVP formulations. | SCR | 2 |
| Compression force | Confidential formulation | Sticking not observed at higher compression force | Pull-up | 21 |

| Parameter | Material | Reported Result | Technique | Reference |
|---|---|---|---|---|
| | | but only evident at lower compression force. | | |
| Concentration of active ingredient | Ibuprofen | Sticking increases with increasing levels of ibuprofen. | HPLC | 39,56 |
| Concentration of active ingredient | Ibuprofen | Sticking increases with increasing levels of ibuprofen. | HPLC | 9 |
| Water content | Lactose | Sticking increases as water content increases up to 3%. Beyond 3%, sticking reduces. | SCR | 2 |
| Punch hydrophobicity | Lactose | CN+ is hydrophobic compared to HC punch. Capillary bridges form easily with HC than CN+ at low RH. | AFM | 1 |
| Punch coating | Lactose, starch, calcium carbonate | CN coating reduced powder adhesion more than steel and chromium carbide. | CFG | 69 |
| Humidity | Lactose | Capillary formation on HC & DLC punch surfaces occurs at low RH. | AFM | 1 |
| Solid fraction | Tartaric acid and Malic acid | Sticking decreases with increase in solid fraction. | HPLC, SEM/EDS | 5 |
| Lubricant | Tartaric acid and Malic acid | Sticking decreases with increase in MgSt content. | HPLC, SEM/EDS | 5 |
| Lubricant | Ibuprofen | Sticking increases with high MgSt content (1-2%). | HPLC | 10 |
| Lubricant | ASA | Sticking increases with high MgSt content. | Pull-up | 21 |
| Lubricant | Ibuprofen | Sticking increases with increasing MgSt. | Punch Wt. | 6 |
| Lubricant | Mannitol | Sticking decreases with increasing MgSt content. | Punch Wt. | 6 |
| Lubricant | Lactose | Sticking decreases with increasing MgSt content. | TSR | 20 |
| Anti-adherent | Citric acid, tartaric acid, sodium bicarbonate | Addition of 1% sucrose ester powder in formulation significant reduced sticking. | Punch Wt., TSR | 64 |
| Powder processing | Mannitol | Mannitol powder shows higher sticking that spray | Punch Wt. | 6 |

| Parameter | Material | Reported Result | Technique | Reference |
|---|---|---|---|---|
| | | dried granulated grade of mannitol. | | |
| Powder processing | Confidential drug | Dry granulation of formulation by roller compaction eliminated sticking. | Visual | 80 |
| Punch Surface Roughness | Ibuprofen | Increased surface roughness did not increase sticking. | HPLC | 9 |
| Punch Surface Roughness | Ibuprofen | Increased surface roughness of EIP and MH punches showed significant reduction in sticking compared to HCr-coated punch. | HPLC, SCR | 60 |
| Punch Surface Roughness | Confidential drug | The pitted surface in a punch face increased surface roughness and reduced sticking | Visual | 62 |
| Punch geometry | Ibuprofen | Decrease sticking observed with concave punches compared to flat-faced punches. | HPLC | 63 |
| Punch geometry | Ibuprofen | Decrease sticking observed with concave punches compared to flat-faced punches. | SCR | 59 |
| Temperature | butyl p-hydroxybenzoate, sulfadimethoxine | Increasing the heat treatment temperature from 0.90 to 0.95 (T/Tm) results in significant increase in adhesion to glass substrate. | IMP | 12 |
| Static charge | Toner particles | Triboelectric charging can be the dominating mechanism of adhesion of toner particles. | CFG | 11 |
| Surface chemistry of crystal faces | ibuprofen, ketoprofen, flurbiprofen | Increased surface energetics correlates with increased sticking. | AFM, MOD | 23 |
| Surface chemistry of crystal faces | Mefenamic acid | Needles adhere stronger than plates due to surface energy and polar groups. | AFM, MOD | 61,68 |
| Cleaning of punch | Tickopur R33 | Treating punch faces with Tickopur R33 cleaning | Contact angle. | 1 |

| Parameter | Material | Reported Result | Technique | Reference |
|---|---|---|---|---|
| | | solution improves punch hydrophilicity. | | |
| Conditioning of punch | Confidential drug | Elimination of sticking observed by pre-compressing with placebo blend of MCC PH102 & MgSt prior to manufacture with active blend. | Visual | 62 |
| Conditioning of punch | Confidential drug | No sticking with punches treated using chromium nitride Ion bombardment and increased sticking with chromium plated punch. | Visual | 62 |
| Conditioning of punch | Confidential drug | Dusting punch faces with MgSt prior to compaction start did not reduce sticking. | Visual | 62 |

# CHAPTER 3: METHODS & MATERIALS

## 3.1: Punch tip specifications and characterization

In this work, modified upper punches with removable tips were used to study sticking in ibuprofen and Acetylsalicylic Acid (ASA) blends. The modified punches were also used to evaluate the sticking propensity of three formulations of a confidential drug. Modified B-type upper punches with removable tips were manufactured at Natoli Engineering (Saint Charles, MO, USA). Photographs of the punch with a removable tip is shown in Figure 12. The punch tips were made of S7 steel (approximate composition as per manufacturer specifications: 0.45-0.55% carbon, 0.20-0.80% manganese, 0.20-1.00% silicon, 3.00-3.50% chromium, 0.00-0.35% vanadium, 1.30-1.80% molybdenum) with standard polishing. Three tip geometries (two of each) were manufactured: standard cup (SC), deep cup (DC), flat faced radius edge (FFRE) each weighing under 2 grams. The tip geometries and specifications are shown in Figure 13. Only the SC and FFRE tip geometries were used this work.

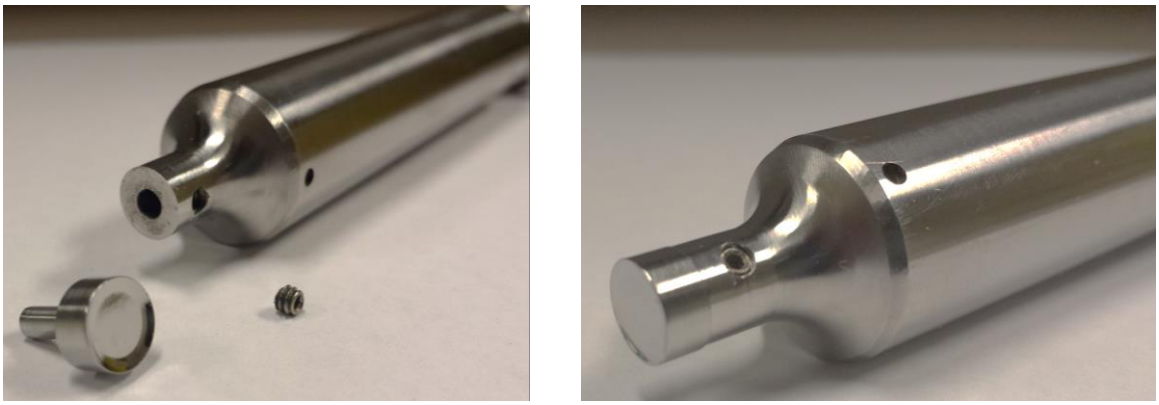
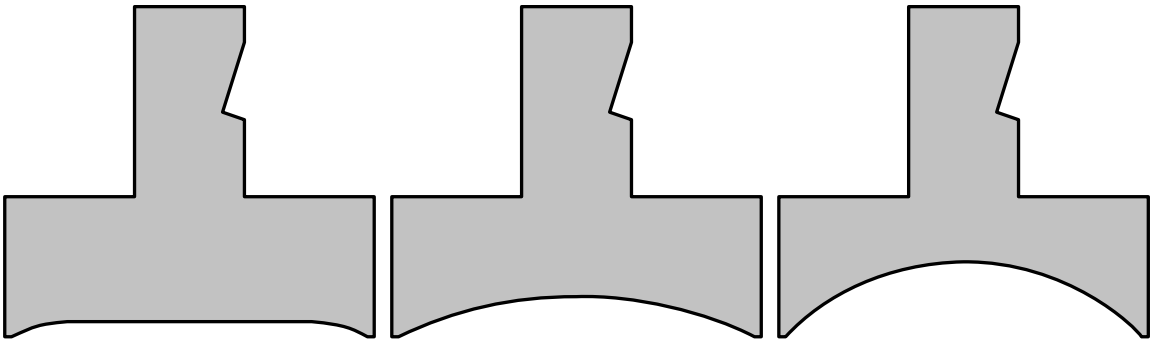


*Figure 12 – Photographs of the punch with removable punch tip. Left: disassembled view. Right: the punch tip is fastened to the punch body using a set screw.*



| Flat Face Radius Edge | Standard Cup | Deep Cup |
|---|---|---|
| Diameter = 8mm | Diameter = 8mm | Diameter = 8mm |
| Mass = 1.854 grams | Mass = 1.700 grams | Mass = 1.889 grams |
| Cup Depth = 0.86mm | Cup Depth = 1.62mm | Cup Depth = 0.35mm |
| Cup Volume = 20.92mm$^3$ | Cup Volume = 41.05mm$^3$ | Cup Volume = 13.37mm$^3$ |
| Land = 0.10mm | Land = 0.10mm | Land = 0.10mm |
| Material = S7 Steel | Material = S7 Steel | Material = S7 Steel |

*Figure 13 – Schematic drawings of punch tips and their properties.*

The surface profile of the punch tips were examined using a Zigo optical profilometer. The surface profile data is shown in Figure 14 and optical photomicrographs of the scanned areas are shown in Figure 15. A scan area of 0.70mm x 0.53mm was examined for each punch tip. The root mean square (RMS) roughness values typically varied between 50nm and 200nm for all tips. A sphere baseline subtraction was applied to the standard and deep cup tips in order to compensate for the tip geometry. A tabulated list of surface roughness measurements are presented in Table 1.

| | PV (µm) | RMS (µm) | Ra (µm) |
|---|---|---|---|
| **Standard Cup A** | 1.191 | 0.179 | 0.139 |
| **Standard Cup B** | 2.967 | 0.064 | 0.050 |
| **Deep Cup A** | 1.961 | 0.111 | 0.080 |
| **Deep Cup B** | 0.989 | 0.120 | 0.084 |
| **Flat Face Radius Edge A** | 1.586 | 0.099 | 0.075 |
| **Flat Face Radius Edge B** | 1.126 | 0.180 | 0.144 |

*Table 1 – Surface roughness measurements of removable punch tips. PV (minimum peak minus maximum valley), RMS (Root Mean Square roughness), RA (Average roughness).*

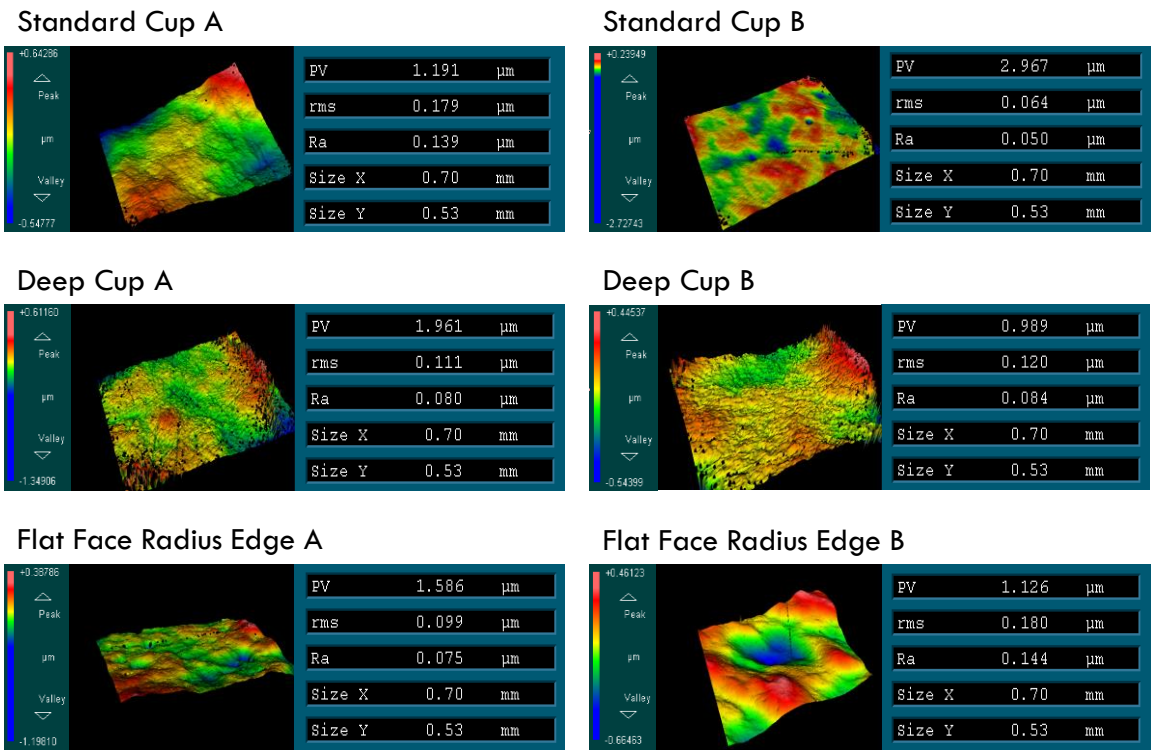



*Figure 14 – Surface profile of punch tips using an optical profilometer. PV (minimum peak minus maximum valley), RMS (Root Mean Square roughness), RA (Average roughness), Size X (scan length in x-direction), Size Y (scan length in y-direction).*

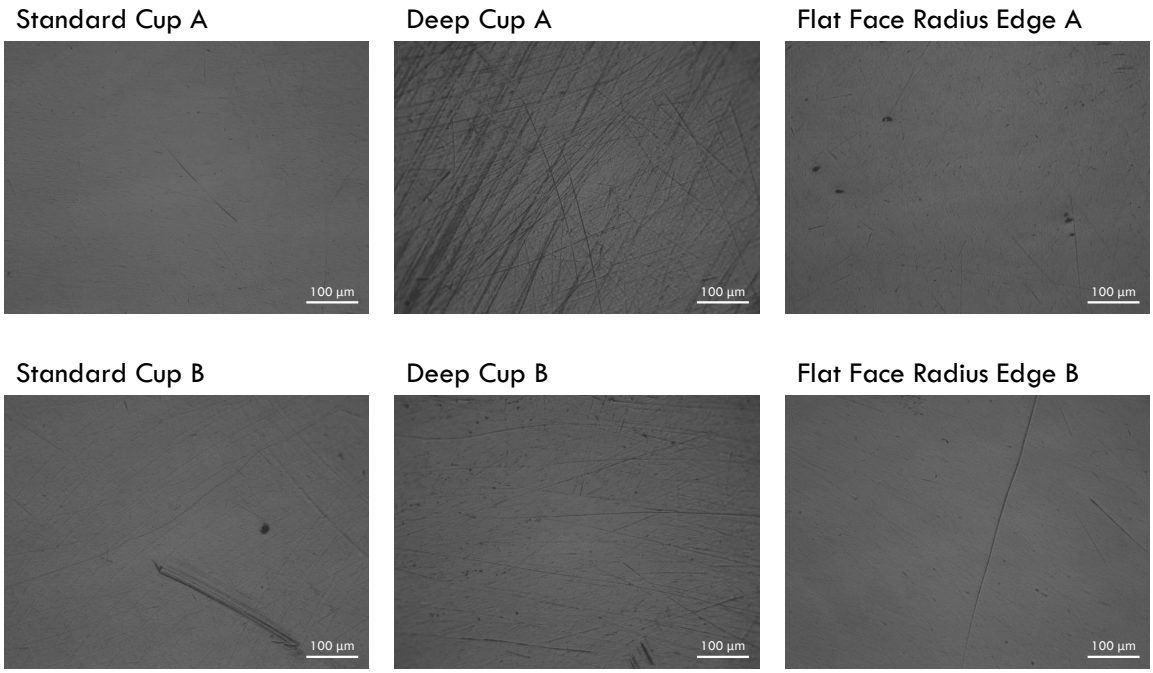



*Figure 15 – Photomicrographs of the punch tips. Showing the area scanned by the optical profilometer.*

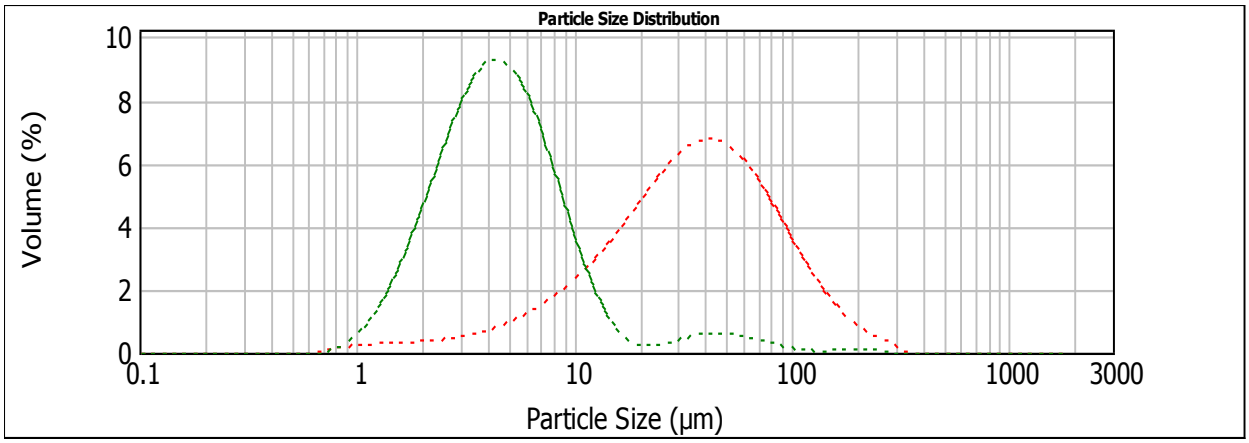
### 3.2: Equipment and materials

The Ibuprofen used in this work was obtained from Spectrum Chemicals. Acetylsalicylic Acid was obtained from MP Biomedicals. True density measurements of all tested formulation were obtained using an AccuPyc II 1340 pycnometer (Micromeritics Instrument Corporation, Norcross, USA). Particle size measurements were conducted by laser light scattering using Malvern Instruments Mastersizer 2000 (using µP and Scirocco modules). All formulations tested were blended using a Turbula blender (Willy A. Bachofen, Muttenz, Switzerland). The various formulation blends prepared and evaluated in this work are summarized in Table 2.

| Formulation Name | True Density ($g/cm^3$) | Tip | Formulation |
|---|---|---|---|
| 100% IBU | 1.1163 | FFRE | 100% IBU |
| 30% IBU | 1.4072 | FFRE | 30.0% IBU, 0.5% MgSt, 69.5% MCC PH102 |
| 30% IBU-MIC | 1.4538 | FFRE | 30.0% IBU, 0.5% MgSt, 69.5% MCC PH102 |
| 30% ASA | 1.5152 | FFRE | 30.0% ASA, 0.5% MgSt, 69.5% MCC PH102 |
| 21% X-B1 | 1.4957 | SC | 20.9% X, 1.5% MgSt, 59.5% MCC PH102, 18.1% Mannitol |
| 21% X-B2 | 1.4980 | SC | 20.9% X, 1.5% MgSt, 62.6% MCC PH102, 15.0% Mannitol |
| 21% X-B3 | 1.4902 | SC | 20.8% X, 2.0% Compritol, 62.3% MCC PH102, 14.9% Mannitol |

*Table 2 – List of formulations evaluated using removable punch tip. FFRE – Flat Face Radius Edge, SC – Standard Cup, IBU – Ibuprofen, MgSt – Magnesium Stearate, MCC – Microcrystalline Cellulose, ASA – Acetylsalicylic Acid.*

Micronization of Ibuprofen was achieved by air jet milling on a Jet-O-Mizer. The grinding nozzle pressure was set to 80 Psi and the pusher nozzle to 90 Psi. A yield of 86% was achieved. Micronized Ibuprofen was observed to be highly static charged and difficult to handle. The particle size of the starting Ibuprofen material (as received from supplier) is 35.6µm (x50 percentile) and that of the micronized material is 4.4µm (x50 percentile) which corresponds to an approximate 90% size reduction. The particle size distribution curve is shown in Figure 16.




| | x10 | x50 | X90 |
|---|---|---|---|
| Ibuprofen AS-IS | 8.505 | 35.625 | 103.833 |
| Ibuprofen Micronized | 1.944 | 4.415 | 10.785 |

*Figure 16 – Particle size distribution of micronized and non-micronized Ibuprofen.*

### 3.3: Blending procedures

*Blending procedure - 30% Ibuprofen*

Ibuprofen (as received from supplier) and MCC PH102 was first screened separately through a 710µm sieve for delumping. The materials were mixed in the Turbula blender for 5 mins at 35 rpm. The mixture was screened through a 425µm sieve and mixed again for 5 mins at 35 rpm. The mixture was screened through a 425µm sieve again into a collection pan. Magnesium stearate was also passed through the 425µm sieve into the collection pan. The screened materials were mixed in the Turbula blender for 3 minutes at 35 rpm. This formulation will be referred to as 30% IBU in this text.

*Blending procedure - 30% Ibuprofen Micronized*

Micronized Ibuprofen was highly static charged and very difficult to sieve. For this reason, micronized Ibuprofen and MCC PH102 was first hand mixed by spatula in a collection pan for 3 minutes. The mixture was then mixed in the Turbula blender for 10 mins at 35 rpm. The mixture

revealed large lumps of Ibuprofen and therefore a more vigorous mixing was conducted at 51 rpm for 10 mins. The mixture was screened through a 600µm sieve and mixed for 10 mins at 105 rpm. The mixture was then screened through a 425µm sieve into a collection pan. Magnesium stearate was also passed through the 425µm sieve into the collection pan. The screened materials were mixed in the Turbula blender for 3 mins at 35 rpm. This formulation will be referred to as 30% IBU-MIC in this text.

*Blending procedure - 30% Acetylsalicylic Acid*

Acetylsalicylic Acid (as received from supplier) and MCC PH102 was first screened separately through a 710µm sieve for delumping. The materials were mixed in the Turbula blender for 5 mins at 35 rpm. The mixture was screened through a 425µm sieve and mixed again for 5 mins at 35 rpm. The mixture was screened through a 425µm sieve again into a collection pan. Magnesium stearate was also passed through the 425µm sieve into the collection pan. The screened materials were mixed in the Turbula blender for 3 mins at 35 rpm. This formulation will be referred to as 30% ASA in this text.

*Blending procedure - 21% Compound X, Blend 1*

Compound X, Mannitol and MCC PH102 was first screened separately through a 800µm sieve for delumping. The materials were mixed in a Pharmatech 2 Liter capacity bin blender for 20 mins at 17 rpm. The mixture was screened through a 250µm sieve again into a collection pan. Magnesium stearate was also passed through the 250µm sieve into the collection pan. The screened materials were mixed in a Turbula blender for 3 mins at 24 rpm. This formulation will be referred to as 21% X-B1 in this text.

*Blending procedure - 21% Compound X, Blend 2*

Compound X, Mannitol and MCC PH102 was first screened separately through a 800µm sieve for delumping. The materials were mixed in a Pharmatech 2 Liter capacity bin blender for

20 mins at 17 rpm. The mixture was screened through a 250µm sieve again into a collection pan. Magnesium stearate was also passed through the 250µm sieve into the collection pan. The screened materials were mixed in a Turbula blender for 3 mins at 24 rpm. This formulation will be referred to as 21% X-B2 in this text.

*Blending procedure - 21% Compound X, Blend 3*

Compound X, Mannitol and MCC PH102 was first screened separately through a 800µm sieve for delumping. The materials were mixed in a Pharmatech 2 Liter capacity bin blender for 20 mins at 17 rpm. The mixture was screened through a 250µm sieve again into a collection pan. Compritol was also passed through the 250µm sieve into the collection pan. The screened materials were mixed in a Turbula blender for 3 mins at 24 rpm. This formulation will be referred to as 21% X-B3 in this text.

### 3.4: Testing procedure

A Globepharma Minipress II rotary press was used to evaluate all formulations in this work. Only one of the 10 stations were used to manufacture tablets. Punches and removable tips are cleaned using methanol and stored at room temperature and ambient relative humidity for at least 2 days prior to use. The instrument settings were generally kept constant for all experiments performed in this work. The turret speed was set to 30rpm which produced on average 16 tablets per minute using a single station. A force feeder was used for all testing and the feeder speed was set to 30rpm. Pre-compression of powder was conducted by manual adjustment of pre-compression roller to an arbitrary vertical displacement which was kept constant for all testing in this work.

The manual adjustments of vertical displacement on the main compression roller and powder fill height are initially adjusted for each formulation tested such that tablets are compacted to an approximate relative density of 0.85 and fill weight of approximately 230mg. The dimensions and weight of compacted tablets are measured periodically throughout the compression cycle. The actual recorded relative densities and tablet weights are presented. The tablet dimensions are measured using a digital caliper and tablet weights are measured using a Mettler AX205 analytical balance. The appearance of the tablets faces are photographed as necessary when sticking is observed. A bright fiber optic light is used to illuminate the surface of tablets in order to inspect and document the subtle features that are otherwise difficult to observe. The tablet break force is measured by diametrical compression using a Pharmatron 8M hardness tester. The break strength of tablets compacted using the flat face radius edge tip are calculated using Equation (1) where P is the applied load at fracture, D is diameter and t is the thickness of tablet (57,65).

$$\sigma_f = {}^{2P}/_{\pi Dt} \tag{1}$$

The break strength of tablets compacted using the standard cup tip are calculated using Equation (2) where P is the applied load at fracture, D is diameter, t is thickness of tablet and W is the cylindrical wall thickness of the tablet (57,66).

$$\sigma_f = \frac{10P}{\pi D^2}\left[\frac{2.48t}{D} - \frac{0.126t}{W} + \frac{3.15W}{D} + 0.01\right]^{-1} \tag{2}$$

The relative density of tablets are calculated using Equation (3) where ρ is the apparent density of the tablet and $\rho_t$ is the true density of the powder.

$$Relative\ Density = {}^{\rho}/_{\rho_t} \tag{3}$$

The apparent density of tablets are calculated using Equation (4) where M is tablet weight, $V_c$ is the punch tip cup volume and $V_w$ is the cylindrical volume calculated using the tablet diameter and wall thickness.

$$Apparent\ Density, \rho = \frac{M}{(2\times V_c)+V_w} \quad (4)$$

The cup volume of the punch tips are listed in Figure 13.

The punch tip is also removed periodically throughout the compression cycle. Removal of the punch tip is done carefully by handling the tip only by its side wall while avoiding contact with the face of the tip. After removal, the side wall of the tip is wiped clean with a tissue (Kimtech Science KimWipes). The appearance of the removable upper punch tip and the lower punch tip is photographed as necessary when sticking is evident. The weight of the tip is measured using a Mettler MX5 Microbalance. The weight of the material adhered to the removable punch tip is calculated by subtracting the starting weight of the tip. The tip is carefully replaced back on the upper punch and fastened while avoiding contact with the tip face. Compression cycles are resumed and this procedure is repeated at a various sampling time points.

# CHAPTER 4: RESULTS & OBSERVATIONS

## 4.1: Evaluation of blend containing 30% Ibuprofen

The sticking profile of the 30% IBU blend is shown in Figure 17. The 30% IBU blend shows a rapid rate of increase in adhered weight after about 200 compression cycles. The tablet break strength is observed to gradually decrease throughout the experiment. The decrease in break strength may be due to the decrease in tablet weight between cycle # 50 and 350. The relative density of the tablets remained fairly constant throughout the experiment (RD≈0.9). The images of tablets and punch faces captured in this study are shown in Figure 18. Sticking on the upper punch face is evident after just 10 compression cycles. The adhered material at this point appears as a light dusting of powder on the punch face. The bottom punch face showed very minimal sticking throughout the study. By cycle #30, a thin and roughly circular spot of material was observed on the center of the upper tip face. Note that the weight of the adhered material is less than 200µg. After 50 compression cycles, the spot appears to have more defined edges on the periphery. The size of the spot and weight of the adhered material appears to be maintained roughly constant up to about 200 cycles. However the shape of the spot edge contour is observed to change.

As the adhered material grows to become more defined by cycle #50 (ie: from an appearance of light dusting of powder to a thin film-like spot with distinct edges), impressions left on the tablet face become more evident. A slightly darker shaded spot whose geometry is complimentary to the spot on the tip face can be observed on the tablet face by cycle #50. At this point, this feature on the tablet face is nearly invisible to the naked eye until illuminated by light. The difference in appearance of light reflected from the within the spot and the periphery makes the feature observable. An SEM image of the top face of the tablet is shown in Figure 19.

The contour of the region affected by sticking on the tablet face is indicated by a blue line. No gross difference in appearance between the affected and peripheral regions on the tablet were noticed. The affected area appeared to be embossed by the material adhered to the punch tip. The weight of the material adhered to the tip increases significantly after 200 cycles. The thickness and diameter of the adhered spot is observed to be larger by cycle #350. Between cycle# 350 and 450, the material remaining in hopper had become insufficient and proper die filling of powder was inadequate. No tablets were tested in this range. However, both punch faces showed a considerable increase by cycle #450. An SEM image of the material adhered to the punch face after the 450$^{th}$ cycle is shown in Figure 20. Chunks of loose material was observed to adhere to the punch face as die filling became inadequate. A Stitched SEM image of the top face of Tablet #49 is shown in Figure 21.

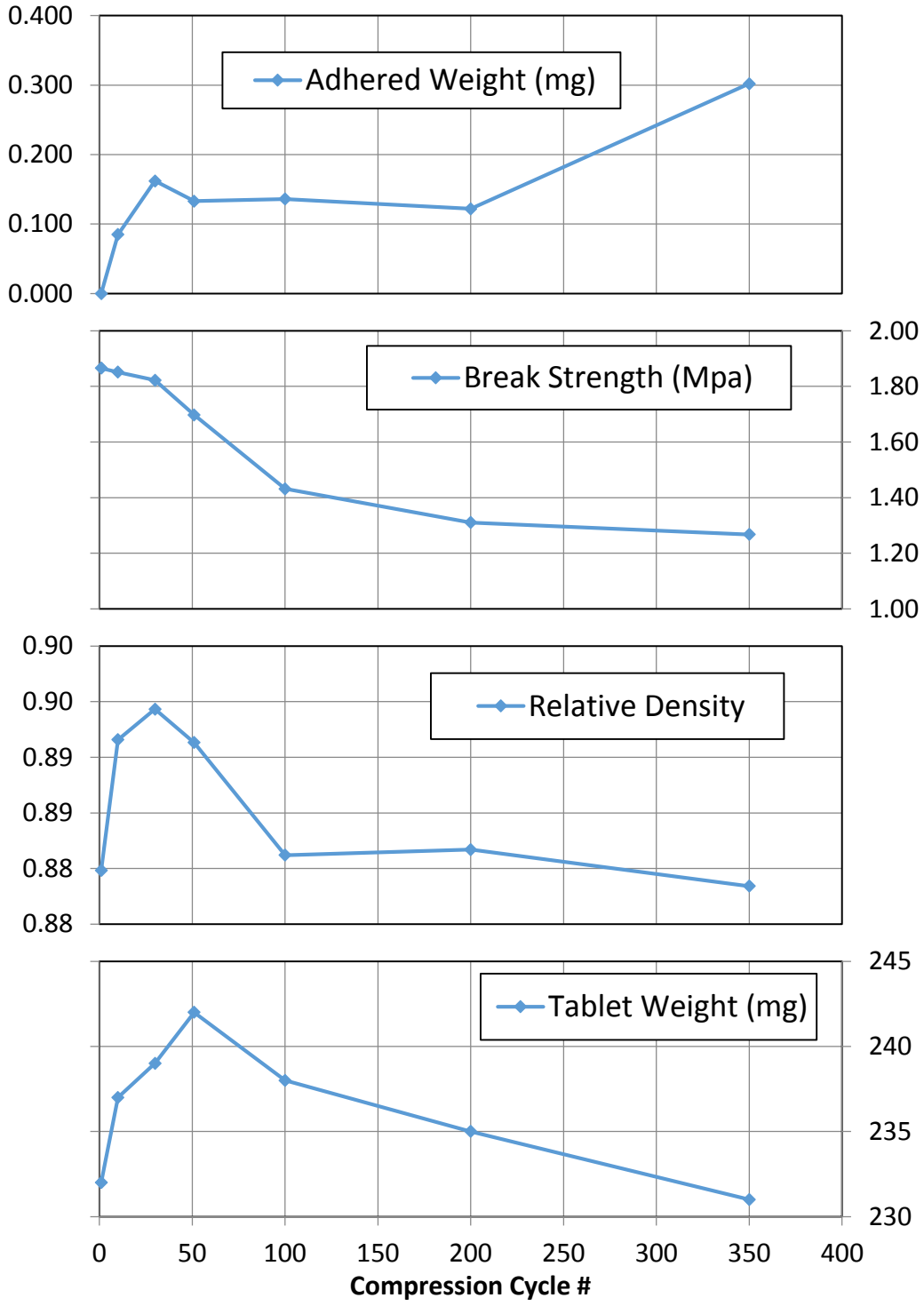



*Figure 17 – Data obtained for 30% IBU formulation.*

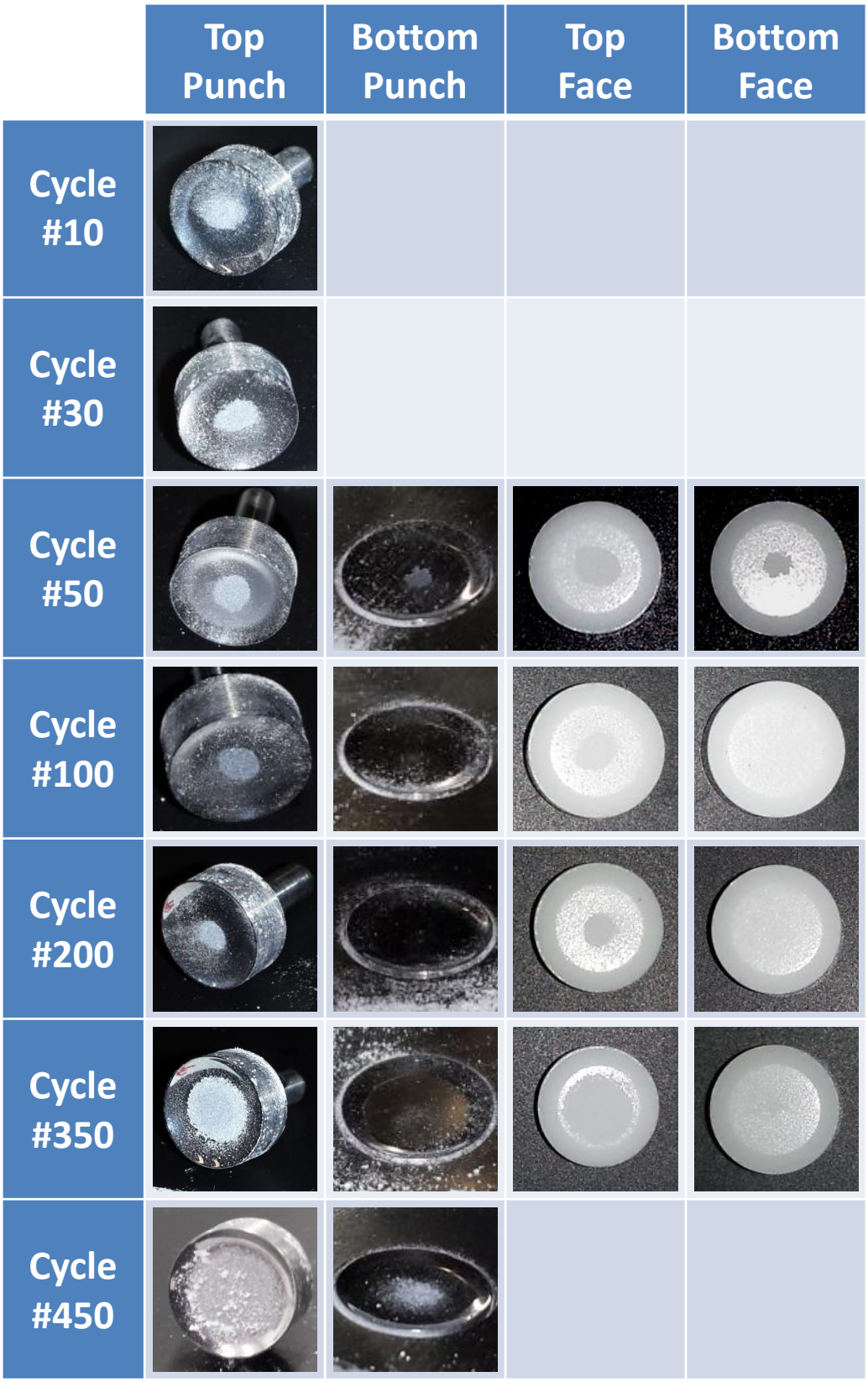



Figure 18 – Photographs of punch faces and tablets for 30% IBU formulation.

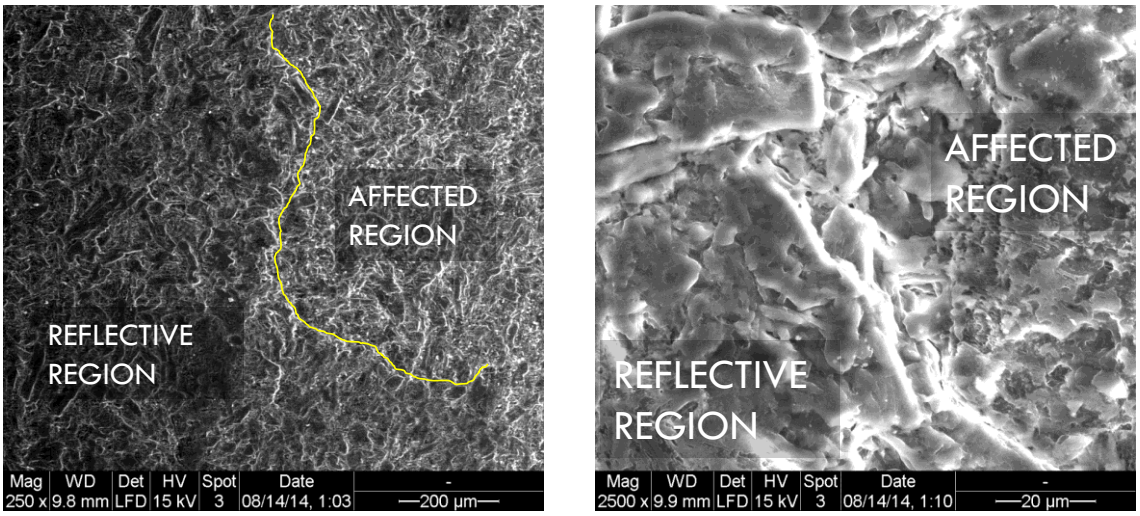



*Figure 19 – SEM images of the top surface of tablet #50 from the 30% IBU study. Left: low magnification image showing both the reflective region on the tablet and the region affected by sticking. A contour is drawn on the image to help identify the boundary between the two regions which is otherwise difficult to observe. Right: magnified image showing the two regions.*

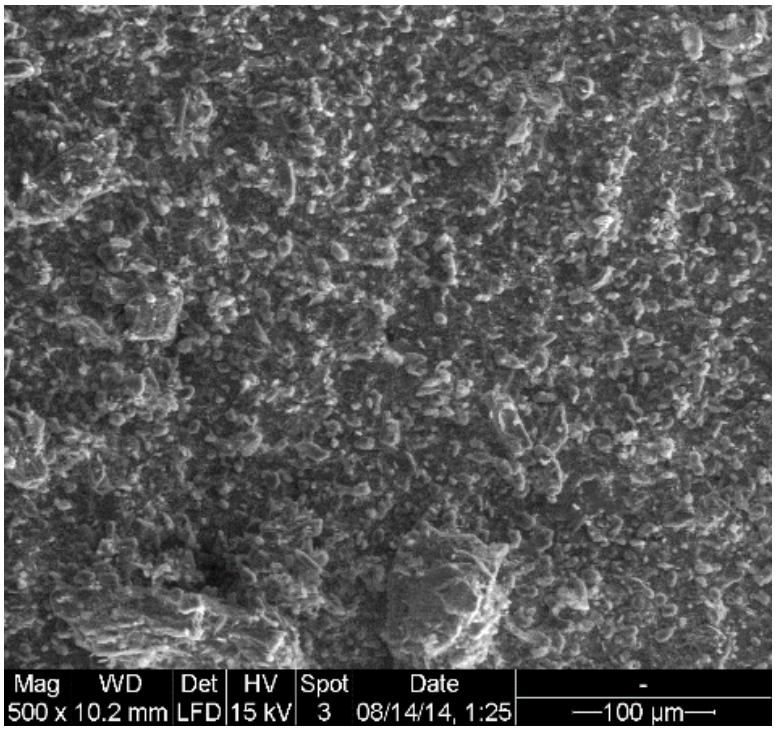



*Figure 20 – SEM image showing the surface of the adhered material on the punch face for the 30% IBU formulation after the 450$^{th}$ compression cycle.*

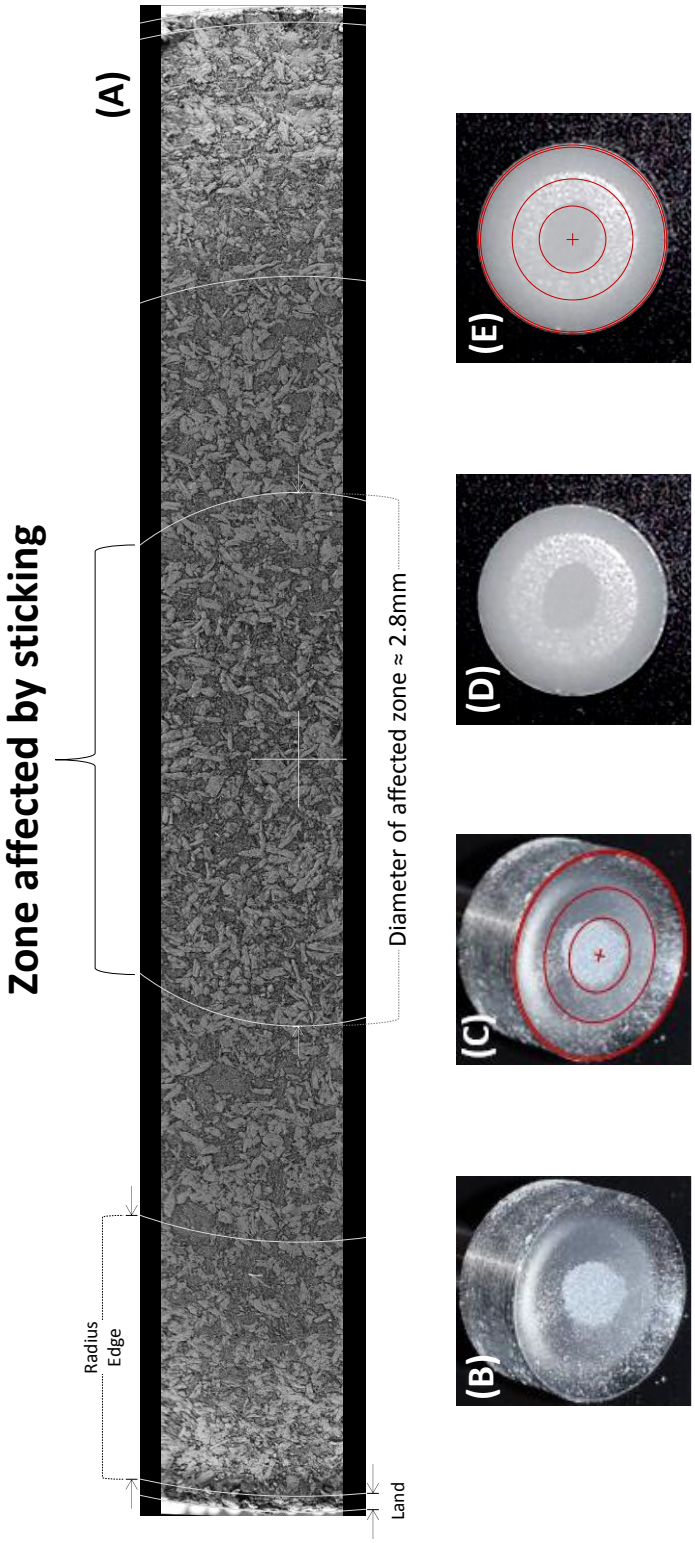



*Figure 21 – (A) Stitched SEM image of the top face of Tablet #49 from 30% IBU Study. (B) Photograph of punch face after cycle #50. (C) Photograph of upper punch face after cycle #50 with coordinates. (D) Photograph of the top face of tablet #50. (E) Photograph of the top face of tablet #50 with coordinates.*

### 4.2: Evaluation of blend containing 30% micronized Ibuprofen

The sticking profile of the 30% IBU-MIC blend is shown in Figure 22. Testing on micronized Ibuprofen showed to have a profound effect on sticking. Die filling was observed to be inadequate and to progressively worsen past 50 compression cycles. Consequently, tablet strength and relative density are also observed to show large fluctuations. After just 10 compression cycles, a thin film of adhered material (see Figure 23) weighing just under 200µg is observed. At this point, the upper punch body is observed to accumulate a dusting of fine powder. After about 19 compression cycles, the neck of the upper punch body is fully covered with fine powder. An increase in the sound coming from the instrument during each compression cycle, just as the top punch leaves contact with the main compression roller was noted. Sticking on the punch face was visible from cycle #2 onwards. Stitched SEM images of the top face of tablets #2 & #5 are shown in Figure 24.

A significant increase in adhered weight is recorded just after 30 compression cycles. Considerable sticking is also observed on the bottom punch throughout the study. The fluctuation of adhered weight caused by the accumulation and detachment of material is evident from the pictures shown in Figure 23. The detachment of a section of material from the film is observed at cycle #30 while cycle #50 shows that the affected region has re-accumulated material. The punch tip at cycle #112 shows the detachment of a large section of material which occurred when die filling and tablet strength was just briefly improved. It was also observed that the material adhered to the bottom punch was removed. A snapshot of the die filling just prior to this cycle (at cycle #110) is also shown in Figure 23. Tablet #112 showed an impression on its surface that was complimentary to the geometry of the material adhered to the punch tip.

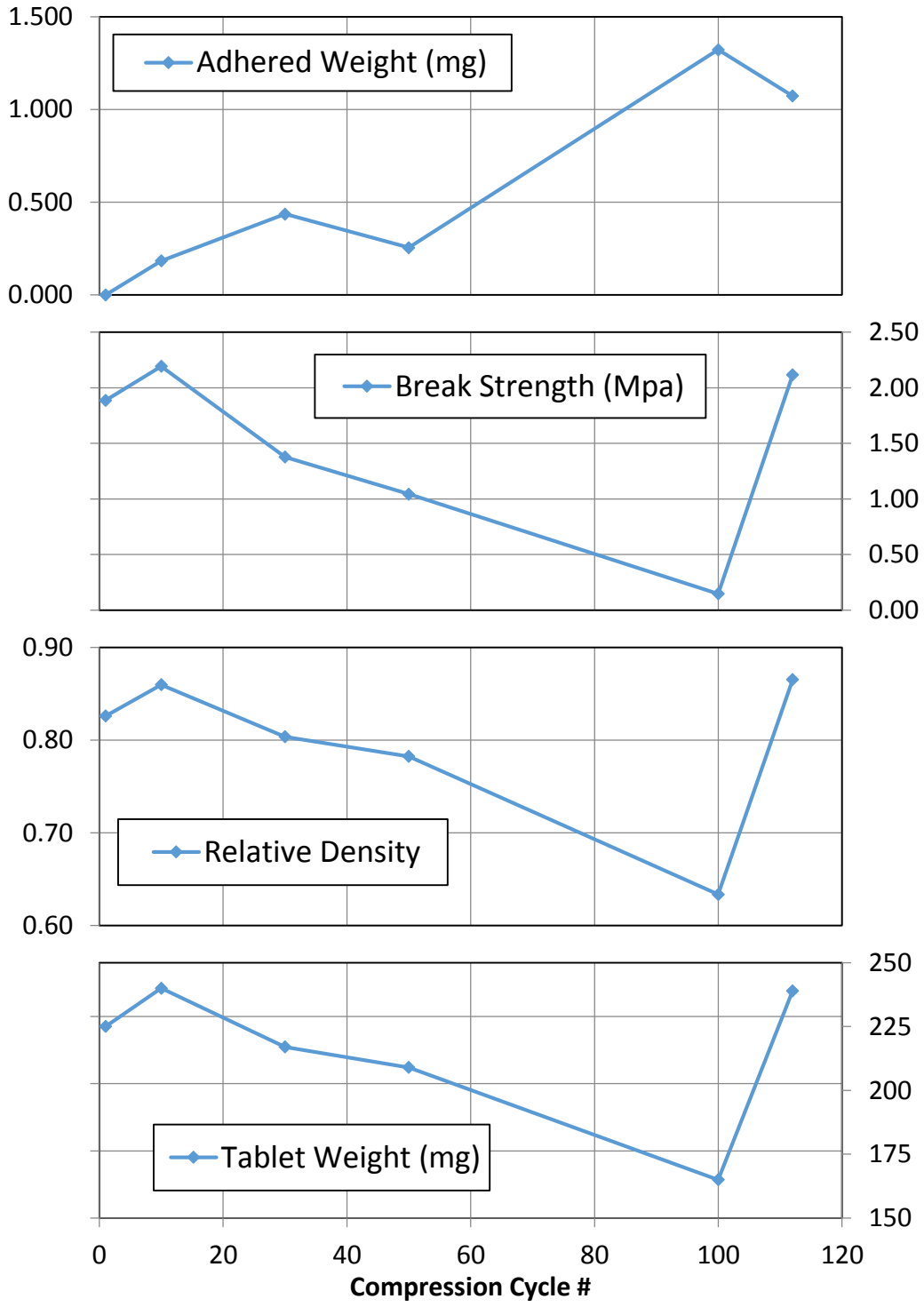



*Figure 22 – Data obtained for 30% IBU-MIC formulation.*

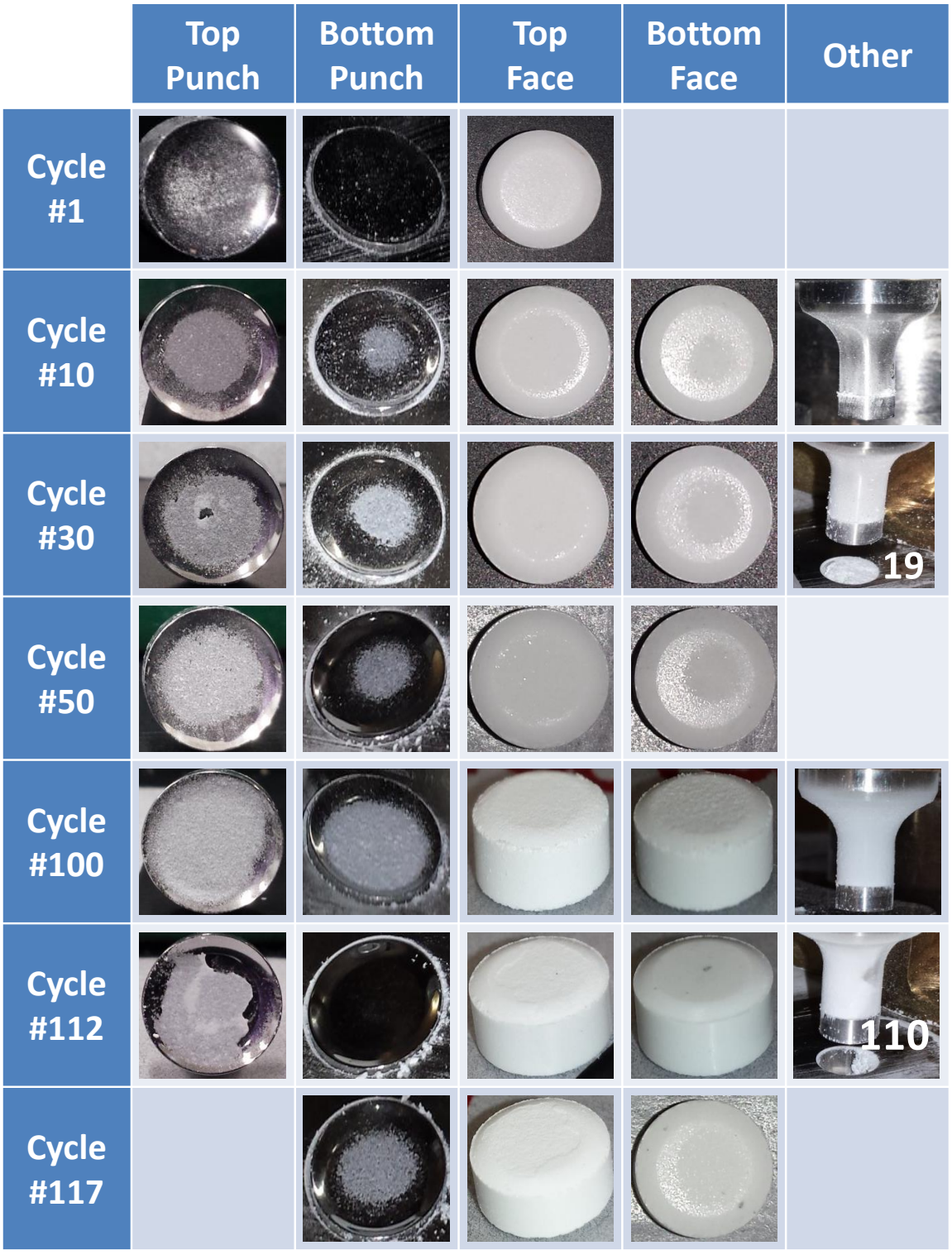



*Figure 23 - Photographs of punch faces and tablets for 30% IBU-MIC formulation.*

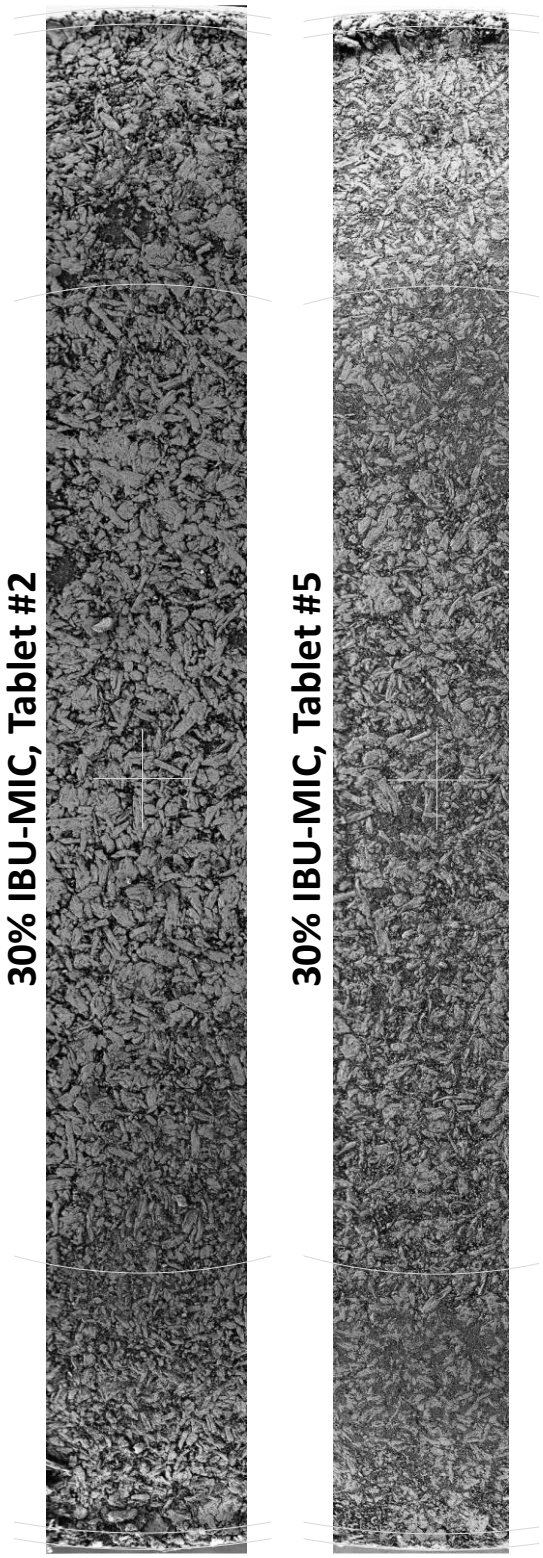



*Figure 24 – Stitched SEM image of the top face of Tablet #2 and #5 from 30% IBU-MIC Study. The bright regions are the surfaces of MCC particles while the dark regions consists of ibuprofen, MgSt and surface cavities.*

### 4.3: Evaluation of blend containing 30% Acetylsalicylic Acid

The sticking profile of the 30% ASA blend is shown in Figure 25. Evaluation on the 30% ASA blend showed a slow process of sticking. For 350 compression cycles, all recordings of adhered weight stayed below 100μg. The bottom punch face was always observed to be free of adhered particles and the top punch face showed minimal sticking that appeared only as a light dusting of particles (see Figure 26). Both the tablet weight and relative density was observed to increase.

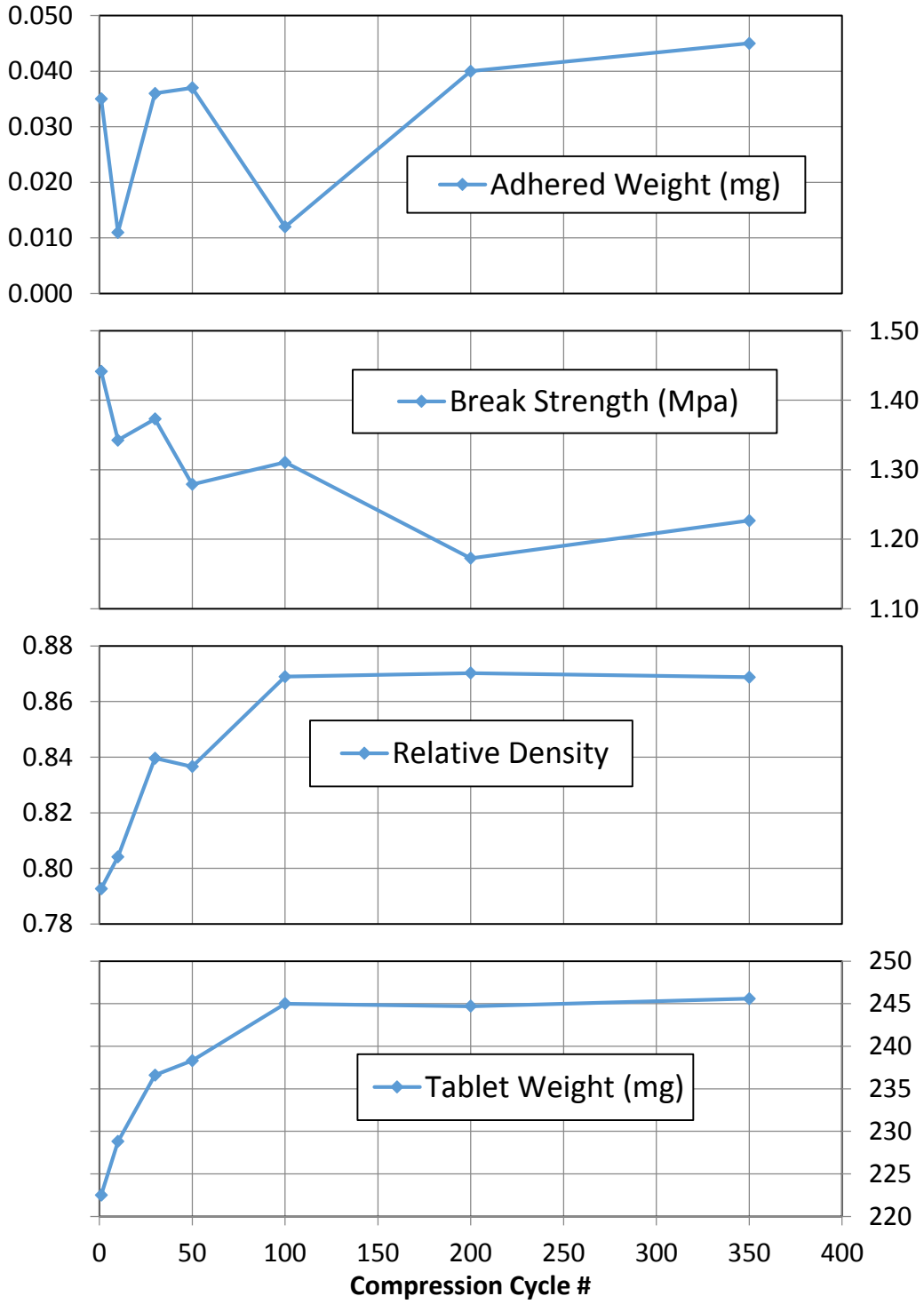



*Figure 25 – Data obtained for 30% ASA formulation.*

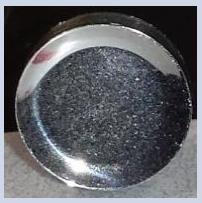
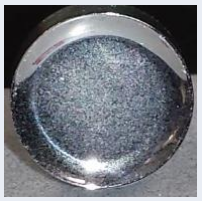
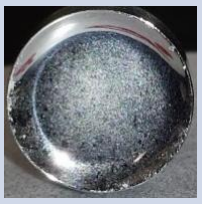
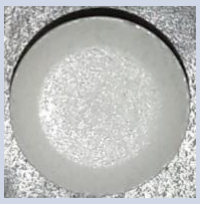
| | Top Punch | Bottom Punch | Top Face | Bottom Face |
|---|---|---|---|---|
| Cycle #1 |  |  |  |  |
| Cycle #10 |  |  |  |  |
| Cycle #30 |  |  |  |  |
| Cycle #50 |  |  |  |  |
| Cycle #100 |  | |  |  |
| Cycle #200 |  | |  |  |
| Cycle #350 |  | |  |  |

*Figure 26 - Photographs of punch faces and tablets for 30% ASA formulation.*

### 4.4: Evaluation of blend containing 21% Compound X - Batch 1

A schematic of the tablet shape chosen for manufacturing compound X is shown in Figure 27. Formulations containing compound X were found to exhibit sticking at certain curved regions of the tablet face as indicated in red in Figure 27. Three formulations of compound X (21% X-B1, 21% X-B2 & 21% X-B3) were evaluated using the standard cup tip. The sticking profiles from the three studies are shown in Figure 17. Each of the three formulations contain 21% drug loading. Formulations 1 and 2 (21% X-B1 & 21% X-B2) only differ slightly in that formulation 1 contains slightly higher mannitol and lower MCC. Formulation 3 (21% X-B3) is similar to formulation 2 except that the lubricant used is Compritol as supposed to Magnesium Stearate.

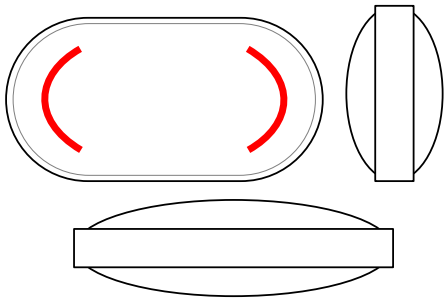


*Figure 27 – Schematic of tablet shape for compound X*

The sticking profile of the 21% X-B1 blend is shown in Figure 29. After 350 compression cycles of the 21% X-B1 formulation, the hopper was nearly empty and loose powder that was collected off the die table was poured back into the hopper. The break strength and tablet weight is found to increase after 350 cycles which is likely caused by the presence of densified material in the reclaimed loose powder. The densified material is shown in Figure 28. The densified material is likely shavings of compacted material from adhering to the side wall of the upper punch and the surface of the die table. Photographs of the tablet and punch faces for this study is shown in Figure 30. The upper punch tip initially shows a light dusting of powder at cycle #30 which progressively develops into a cap of adhered material in the center of the punch cavity. Sticking was not evident on the bottom punch for 21% X-B1.

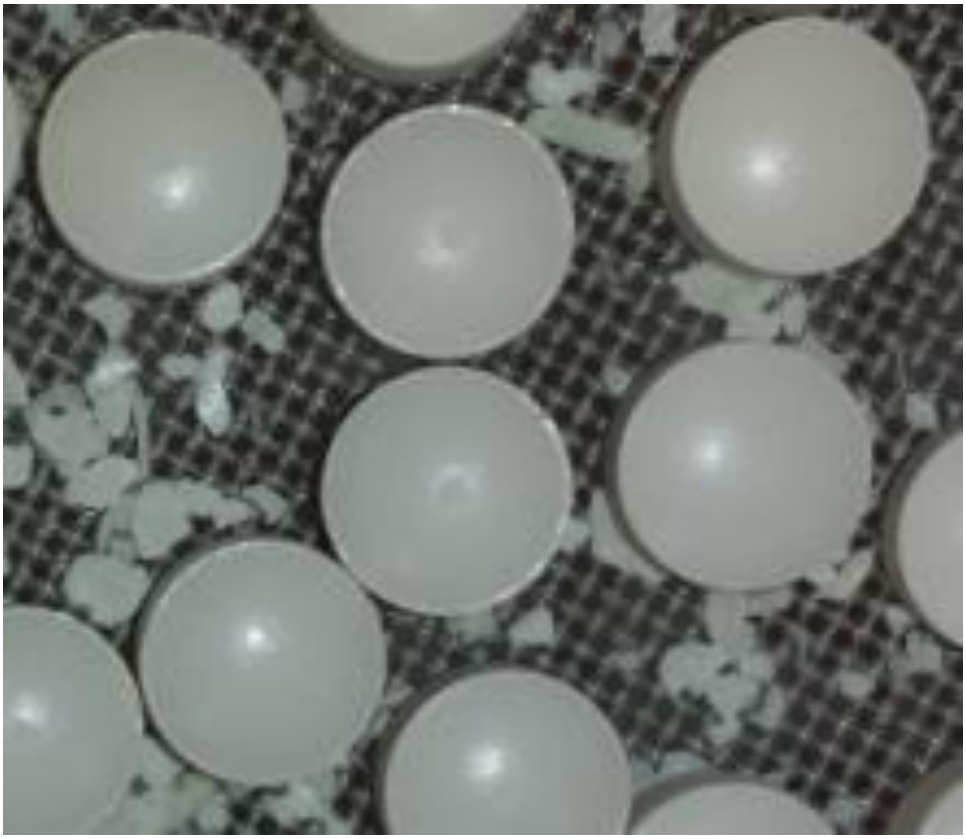


*Figure 28 – Reclaimed material from the 21% X-B1 formulation was sieved using a sieve with a 600µm opening (30 mesh). Compacted plate-shaped fragments are observed in the reclaimed powder.*

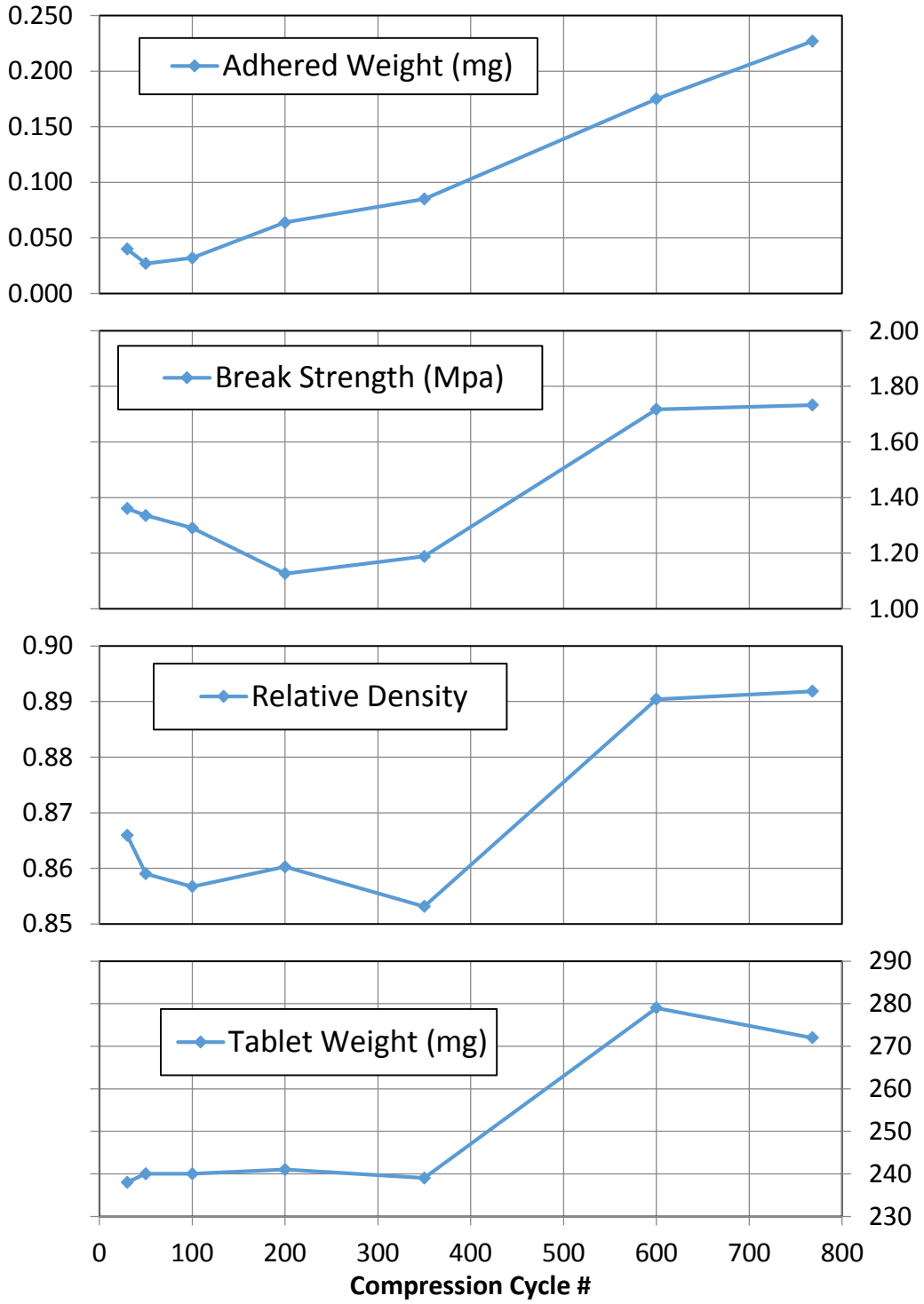



*Figure 29 – Data obtained for 21% X-B1 formulation.*

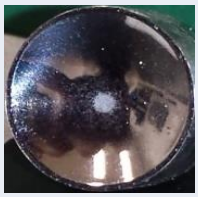
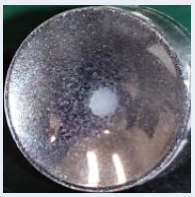
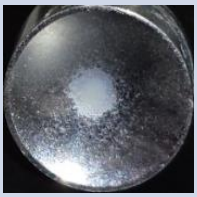
| | Top Punch | Bottom Punch | Top Face | Bottom Face |
|---|---|---|---|---|
| Cycle #30 |  |  | | |
| Cycle #50 |  | | | |
| Cycle #100 |  | | | |
| Cycle #200 |  | | | |
| Cycle #350 |  | |  |  |
| Cycle #600 |  |  |  | |
| Cycle #768 |  | |  | |

*Figure 30 - Photographs of punch faces and tablets for 21% X-B1 formulation.*

### 4.5: Evaluation of blend containing 21% Compound X - Batch 2

The sticking profile of the 21% X-B2 blend is shown in Figure 31. For the 21% X-B2 blend, the upper punch tip also initially shows a light dusting of powder at cycle #30 which progressively develops into a cap of adhered material in the center of the punch cavity. The tablet geometry is also observed to evolve as the punch face geometry is altered by adhered material. A picture of the top tablet face at cycle #200 is shown in Figure 32. A flat region in the center of the top face of the tablet is observed which results from the flat surface of the cap adhered to the upper punch tip. Furthermore, a film of material adhered to the periphery of the cap is formed by cycle #600. This film appears to have grown in thickness by cycle #650 at which point the film and the cap is observed to leave a noticeable impression on the tablet face. Between cycle #600 and #650, the bottom punch tip appears to have developed a circular ring of adhered material.

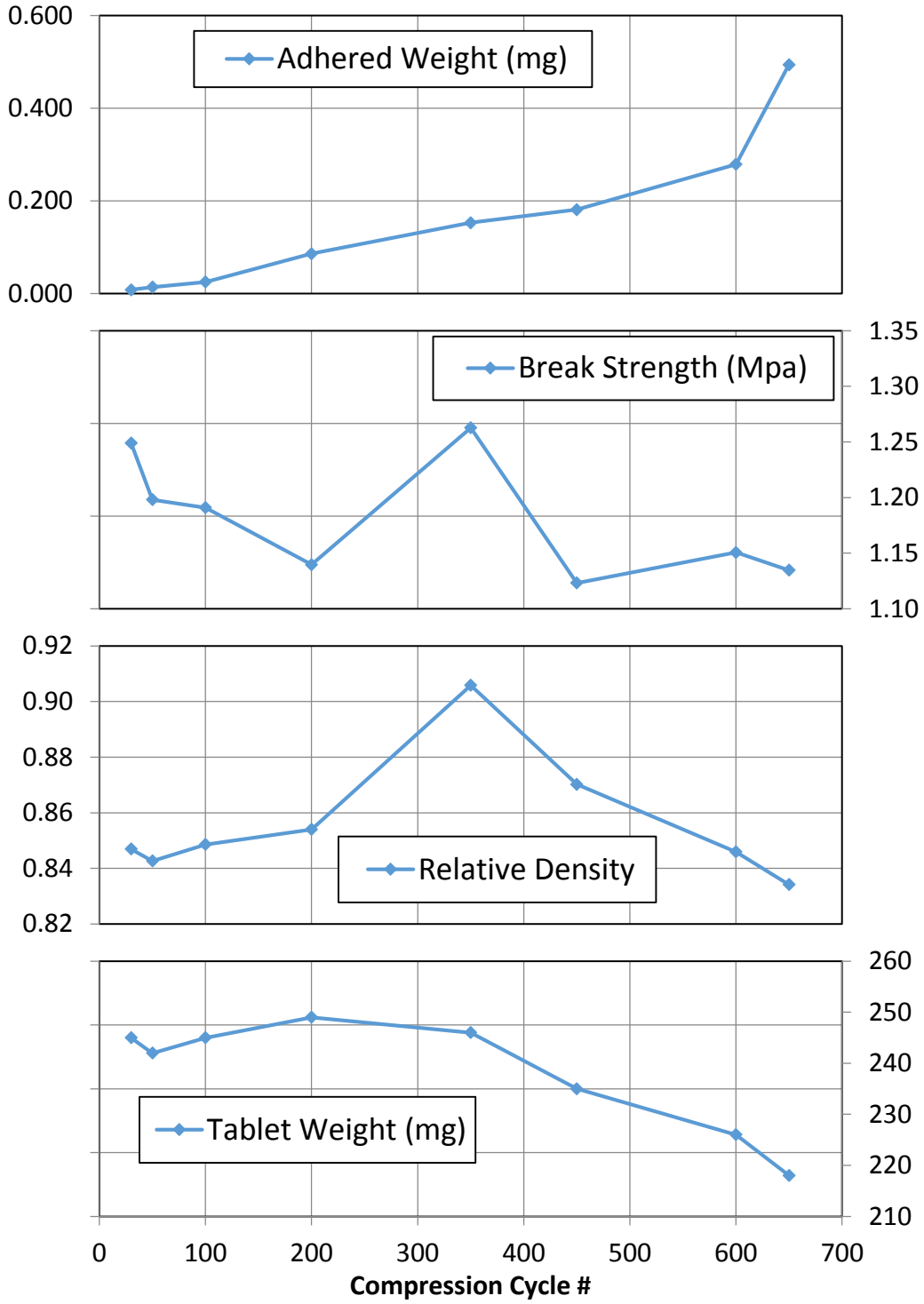



*Figure 31 – Data obtained for 21% X-B2 formulation.*

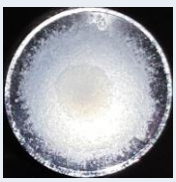
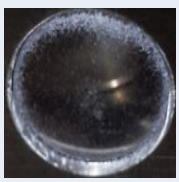
| | Top Punch | Bottom Punch | Top Face | Bottom Face | Other |
|---|---|---|---|---|---|
| Cycle #30 |  | |  |  | |
| Cycle #50 |  | |  |  | |
| Cycle #100 |  | |  |  | |
| Cycle #200 |  | |  |  |  |
| Cycle #350 |  |  |  | | |
| Cycle #450 |  | |  | |  |
| Cycle #600 |  | |  |  | |
| Cycle #650 |  |  |  |  |  |

*Figure 32 - Photographs of punch faces and tablets for 21% X-B2 formulation.*

### 4.6: Evaluation of blend containing 21% Compound X - Batch 3

The sticking profile of the 21% X-B1 blend is shown in Figure 33. For the 21% X-B3 blend, the upper punch tip initially develops a film of adhered material at cycle #30. Then a distinctly observable cap region is developed in the center of the punch cavity at cycle #350. The central cap is observed to grow in thickness with continued compression cycles. The impressions imprinted on the tablet face by the top punch tip becomes evident by cycle #200 and is shown in Figure 34. The bottom punch tip is observed to gradually film at cycle #350. At cycle #550, the bottom punch develops a circular ring of adhered material on top of the film. A complementary geometry is also observed on the bottom face of the tablet. Both 21% X-B1 and 21% X-B2 show similar and reduced sticking behavior while 21% X-B3 shows significant sticking. The break strength of tablets of the 21% X-B3 blend are considerably higher than those of 21% X-B1 and 21% X-B2 while the relative densities are comparable for all three formulations. By comparing the appearance of the upper punch tip in 21% X-B1 and 21% X-B2 at cycle #350, it is evident that 21% X-B2 exhibits more sticking (adhered wt. = 153µg) than 21% X-B1 (adhered wt. = 85µg). In contrast, 21% X-B3 shows a significant increase in sticking at cycle #350 (adhered wt. = 2200µg). All the formulations show different patterns of sticking that evolve with the compression cycles.

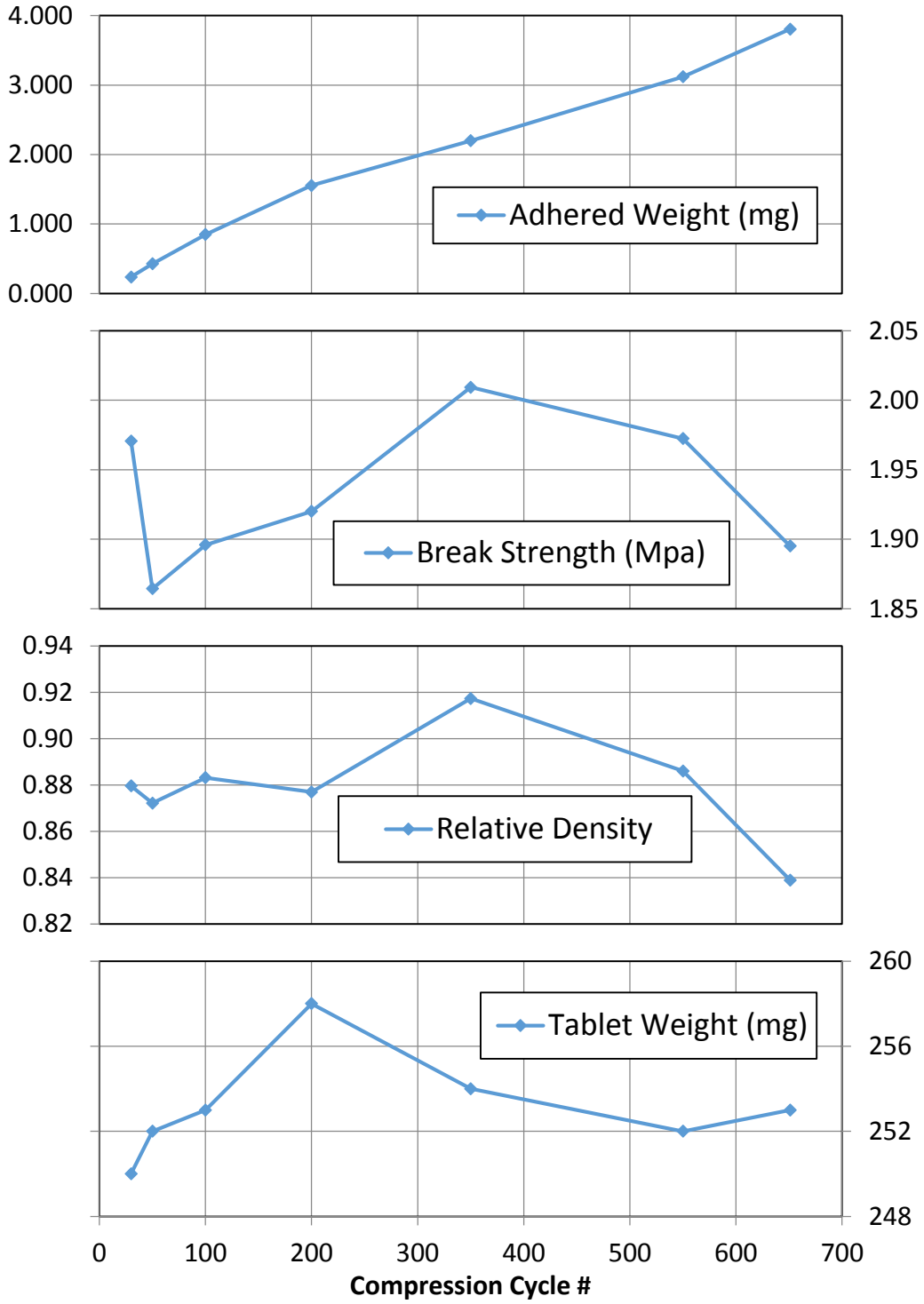



*Figure 33 – Data obtained for 21% X-B3 formulation.*

| | Top Punch | Bottom Punch | Top Face | Bottom Face | Other |
|---|---|---|---|---|---|
| Cycle #30 |  |  |  |  | |
| Cycle #50 |  |  |  |  | |
| Cycle #100 |  |  |  |  | |
| Cycle #200 |  |  |  |  |  |
| Cycle #350 |  |  |  |  | |
| Cycle #550 |  |  |  |  |  |
| Cycle #651 |  |  | | | |

*Figure 34 - Photographs of punch faces and tablets for 21% X-B3 formulation.*

### 4.7: Evaluation of powder containing 100% Ibuprofen

Compaction of pure Ibuprofen (100% IBU) was conducted in a separate study in order to observe the onset of sticking. A different batch of Ibuprofen was used in this work and the average particle size (x50 = 60µm) of this batch (shown in Figure 36) is larger than that used in the 30% IBU formulation (x50 = 36µm, shown in Figure 16). An SEM image of the ibuprofen sample as received from the supplier is shown in Figure 35. The upper punch tip was examined under a scanning electron microscope after the 1$^{st}$ compaction cycle and is shown in Figure 37 and Figure 38. The size of particles that remained adhered to the punch tip were roughly on the order of 50µm and below. A small fraction of particles were observed to be deformed and a larger fraction consisted of un-deformed or minimally deformed particles. A magnified image of a deformed particle is also shown and appears to be completely different in morphology compared to un-deformed Ibuprofen. After approximately 20 compaction cycles with 100% IBU, the upper punch body was observed to accumulate a fine dusting of particles similar to that observed with the 30% IBU-MIC formulation, see Figure 39.

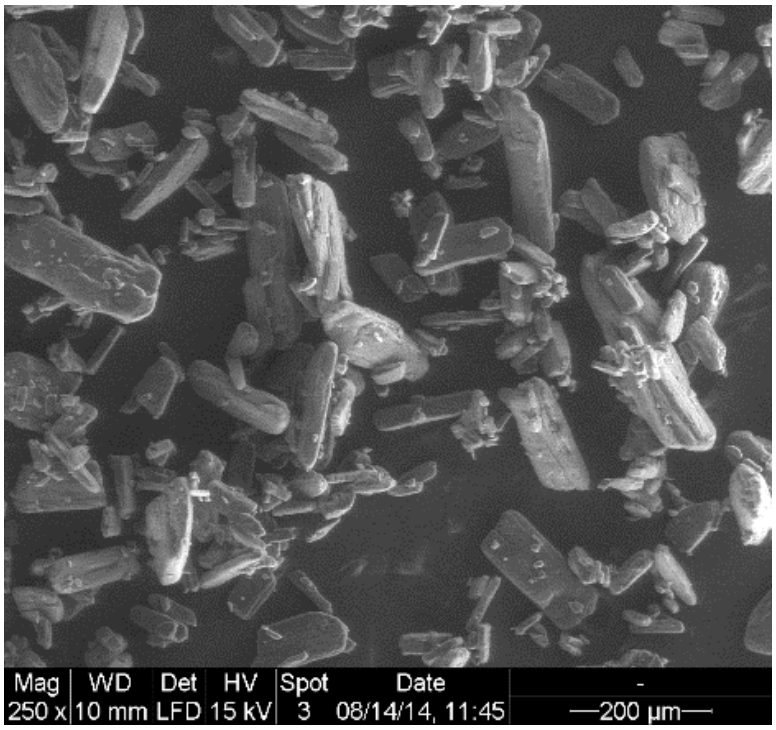
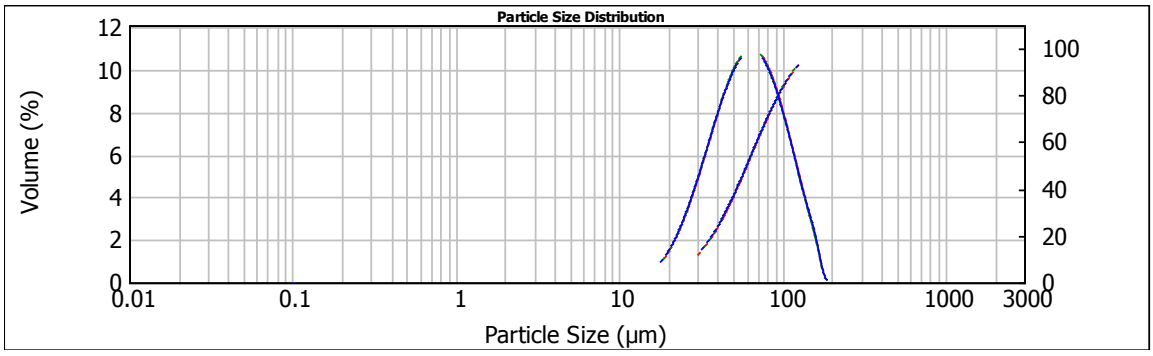



*Figure 35 – SEM image of Ibuprofen (as received from supplier).*




| | x10 | x50 | x90 |
|---|---|---|---|
| Ibuprofen | 27.9 | 60.0 | 114 |

*Figure 36 – Particle size distribution of Ibuprofen used in the 100% IBU study. The secondary axis is showing the cumulative volume percent.*

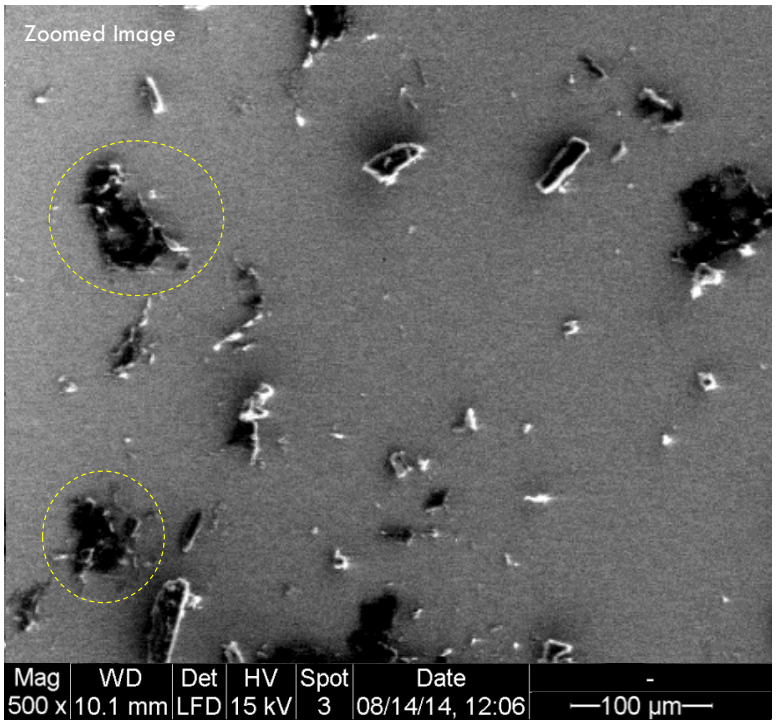



*Figure 37 – Upper punch tip after 1st compaction cycle with 100% Ibuprofen. Particles that are both minimally deformed and some that are heavily deformed are observed. A few deformed particles are highlighted by a circle in the image.*

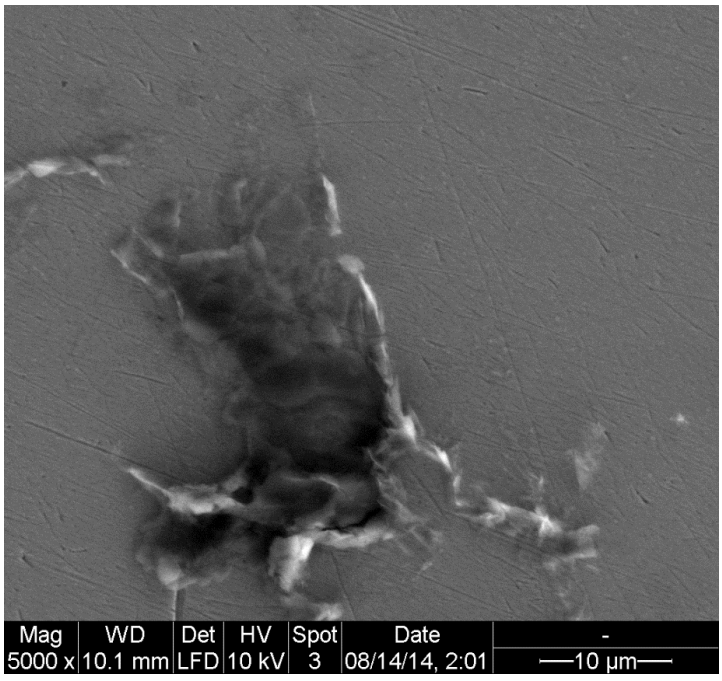



*Figure 38 –SEM image showing a heavily deformed particle after 1st compaction cycle with 100% Ibuprofen.*


*Figure 39 – Compaction with 100% Ibuprofen. Note: the upper punch body covered with fine particles adhered to its surface by static charge.*

### 4.8: Key observations

The following is a list of key observations made throughout all experimentations conducted on ibuprofen.

| # | **Observation** |
|---|---|
| 1 | Compaction with 30% IBU, 30% IBU-MIC and 100%-IBU, all showed an accumulation of fines particles coating the body of the upper punch. |
| 2 | Sticking is more pronounced on the top punch than the bottom punch. |
| 3 | All testing conducted with Ibuprofen showed that sticking started at the center of the punch face. |
| 4 | Milling of Ibuprofen resulted in ~90% reduction in the mean particle size (d50). |
| 5 | Micronized ibuprofen was observed to exhibit significant triboelectric charging and could not be initially sieved through a 710µm screen. Even after vigorous mixing with MCC on the Turbula blender, the powder revealed large lumps of aggregated Ibuprofen which was broken apart and pushed through the sieve. |
| 6 | Particles on the order of 50µm and below were observed on the punch tip after the 1$^{st}$ compaction cycle with 100% IBU. |
| 7 | A few deformed particles were also observed on the punch tip after the 1$^{st}$ compaction cycle with 100% IBU. |
| 8 | Capping was observed in tablets of 100% IBU. |
| 9 | With the 30% IBU formulation, a sudden increase in the amount of material adhered to the top punch was observed when die filling became inadequate. |
| 10 | Die filling with ibuprofen formulations was observed to be adequate initially but become progressively worse. |

| | |
|---|---|
| 11 | All Ibuprofen formulations tested showed ‘ratholing’, ie: improper funnel flow of powder in the hopper. |
| 12 | During compaction with Ibuprofen formulations, the sound coming from the instrument during each compression cycle became progressively louder. |
| 13 | Compaction with 100% IBU showed streaks of adhered material on the side walls of both the upper and lower punch tip. |
| 14 | Ibuprofen is very poorly hygroscopic and only shows a 0.1% moisture uptake from 40% to 90% RH. See Appendix A. |

# CHAPTER 5: DISCUSSION

## 5.1: Patterns in sticking

Sticking in tablet compaction is a complex phenomenon that is typically attributed by multiple factors. This fact is clearly evident due to the various factors reported in literature said to affect sticking. Therefore the mechanism of sticking with one formulation may differ from that observed with another. With the ibuprofen formulations (30% IBU & 30% IBU-MIC) tested in this work, the evolution of sticking involves a filming and layering process. At the very onset of sticking, particles must first adhere to the punch face as shown in Figure 40A. This initial adherence appear as a light dusting of powder on the punch face. Further sticking will result in a filming layer of particles adhering to the punch face. It is this initial layer that is responsible for adhesion on to the punch face. As sticking progresses, particles from the tablet face must now adhere to the surfaces of particles that are already making first contact with the punch face as shown in Figure 40B. Particles will continue to adhere by gradually layering on top of each other as shown in Figure 40C. Particles that form subsequent layers are held together by cohesive forces between them. This event results in the growth in thickness of the adhered material.

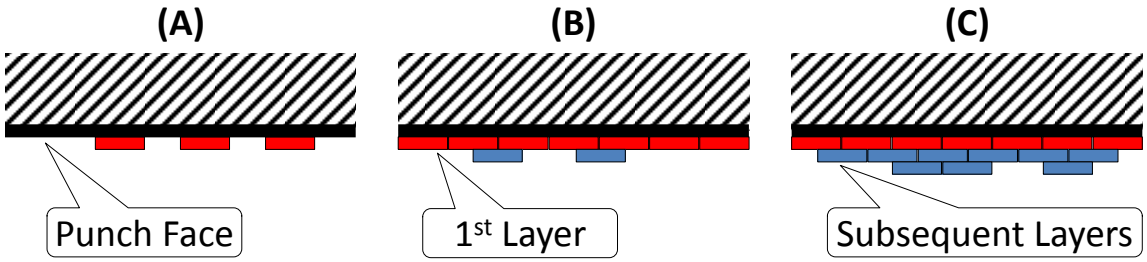



*Figure 40 – Schematic illustrating the filming and layering involved with sticking. The red blocks represent particles that make first contact with the punch face resulting in filming. The blue blocks represent particles that cause the layering and growth of the adhered material.*

The studies conducted in this work reveals that during sticking, the materials adhered to the punch tip can evolve to exhibit various geometrical patterns. It is also observed that the

bottom punch tip consistently exhibits less sticking than the top punch. Sticking in all multi-component formulations tested in this work show that the central region of the punch tip accumulates material faster than the peripheral regions. As the punch tip is accumulating material, the geometry of the compressing face is also evolving. For example, the punch face at cycle #550 in the 21% X-B3 study (see Figure 34) shows a thick cap region in the center of the cavity surrounded by a film. The growth of the film and cap on the upper punch tip is coupled with the growth of the ring of adhered material on the bottom punch face at cycle #550. As the weight of adhered material on the punch face increases, the total weight of the material essentially loaded in the die during compaction increases. This is because the weight of the powder filled into the die (ie: fill weight) plus the weight of the adhered material on the punch tip is higher relative to a situation where the punch tip is clean with no sticking. Compacting a larger quantity of material in the die while keeping the vertical displacement of the main compression roller constant will result in higher compression forces exerted onto the compact.

It was visually observed that inadequate die filling was often coupled with the pickup of large chunks of material on to the punch face. A photograph of the punch face during this event is shown in Figure 18 for the 30% IBU study after at the 450$^{th}$ cycle. However this accumulation of material is not the same mechanism of sticking that was observed prior to this event which is a slow layering process. The large chunks picked up by the punch are fairly loosely adhering material that can be blown off by compressed air.

### 5.2: Pressure dependence

The abrupt and complete detachment of adhered material from the bottom punch and partial detachment from the top punch when die filling was briefly improved was observed in the 30% IBU-MIC formulation at cycle #112. It is interesting to note two observations here: (1) the

upper punch face consistently showed more sticking and accumulated material faster than the lower punch and (2) when the punches showed an abrupt loss in adhered material, a complete loss on the lower punch and a partial loss on the upper was observed. This result indicates that sticking with ibuprofen exhibits a pressure dependence. In order to properly evaluate the effect of pressure on sticking, it would be necessary compress tablets to varying relative densities. Such experiments with ibuprofen have been previously conducted and reported in literature (59,39).

When the die is only partially filled, the maximum compressive force exerted by the punch on the powder bed would be lower than that of a properly filled die. As the die filling suddenly improves when sticking is present, the total weight of material loaded into the die increases. Therefore, the compressive force exerted by the punch would also increase resulting in a harder compact. It is well known that when sticking is present, a remedy to remove the adhered material is to abruptly increase the compressive force (58). This observation is in agreement with results reported in literature for compaction with Ibuprofen formulations (59,39). The accumulation and loss of adhered weight with Ibuprofen is a cyclic a process.

### 5.3: Fragmentation and particle size

The study conducted with micronized ibuprofen (30% IBU-MIC) clearly demonstrates that the reduction in particle size results in increased sticking. The micronization of ibuprofen resulted in a ~90% decrease in mean size and this suggests that ibuprofen is brittle and can be easily fractured. For comparison, micronization of MCC using the same milling conditions resulted in only a ~55% decrease in mean size (see Appendix E). It is also reported in literature that Ibuprofen undergoes fragmentation under compaction (71). Sticking is observed to occur in materials such as lactose, mefenamic acid and Calcium hydrogen phosphate dehydrate which are also reported

to undergo fragmentation (54). A number of other observations documented in the present work strongly indicates that particle size plays a major role in sticking of ibuprofen.

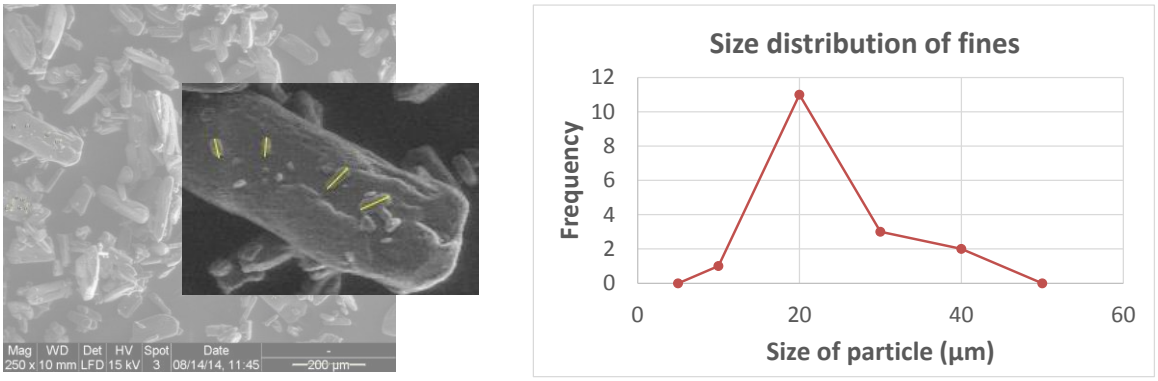



*Figure 41 – Particle size estimation by image analysis on the fine particles observed to adhere on to the surface of the larger particles of ibuprofen (as received from supplier). Mean size is calculated to be ~15µm. The zoomed inset image on the left highlights a few surface particles included in the measurement.*

An SEM image of the ibuprofen crystals used to prepare the formulation for the 30% IBU study is shown in Figure 35. The presence of fine particles on the surface of large particles can be confirmed in this image. Manual measurements were conducted using image analysis in order to estimate the size of the fine particles observed in the image. The results of this estimation are shown in Figure 41. The average size of the fine particles is on the order of 15µm. Particle size data (by laser light scattering) on this batch of ibuprofen (see Figure 16) shows that roughly about 10% of particles by volume have sizes on the order of 10µm and under. Particle size data on the micronized version of this batch used in the 30% IBU-MIC study (see Figure 16) shows that roughly about 90% of particles by volume have sizes on the order of 10µm and under. The marked difference in the fraction of fine particles between the 30% IBU and 30% IBU-MIC blends is the single most obvious powder attribute that qualitatively scales with the marked difference in their sticking behavior.

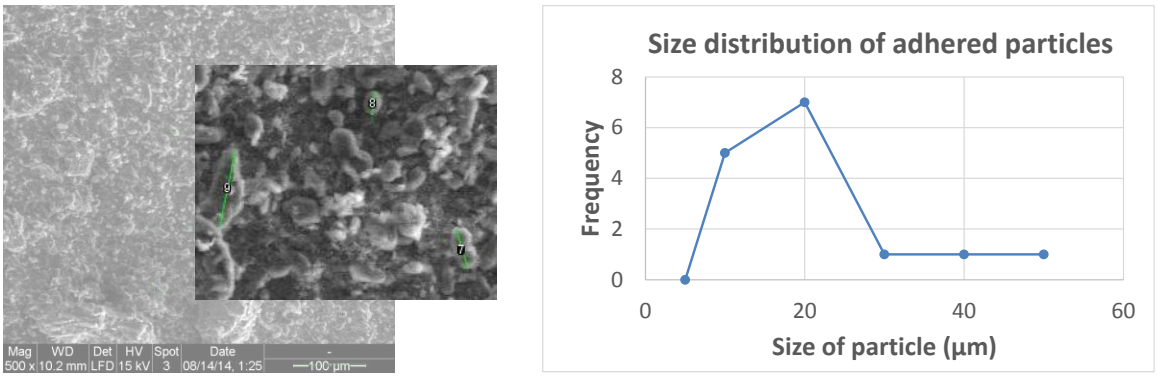



*Figure 42 – Particle size estimation by image analysis on an SEM image showing the surface of the adhered material on the punch face for the 30% IBU formulation after the 450$^{th}$ compression cycle. The zoomed inset image on the left highlights a few particles included in the measurement.*

An SEM image taken of the surface of the punch after the first compression cycle with 100% ibuprofen is shown in Figure 37. Particles that are both minimally deformed and some that are heavily deformed can be observed on the punch tip. It can be seen that the size of the minimally deformed particles were roughly on the order of 50µm and below. An SEM image taken of the surface of the punch after the 450th compression cycle with the 30% IBU formulation is shown in Figure 20. In this image, it is evident that the material adhering to the exterior surface of the adhered mass consists of small particles. Manual measurements were conducted using image analysis in order to estimate the size of these particles. The results of this estimation are shown in Figure 42. The average particle size was on the order of 15µm.

The results presented clearly indicate that the size of the particles adhering to the punch face is small (well below 50µm). The average size of adhering particles is estimated around 15µm and this indicates the existence of a size dependence having to do with sticking. Furthermore, the presence of fine particles during compression can form plugs between the die wall and the side wall of the punch tip. This is evidenced by the streaks of adhered material on the die wall which was observed to occur in both ibuprofen and ASA. This can result in poor air evacuation during

compression and cause air entrapment within the compact. However, it is currently not clear whether this occurs and what its effect would be on sticking.

### 5.4: Triboelectric charging

The various effects of triboelectric charging with ibuprofen was observed numerous times throughout this work. During the micronization of ibuprofen, it was observed that the micronized powder exhibited significant triboelectric charging. The micronized powder was very difficult to handle and could not be easily sieved during formulation preparation for the 30% IBU-MIC study. The material was also observed to be very cohesive. Although the particle size of this powder was on the order of about 5µm on average (see Figure 16), the material by itself could not be sieved through a sieve opening of 710µm (25 Mesh). Mixing of the micronized powder with MCC allowed better handling of the material. It was after this procedure that the material could be sieved.

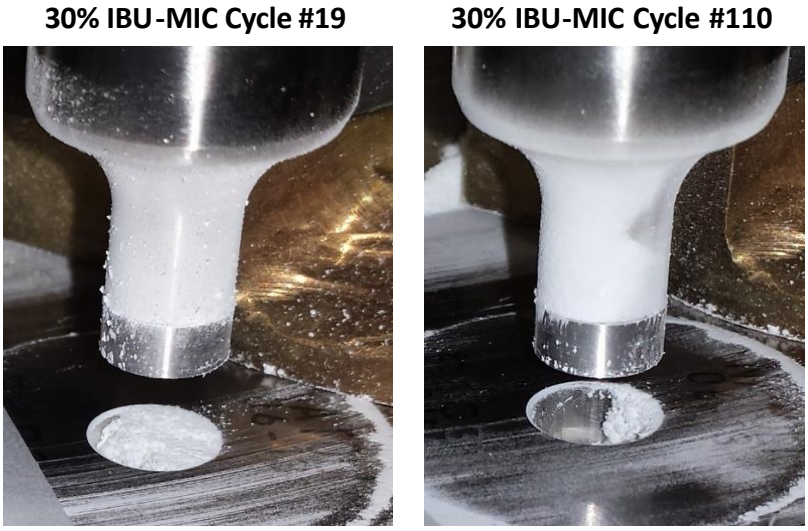



*Figure 43 – Showing the differences observed in die filling for the 30% IBU-MIC formulation. Die filling was observed to worsen with successive compression cycles. The images were captured just before the start of compression. The neck of the upper punch is observed to continually accumulate a dusting of fine statically charged powder.*

The dusting of fine statically charged powder on the punch body was observed in all studies dealing with the compaction of Ibuprofen (100% IBU, 30% IBU & 30% IBU-MIC).

Photographs of the punch showing this effect is presented in Figure 43 The coating of the punch body by fine particles may be further facilitated by the evacuation of air from the powder bed as the top punch plunges into the die. This process can eject some powder upwards from the periphery of the powder bed allowing particles to become airborne and thus adhere onto the punch body. A similar phenomenon is also observed in other materials that are reported to fragment under compaction and also exhibit sticking. An example of such a material is Mefenamic acid. This is evident in the photographs presented by Abdel-Hamid and Betz (54) that show the dusting of powder on the punch body. Moreover, die filling was observed to progressively worsen with ibuprofen formulations, see Figure 43. This may be due to triboelectric charging of the powder in the force feeder as the powder is pushed around by the rotary paddles. Triboelectric charging can increase the cohesiveness of the powder blends and decrease powder flow. This can occur in blends containing components that can charge oppositely causing them to be attracted to each other (73).

An image of a single tablet compacted with 100% ASA is shown in Figure 44B. The tablet is observed to be fully coated with loose particles of ASA that are statically charged. The loose particles were picked from the die tablet as the tablet was ejected. ASA exhibits similar properties with ibuprofen in that it is poorly hygroscopic (see Appendix C) and prone to significant surface charging as observed with the compaction of 100% ASA. It is interesting to note that the ASA powder initially when poured into the die did not exhibit static charging. It was only after the tablet was formed and ejected that loose ASA particles on the die table were observed to attract to the tablet. It may be so that charging of ASA particles on the surface of the tablet occurs as the powder is rubbed against the metal surfaces of the punch and die. The attraction of loose powder from the die table may indicate that the ASA powder and ASA on tablet surface may be oppositely charged. The average particle size of ASA used in this work is on the order of 216µm (see Appendix

I). Low levels of static charging of ASA may not be evident due to the large mass of individual ASA particles.

Similarly, fine charged particles in the powder or from the surface of tablets may adhere to punch surfaces as a result of electrostatic induction. In a lubricated blend, the fragmentation of particles will results in the creation of new non-lubricated surfaces and may facilitate static charging. Furthermore the presence of asperities on the particle surface can cause the accumulation of surface charge. Shimada et al (17) demonstrated this effect on glass particles. In their experiment, glass beads with smooth surfaces exhibited less adhesion while irregular shaped glass exhibited increased adhesion attributed to triboelectric charging.

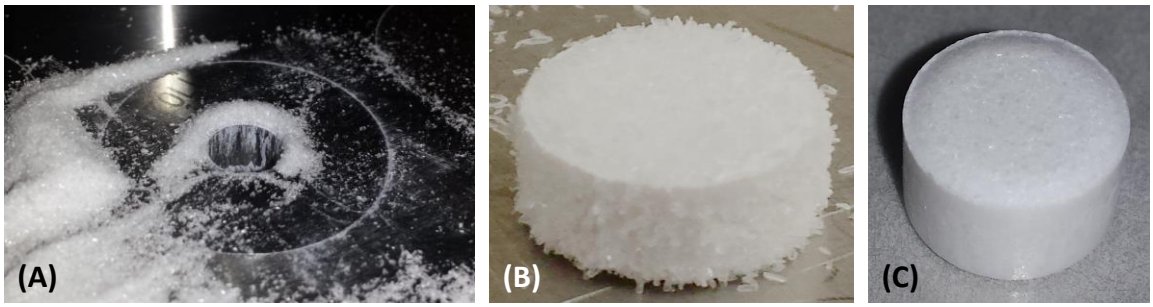



*Figure 44 – Compaction of a single tablet of 100% ASA to a relative density of 0.92. (A) Showing the streaking of die wall by ASA. (B) Ejected tablet is coated with loose statically charged ASA particles that picked up from the die table. (C) Tablet was air-dusted to remove loose particles.*

The fundamental mechanism by which toner particles are deposited on to the surface of paper deals with the manipulation of surface charging. The adhesion of toner particles is demonstrated to be significantly influenced by patchy surface charging due to their irregular morphology (11). The surface morphology of ibuprofen particles tested in this work was found exhibit a rough surface texture. Sharp surface asperities can enhance the ability of the powder to accumulate static charge. An SEM image showing the surface of ibuprofen particles is presented in Appendix F. It is probable that the static charging of particles can contribute to sticking. This

phenomenon may facilitate the pickup of fragmented ibuprofen particles off the tablet face and onto the surface of the adhered mass on the punch tip.

### 5.5: Observations on surfaces of tablets and punch

A number of important observations regarding the appearance of both the punch and tablet surfaces affected by sticking are noted in this work. Some of the interesting observations made with ibuprofen offer certain clues regarding the process of sticking. The surface of the punch tip after the first compression cycle with 100% ibuprofen revealed the presence of both heavily deformed particles and minimally deformed fragments, see Figure 37. The presence of heavily deformed particles adhering directly on the punch face indicates that surely ibuprofen can be squeezed and smeared on to the surface instead of just infinitely fragmenting under compression. The punch tip after the 450$^{th}$ compression cycle with 30% IBU formulation also showed the presence of several minimally deformed fragments, see Figure 20. The presence of minimally deformed fragments observed to adhere either directly on to the metal surface or on to the adhered mass on the punch face indicates that there may be a process that allows these particles to at least initially adhere to the punch face before being pressed on.

Fragmentation of ibuprofen will generate fine particles that are statically charged and consisting of surfaces that are not lubricated. It has been observed in this work that fine charged particles can adhere on to the punch body during compression. It may be also possible for the punch face to pick up fine charged particles off the tablet face. An SEM image of the top central region of a tablet from the 30% IBU-MIC study is shown in Figure 45. The image shown is of the tablet made from the 2$^{nd}$ compression cycle. The interstitial spaces between the MCC particles are observed to primarily consist of cavities and fragments of ibuprofen. It is possible that fragmented particles of ibuprofen can be picked up by the punch tip from these interstitial regions

on the tablet surface. The initial adhesion of these particles on the punch tip may be dominated by electrostatic forces. A schematic illustrating this concept is shown in Figure 46.

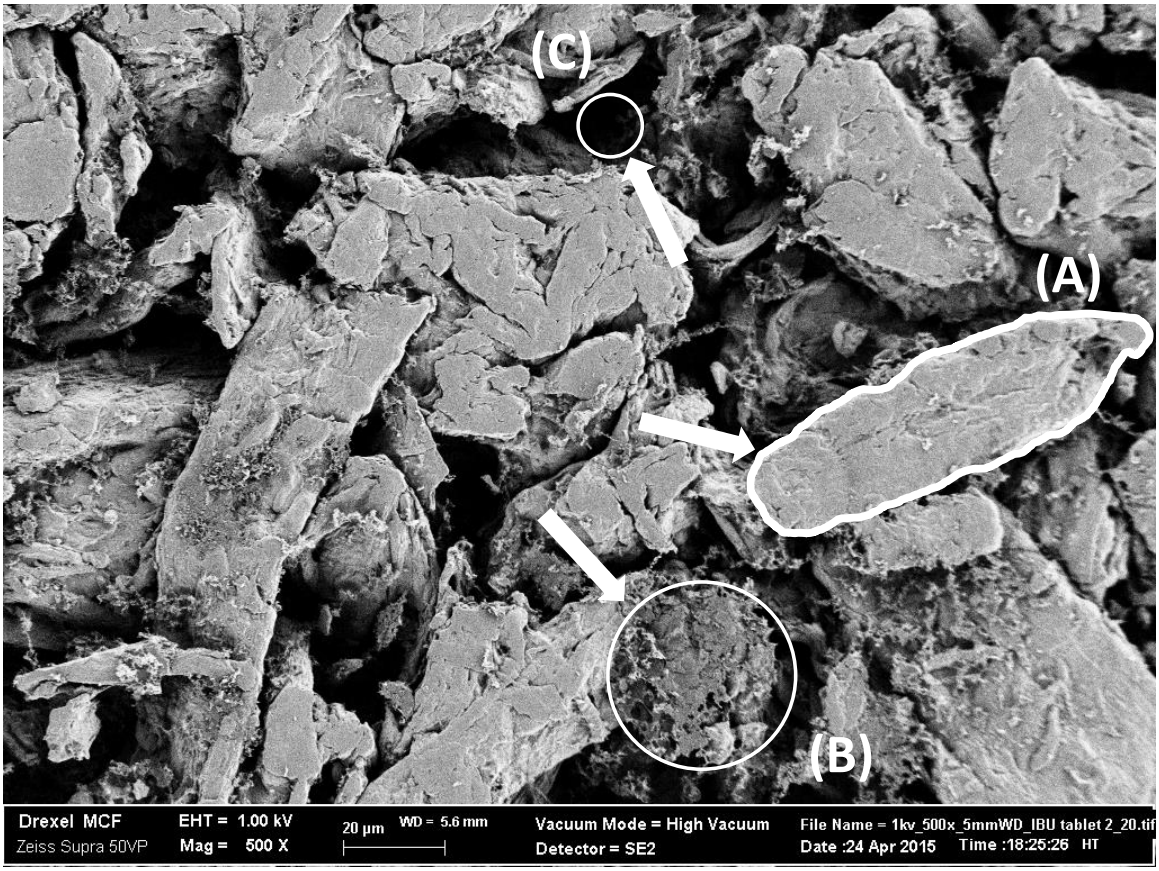



*Figure 45 – SEM image of the top center of a tablet (30% IBU-MIC, cycle #2) consisting of 30% micronized ibuprofen. The bright regions are flattened MCC particles and an example of this particle is shown in (A). The interstitial spaces between the MCC particles primarily consist of fragments of ibuprofen appearing as a slightly darker shade of gray as highlighted in (B) or surface cavities appearing dark regions as highlighted in (C).*

MCC is not expected to adhere to the punch face to any significant extend. This is known because MCC can be visually identified from the SEM images due to its size and morphology. MCC is readily identified by its appearance on the tablet surface as large flattened particles which is not observed on the tip surface. Further evidence can be found in literature where elemental analysis by Energy Dispersive Spectroscopy (EDS) show MCC to not adhere to the punch face but to remain only on the tablet surface after compaction (8). In addition, HPLC analysis of the composition of material adhering to the punch face with Ibuprofen formulations show that the

adhered mass consists primarily of just ibuprofen alone (56). MgSt is also not expected to adhere on to the punch face or to the adhered mass to any significant extent. EDS data reported in literature on sticking formulations show that relatively, the tablet surface exhibits much higher levels of MgSt than the punch face (5,8).

Therefore it is reasonable to assume that in this work, the adhered mass on the punch face with ibuprofen formulations (30% IBU & 30% IBU-MIC) consists primarily of just ibuprofen. With this condition, the filming and layering process of sticking in ibuprofen formulations will require a mechanism that selectively removes ibuprofen off the tablet face and somehow pressed on to the face of the punch or on to the existing adhered mass. The exact mechanism of how this process occurs is not clear. Perhaps, static charging may enable ibuprofen fragments to initially adhere to the punch face by electrostatic forces and then later pressed on to the surface in a following compression cycle resulting in a layering process.

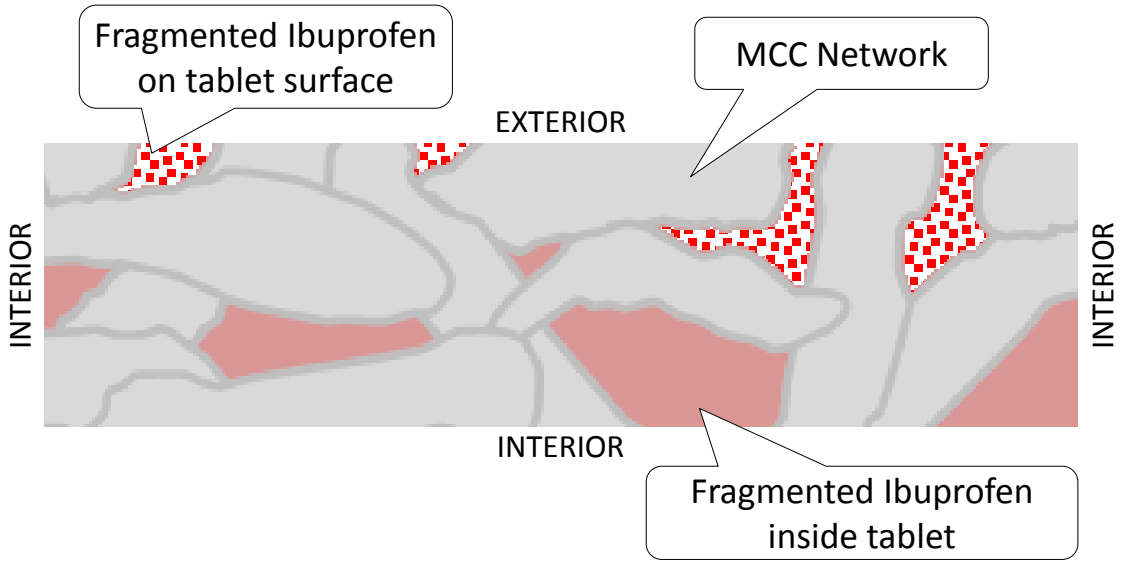



*Figure 46 – Schematic illustration of a compact consisting of ibuprofen and MCC. MCC is depicted as a networking mesh held together by making contact with neighboring MCC particles. Ibuprofen is depicted as the material contained within the mesh. The textured regions depict zones where fragmented ibuprofen that is in contact with the punch face.*

### 5.6: Temperature

Ibuprofen has a low melting onset of about 74$^{o}$C with a glass transition temperature of approximately -46$^{o}$C (see Appendix B). Moreover, ibuprofen and MgSt are reported to form eutectics that lower the melting onset of ibuprofen (10,77). The effect of temperature on sticking is not investigated in this work and is not expected to contribute to the sticking observed in the present studies for ibuprofen formulations. High compaction speeds and elevated temperatures are reported in literature to increase sticking with low melt compounds such as ibuprofen (59) and butyl paraben (4). However, the duration of the compression cycles (from the beginning of powder compression to the end of ejection) used for the present study was approximately 1.3 seconds which is much slower than typical large scale production speeds.

The sound coming from the instrument during each compression cycle (just as the top punch left contact with the main compression roller) was observed to increase progressively for the 30% IBU study. The tablet weights and relative densities in this study remained fairly constant. Therefore, the compression force exerted on the powder must have remained fairly constant as well. This observation thus indicate that the friction at the punch-die interface may have increased with successive compression cycles. This is further evidenced by the observation of streaks of adhered material on the die wall and on the side wall of the upper punch tip. Although such friction can cause a rise in temperature at the tooling interface, the punch tip probably will not accumulate heat with a slow compression speed. Therefore, sticking due to a temperature rise caused by tooling friction is improbable for the present study. Furthermore, it is not clear whether the amorphization of Ibuprofen particles occur at the punch surface when subjected to compressive and shear stresses during tablet compaction. If this event does occur, then it would be necessary to understand its implication on sticking.

### 5.7: Punch cleaning

The conditioning of the punch tip is known to affect sticking. It was discussed in an earlier chapter that factors such as punch surface roughness, punch surface chemistry and moisture can affect the level of sticking observed in various materials. Polished punch surfaces typically show score marks on the punch tip resulting from the polishing process. In some cases, the punch faces can contain contaminants such as residual polishing compound and can be difficult to clean. In a separate experiment conducted in this work, punch cleaning was observed to affect sticking of ibuprofen. A flat faced radius edge tip was cleaned with methanol and then dried with a KimWipe tissue. The tip face was then air-dusted by using compressed nitrogen gas. The punch tip was then immediately used to compression 100% ibuprofen into a tablet of 0.88 relative density. The punch tip was then examined by SEM in order to observe the effect on sticking. An SEM image of the punch tip is included in Appendix G.

The appearance of ibuprofen on the punch face was as if molten ibuprofen was poured on the surface creating an intimate contact and flowing into the polishing score marks. Although no further work was conducted to investigate this, it is evident that the cleaning of the punch face can affect sticking. It is important to note that ibuprofen is highly soluble in methanol on the order of about 50mg/ml according to manufacturer's product data sheet. There are two important factors that need to be considered here. (1) The cleaning of the punch tip in this case could easily seem sufficient since it was both wiped thoroughly and air-dusted. However the results show that this is not sufficient and that the punch tip did not properly dry. (2) The selection of the cleaning solvent was not ideal because ibuprofen is highly soluble in methanol. It is therefore imperative that tablet punches are properly cleaned and stored in order to avoid such complexities during tablet manufacture.

### 5.8: Capping and sticking

Tablets compressed with 100% ibuprofen exhibit the propensity to 'cap'. Capping is a term used to describe the horizontal splitting of the tablet that separates the top cap of a tablet from its body. Capping typically occurs at the top band edge of the tablet. Capping in tablets have been shown to be attributed to various factors such as the stress concentrations in the compact during compression and ejection, presence of fine particles and poor air evacuation during compression (58,81). An example of capping observed during diametrical compression of the tablet composed of 100% ibuprofen is shown in Figure 47A. In a separate experiment conducted in this work, 100% ibuprofen was compacted to a relative density of 0.91. The tip used to form this compact was not cleaned prior to testing. Partial capping was observed to have occurred after ejection of the tablet. The separated cap in this case remained adhered to the punch tip. The occurrence of capping and sticking is also observed with formulations of mefenamic acid (54). The observations presented here demonstrates that sticking can occur by failure in the compact at defect locations. In this case, the defect location lies in the capping zone. Capping was not observed in any of the studies involving MCC mixtures of ibuprofen (ie: 30% IBU & 30% IBU-MIC). It is also important to note that sticking with 100% ibuprofen does not always involve capping. It can occur as the adhesion of individual particles and also as randomly scattered islands of particles on the punch tip. This highlights the complex nature of sticking in that a single component powder like ibuprofen alone can exhibit various types of sticking by various processes.

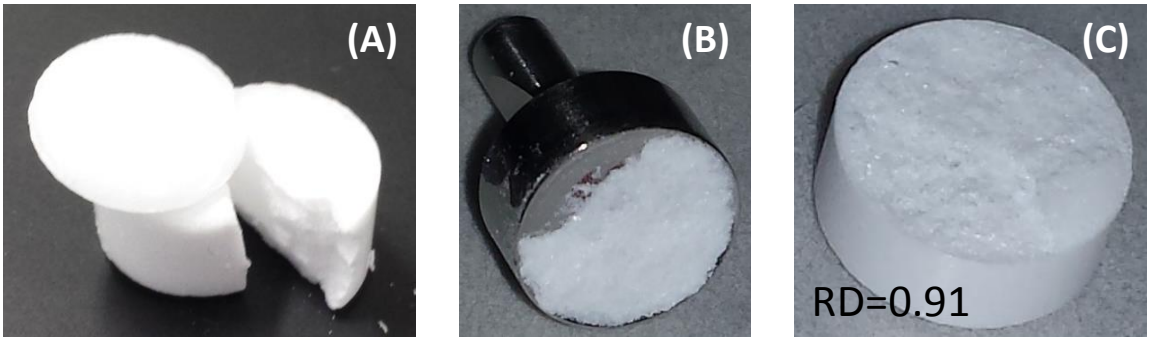



*Figure 47 – (A) Showing the fractured pieces of a tablet after diametrical compression. The tablet is composed of 100% ibuprofen was compressed to a relative density of ~0.85. (B) Showing the punch tip with a capped region adhered to its face after compressing 100% ibuprofen to a relative density of 0.91. (C) Showing the surface of the same capped tablet.*

### 5.9: Removable punch tip

The results presented in this work clearly demonstrate that the removable punch tip is a very useful tool to study sticking. It allows for the direct quantification of sticking by measurement of adhered weight as low as at least a 100µg. The small size of the tip makes it convenient to study the phenomenon of sticking compared to handling the entire punch. The small size also allows for a host of experimental techniques to be employed directly on the tip surface with ease. The punch tip method offers the advantage of quickly quantifying sticking by simple weighing and allowing for testing to resume by simply replacing the tip. This technique avoids having to remove the entire punch in order to inspect the tip or to clean its surface. However, handling of the tip must be done carefully not to disturb the adhered material. In the present punch tip design, material adhered to the side wall of the tip will be disturbed since this location is used to grip the tip when being handled.

The amount of material required to assess the propensity of sticking in a given formulation can vary depending on the equipment used and rate at which material can accumulate on the punch tip. For example, about 140 grams of material was prepared for the 30%

IBU study for testing on a rotary press. However, only about 80 grams (~340 tablets at 235mg each) could be comfortably used for the study. This is because about 60 grams of material was wasted in various ways such as priming the force feeder, loose powder on the die table, trial tablets prepared to adjust instrument to desired settings. In contrast, the data collected in this work show that the sticking propensity of formulations can be assessed in just a minimal number of compression cycles. For example, 50 compression cycles would be sufficient to compare the 30% IBU to 30% IBU-MIC formulations. However, the 30% ASA formulation showed a very slow process of sticking and may require over a 1000 compression cycles until the accumulation of adhered weight can reach detectable levels.

An alternative method to weighing the punch tip could be to measure the quantity of adhered material by liquid chromatography (HPLC). Quantification with this technique may reduce the number of cycles required assess sticking propensity and could allow for much improved resolution and accuracy. However, this technique can be time consuming and will require dissolving material on the punch tip. Therefore testing will need to be repeated to collect information at higher compression cycles. Sticking can be detected and qualitatively assessed by examining the punch tip by microscopic techniques such as SEM analysis. Such methods will only require very little material to test formulations.

The removable punch tip method is a quick and easy tool for formulators to evaluate sticking of various compression blends. In addition, the punch tips can be manufactured for relatively much cheaper than entire punches. However this technique does not allow for real time measurement of sticking and requires having to stop the tablet press to remove the tip. Therefore this technique is suitable for research use but may not be ideal for use as a manufacturing quality control. Furthermore, the removable punch tip may impose limitations on the maximum load that can be applied to the powder bed depending on design. For example, the threaded hole on the

punch tip where the set screw is placed to fix the punch tip on to the punch body can become a stress concentration point at high loads.

Although the removable punch tip method was used to assess sticking in the present work, the repeatability of this technique was not assessed. Therefore it would be necessary to assess how reproducible the results really are. For example, this would answer if the small difference observed in sticking between the 21% X-B1 & 21% X-B2 studies is real and reproducible. Nevertheless, the punch tip method by far offers significant advantages over many of the techniques found in literature that were discussed earlier. In summary, these advantages include cost, ease of use, quick and direct quantification of sticking and most importantly, the small form factor readily enables various experimentation of the surface to help researchers to begin to unlock the mysteries behind sticking.

# CHAPTER 6: FUTURE WORK

The data presented in this work clearly demonstrates the complex nature of sticking due to the several parameters that can simultaneously contribute to the issue. There are several questions that arise from this work that will definitely require further detailed studies on this topic. Without such work, it would be impossible to de-convolute the complexity of sticking. It is necessary to understand exactly how certain parameters affect sticking in order to effectively engineer formulations to mitigate this issue. Therefore the discussion below will present some of these questions and possible experimentation that can be conducted to answer them.sdf

## 6.1: Patterns in sticking

It was mentioned earlier that the appearance of sticking on the punch tip after the very first few compression cycles with the ibuprofen formulations (30% IBU & 30% IBU-MIC) appeared as a light dusting. SEM analysis on 100% ibuprofen revealed that both heavily reformed particles and minimally deformed fragments adhere on to the punch tip. It is not clear whether the minimally deformed fragments are strongly adhered to the tip or just loosely adhered perhaps by static charge. Therefore a statistical evaluation of the relative adhesion forces between these particles and the punch tip could measure how strongly they adhere to the punch tip. A common method described in literature to perform this type of evaluation is the centrifugal technique that was discussed in an earlier chapter. It may also be possible to qualitatively perform this assessment by examining the punch tip after subjecting the surface to compressed air.

It is necessary to identify whether there are physical differences between the various particles adhered to various locations on the punch tip. For example, it would be necessary to confirm whether the heavily deformed particle on the punch tip resulted in its amorphization

during compression. Similarly it is of interest to confirm whether the material observed to adhere on to the side wall of the punch tip exhibits any physical changes. Such physical changes to particles can bring about changes to their mechanical properties and may affect sticking. X-ray powder diffraction and spectroscopic techniques such as infra-red and Raman analyses may prove useful to answer these questions.

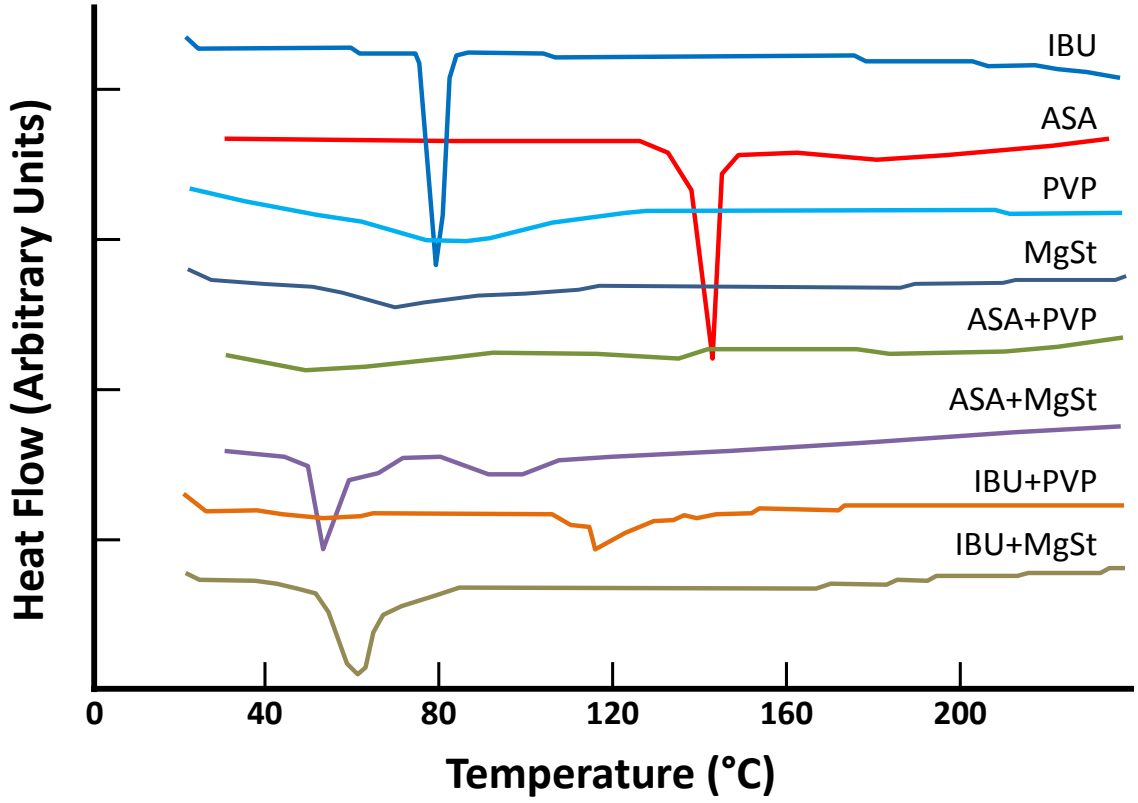



*Figure 48 – Schematic representation of the data reported by Tita et al (82) on ibuprofen and by Tita et al (83) on ASA. This plot shows the DSC thermograms of pure components and 1:1 mixtures of compound to excipient for ibuprofen and ASA.*

Furthermore, it is necessary to confirm the compatibility of the compound in question with the excipients chosen in the formulation. It was discussed earlier that MgSt is reported to increase sticking in ibuprofen and ASA. MgSt is also known to form eutectics with ibuprofen resulting in a reduction in the melting onset of ibuprofen. It is therefore imperative to understand how exactly MgSt causes the increase in sticking. Is it a thermal effect, a lubrication effect or

something else? Polyvinylpyrrolidone (PVP) is another excipient reported to affect the thermal properties ibuprofen and ASA. Differential Scanning Calorimetry (DSC) is a useful technique to study these effects. An overlay of the DSC data reported by Tita et al (82) on ibuprofen and by Tita et al (83) on ASA is illustrated in Figure 48. It can be seen that both Ibuprofen and ASA are affected by MgSt and PVP. HPLC can be used as a technique to identify if these interactions produce degradation products of the compound. This indicates that the impact of excipients on sticking of compounds may not only be purely mechanical in nature but may also involve chemical interactions.

The results presented in this work demonstrates that there are certain patterns to sticking. For example, sticking was observed to be more significant in central region of the punch tip. In studies where sticking gradually started out in the central region, the adhered film on the punch was only grossly in the center and grossly circular. In other words, the adhered film was neither perfectly circular nor perfectly in the center. It is curious why this occurs and one would need to examine if this is a random event or if it is dependent on some parameter. Perhaps one could repeat the experiment and verify if the same geometry occurs in the same orientation. If this is the case then the results would suggest that the punch surface is somehow responsible. If the same geometry and orientation is not reproduced, then one can argue that there must be some random process that results in the variation of circularity and orientation of the film.

Various other patterns of sticking were also observed in this work. For example, sticking was observed to be more pronounced on the upper punch than the bottom. The formulations with compound X using concave tips showed various geometrical patterns of sticking. This means that there exists some local conditions throughout the compact during the compression process that results in such patterns. In order to understand these conditions, it would be necessary the study the local properties, events and their evolution during the compression process. For

example, it would be necessary to understand factors such as friction coefficient at the die wall interface, internal angle of friction, local stresses and density distribution in the compact and powder displacements throughout the compression process. Numerical modeling of the compression of powders using Finite Element Method (FEM) would provide valuable insight regarding such local conditions in the compact. A popular model used for FEM analysis of pharmaceutical powders is the Drucker-Prager Cap (DPC) model. The model is particularly useful because it incorporates important factors such as inter-particle cohesion, friction, and the dependency of material properties on relative density.

The removable punch tip method can be used to conduct for a number of controlled experiments to investigate the effect of various parameters on sticking. For example, cleaning of the punch tip was demonstrated to complicate this issue with ibuprofen. Given the complexity of sticking, it is absolutely necessary that studies conducted on this topic are designed as well controlled experiments. This would require that a certain protocol is used for cleaning and storing the punch tips before testing.

### 6.2: Fragmentation

The data presented in this work suggests that the fragmentation of particles contributes to the sticking of ibuprofen. In order to study this effect, it is necessary to evaluate the extent of fragmentation in ibuprofen. Several methods can be used to assess this property and some may be better than others. For example, pure compacts of ibuprofen compressed to various relative densities can be broken apart and dispersed into an appropriate medium in order to conduct Particle Size Analyses (PSA) by laser light scattering. The dispersing media would possibly contain some surfactant and pre-saturated with ibuprofen. A clear dispersant can be produced by filtering the pre-saturated media. The poor solubility of ibuprofen in water (about 21µg/ml according to

manufacturer specifications) may allow for the dispersant to be aqueous based. A saturated dispersant with surfactant would to prevent dissolution of tablet fragments and aid in the dispersion of fragments into the media. Sonication may help to disperse the tablet fragments into individual particles. Similarly, PSA can be conducted on the material adhered to the punch tip. Other techniques may involve milling of ibuprofen and subsequently testing for particle size. Several milling techniques are employed in pharmaceutical industry such as air-jet milling and wet bead milling.

It was discussed earlier that the presence of fine particles can result in poor air evacuation and increased friction between the wall of the punch tip and the die wall. This condition can occur when fine particles begin to plug the tolerance space between the punch and the die. The more material plugging the tolerance space the more difficult it is for air evacuation. In this situation, air will need to escape the die with greater velocity. The air evacuation of the die can expel fine particles upwards as the upper punch plunges into the die downwards. Fine particles are observed to coat the neck of the punch body and this may be a result of air evacuation and statically charged particles. It would be interesting to determine the size of the particles coating the punch body and whether it is comparable to the size order of the interstitial spaces between the MCC particles on the surface of the tablet or to the size order of the particles adhering to the punch face. Furthermore, it is important to evaluate whether the fragmentation of ibuprofen can create weakly cohesive defect zones that can initiate cracks. Sticking in compacts of 100% ibuprofen was observed to appear as a pitted surface (see Appendix H). The pickup of large bodies of material that are a few hundred microns in size may be due to the presence of surface defects that can initiate cracks. FEM modeling of such conditions may provide insight into how surface defects can affect sticking.

### 6.3: Triboelectric charging

The data presented in this work suggests that static charge may play a role in sticking. The charging of particles was observed in both ibuprofen and ASA. In order to understand this effect, it would be necessary to somehow quantity the charging propensity of particles. An established technique cited in literature to conduct this type of work involves the use of a cyclone charger (74). In this technique, particles are spun around in a cylindrical container by a cyclone of air such that they interact with the inner surface of the container. The relative humidity and velocity of the air is controlled and the inner wall of the cylindrical container can be modified by inserts. Specialized metal inserts may be used such that the particle contacting surface closely resembles the face of the punch. The net specific charge accumulated by the powder can be measured by using a Faraday pail. The Faraday pail consists of two metal cups separated by an insulator such that the outer cup protects the inner cup from disturbances by external electric fields (73). The powder can be poured into the Faraday pail and the charge can be measured using an electrometer.

The cyclone charger technique can be a useful technique to not only measure the charging propensity of powders but also to study how charged powders interact with surfaces. Several factors can affect triboelectric charging of powders such as morphology, conductivity and humidity to name a few. Testing the electrical properties of powders and compacts such as resistance may provide useful information regarding the propensity of static charging. The effect of various parameters on powder charging can also be tested using the cyclone method in order to investigate their relationship with sticking. For example, it would be of interest to know how particle size and fragmentation affects triboelectric charging. Studies conducted on α-lactose monohydrate by Rowley (74) show that the accumulation of powder charge increases inversely with particle size when contacting a stainless steel surface. Rowley (74) also demonstrated that

α-lactose monohydrate becomes negatively charged when contacting stainless steel but positively charged when contacting PVC. However, ibuprofen in a formulation can rub against neighboring ibuprofen, MgSt, MCC, metal surface of a sieve, glass surface of blending jar and other possible surfaces before the powder even arrives at the press. Therefore it may be necessary to consider the effect of powder processing and choice of excipients that can affect charging.

An interesting question is whether charged fragments of ibuprofen on the tablet surface is picked up directly by the metal punch tip or by the existing adhered mass of ibuprofen on the tip or both. It is probable that this event occurs because fine particles were observed to coat the neck of the punch body. Die filling was observed to worsen with the ibuprofen formulations (30% IBU & 30% IBU-MIC). It was suggested earlier that this may be due to the charging of powder in the force feeder. In order to verify whether this event occurs, the net specific charge of the powder in force feeder frame can be measured at say cycle #200. The results can be compared to the net charge of the powder at the start of experimentation. If sticking of ibuprofen is facilitated by triboelectric charging, then powder charging in force feeder may increase the rate of sticking. The adhesion of particles mediated by surface charging is a well understood topic in the field of toner technology in laser printing. Perhaps it would be useful to explore the existing knowledge in this field in order to address such questions related to sticking.

Perhaps experimentation involving the manipulation static charge in powders can be studied to evaluate their effect on sticking. For example, humidity and powder moisture can affect the behavior of powder charging (73). However moisture can lead to the formation of liquid bridges between particles. It would be interesting to observe the effect of powder moisture on sticking in pure ibuprofen. Ibuprofen is poorly hygroscopic (see Appendix A) and exposing the powder to high humidity will not readily increase moisture content. A forceful technique can be

used instead in which water is directly sprayed on to the powder bed using a micro sprayer as described by Nokhodchi et al (84). Another example of charge manipulation is the use of formulation components that can oppositely charge with the compound in order to neutralize net charge (73).

# CHAPTER 7: CONCLUSIONS

Sticking of powders during tablet compaction is a multifaceted phenomenon. There exists way too many parameters that can contribute to problem and some of which are discussed in this work. Therefore identifying the specific parameters that are responsible for sticking in a given formulation is a complicated task. One would need to carefully study the powder properties, tooling properties and compression conditions in order to distill down the list of parameters that can possibly contribute to the issue.

The experiments conducted in this work were aimed at understanding the behavior of sticking in materials and to explore how this phenomenon occurs in particularly with ibuprofen. The data collected in this experiment provides clues as to what may be the driving forces behind sticking. For example, the particle size reduction of ibuprofen was demonstrated to have a profound effect on sticking. Milling of ibuprofen resulted in the excessive static charging of the powder. It is not clear whether the increase in sticking with milled ibuprofen was due to the size reduction, triboelectric charging or both. However the data collected in this work suggests that both factors may contribute to the problem. Micronization of ibuprofen resulted in a significant reduction in particle size relative to MCC which indirectly suggests that ibuprofen has a higher propensity to fragment. Fragmentation of ibuprofen during tablet compaction would result in the generation of fine particles and it is suggested that this may be part of the mechanism by which sticking occurs.

Further work on the topic of sticking is absolutely necessary to understand the mechanisms by which this phenomenon occurs. Without such efforts, attempts at modifying formulations that are prone to sticking would largely be an expensive trial and error exercise. Sticking is currently an issue that plagues the tablet manufacturing industry. Often times, this

issue goes undetected during research scale operations and are only evident during large scale manufacturing. Therefore, there is a great unmet need to properly understand the issue, identify sticking of formulations early on during research and development and to effectively engineer formulations to mitigate this issue.

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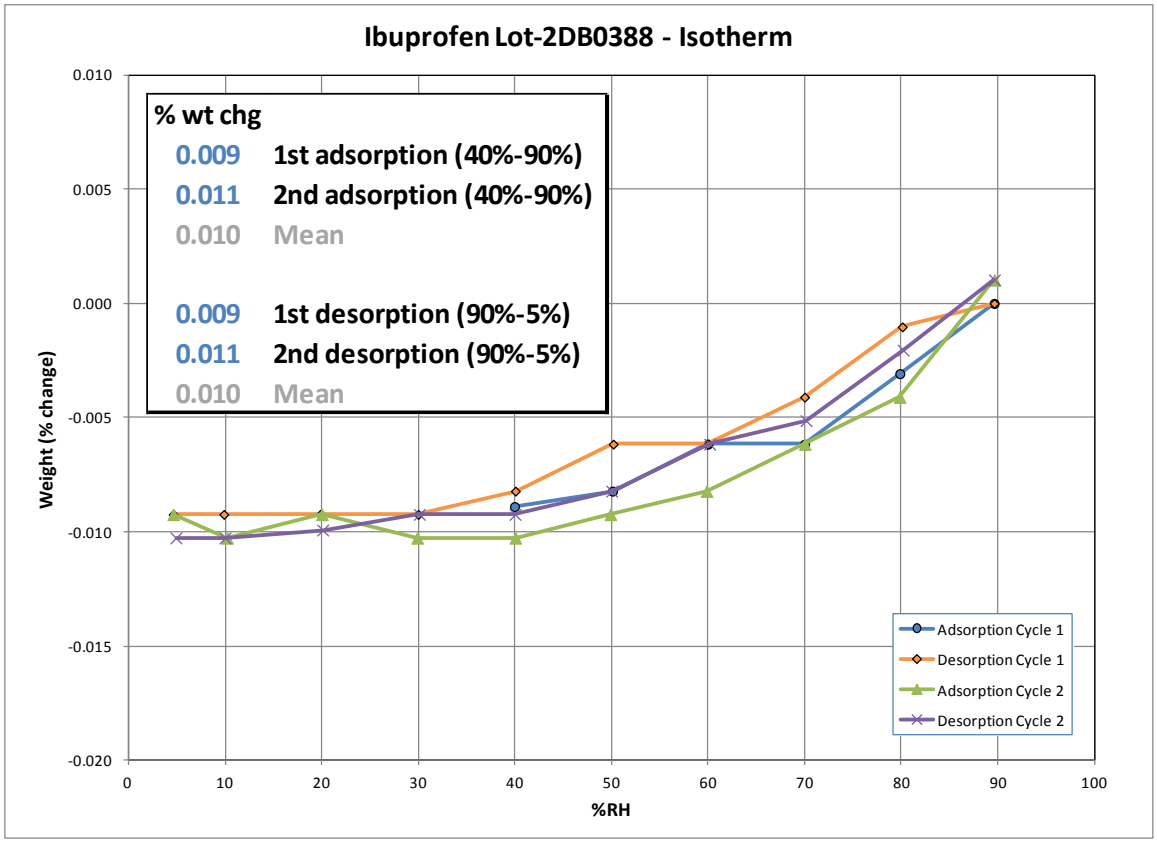
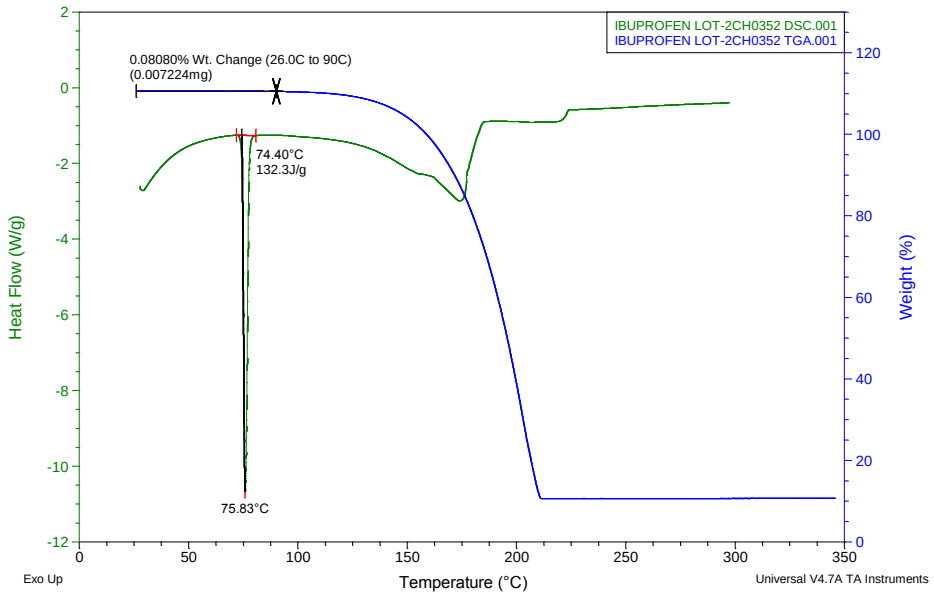
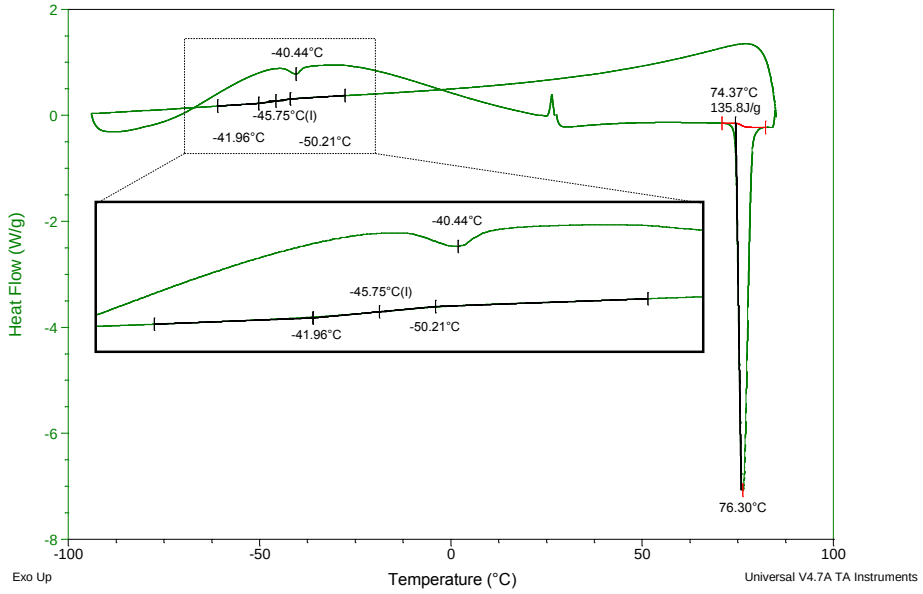
# Appendix A: Moisture Sorption of Ibuprofen.



## Appendix B: Thermal data on Ibuprofen.

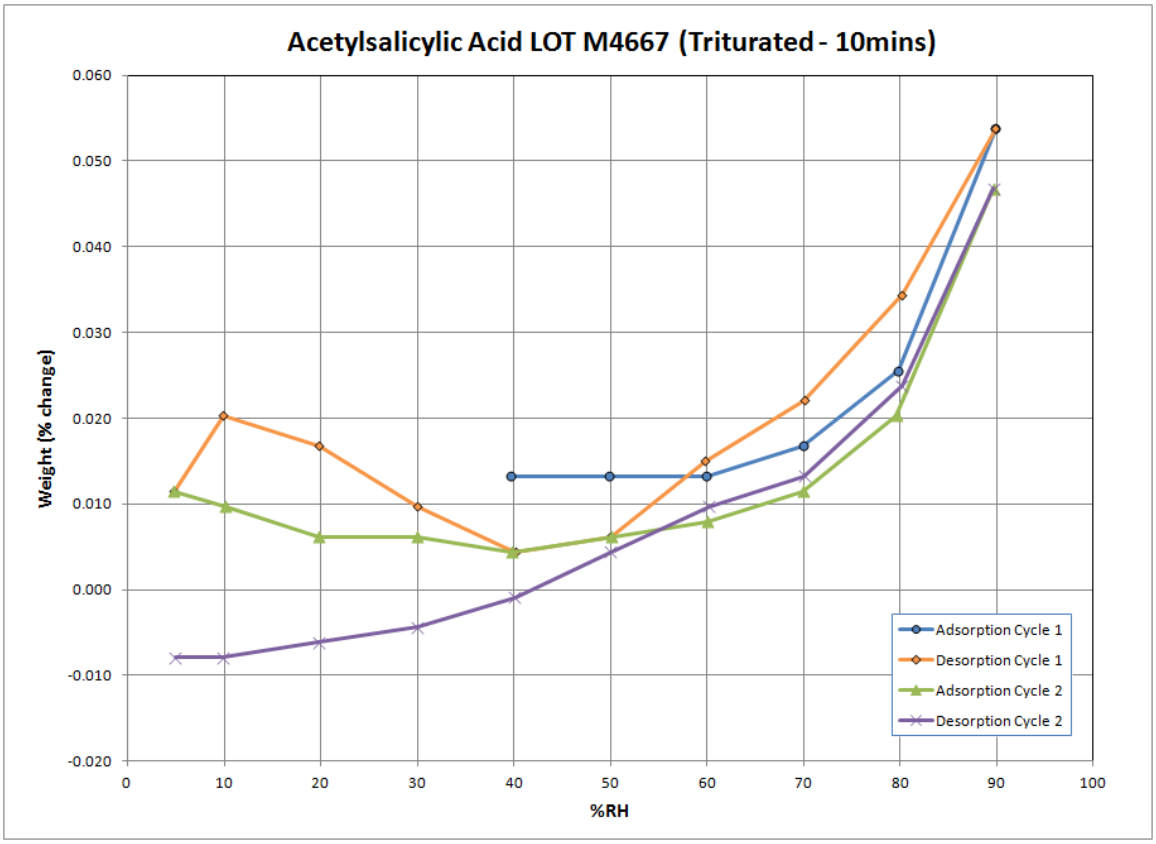



Differential scanning calorimetry and thermogravimetric analysis of Ibuprofen. Data collected at a heating rate of 10°C/min.



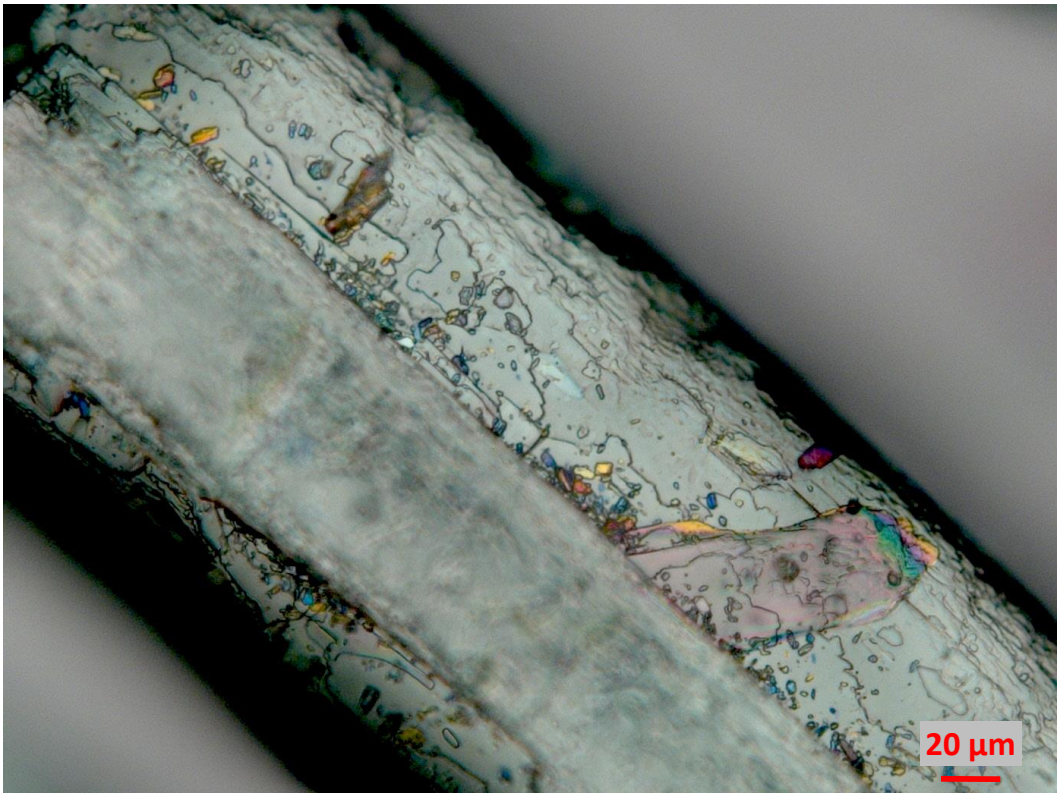

Differential Scanning Calorimetry of Ibuprofen. Ibuprofen was heated at 10°C/min to melt and then quench cooled to -100°C. Ibuprofen was re-heated at 20°C/min to room temperature. The glass transition of amorphous Ibuprofen is estimated to be at approximately -46°C.

## Appendix C: Moisture Sorption of Acetylsalicylic Acid



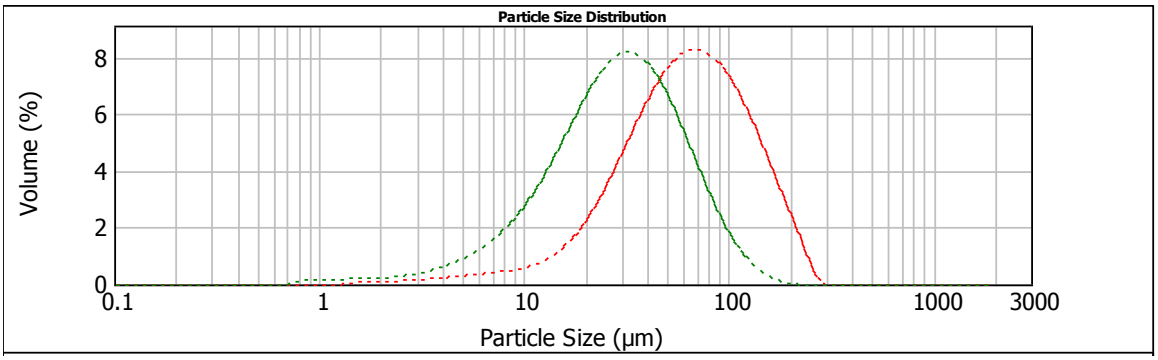
## Appendix D: Photomicrographs of Acetylsalicylic Acid


ASA (AS-IS), 5x Objective, Partially-polarized light.




ASA (AS-IS), 40x Objective, Partially-polarized light.

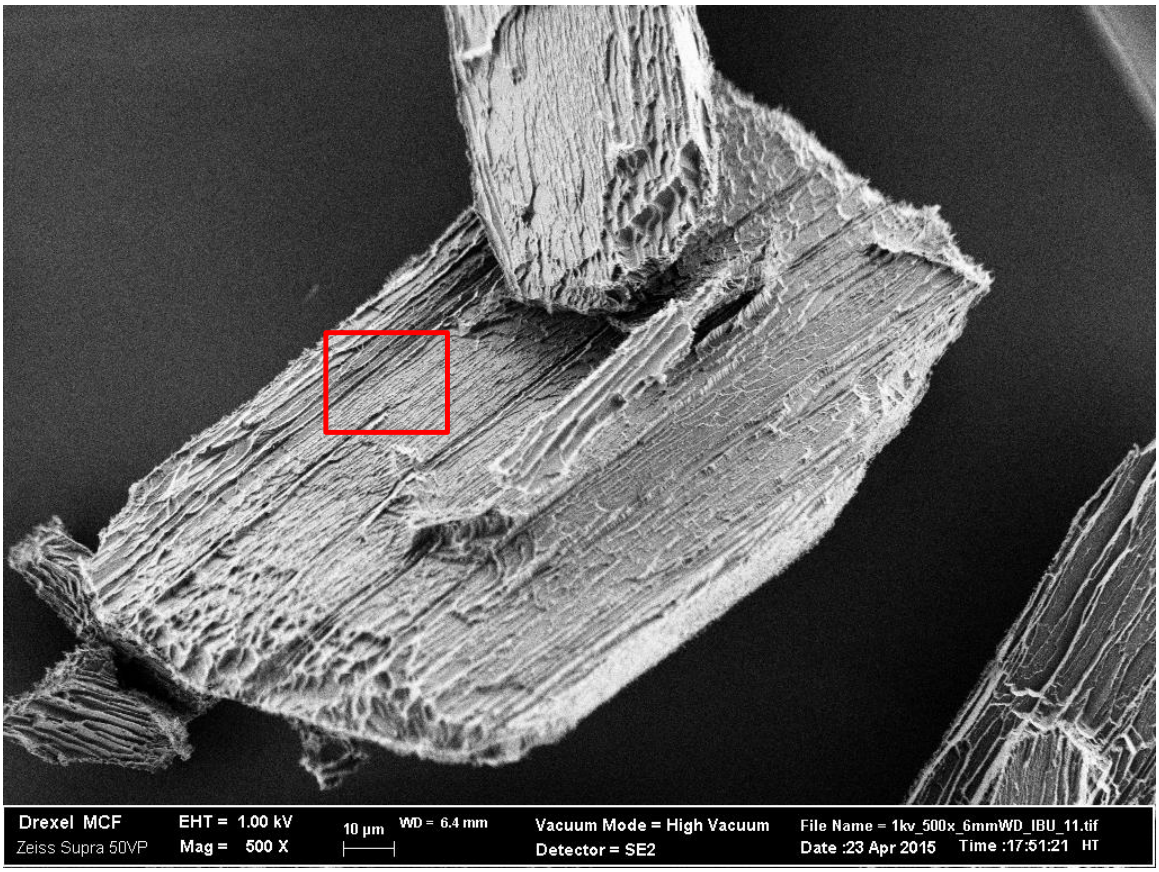
## Appendix E: Particle size of micronized MCC



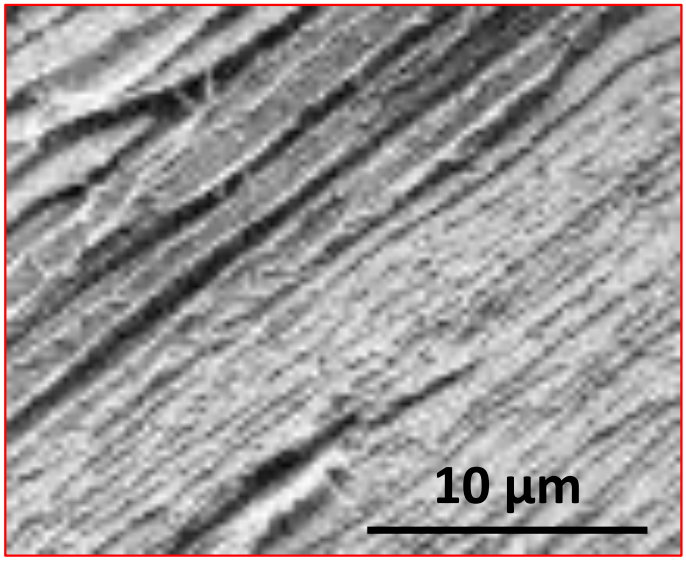

| | x10 | x50 | X90 |
|---|---|---|---|
| Avicel PH101 AS-IS | 21.992 | 62.750 | 146.821 |
| Avicel PH101 Micronized | 9.240 | 28.815 | 69.704 |

Micronization of Avicel PH101 (also referred to as Microcrystalline Cellulose, MCC) using the same milling conditions used for micronization of ibuprofen. Micronization of MCC resulted in an approximately 55% reduction in mean size (x50). This data is presented here for comparing the ease of particle size reduction by air-jet milling between MCC and ibuprofen.

## Appendix F: SEM of Ibuprofen

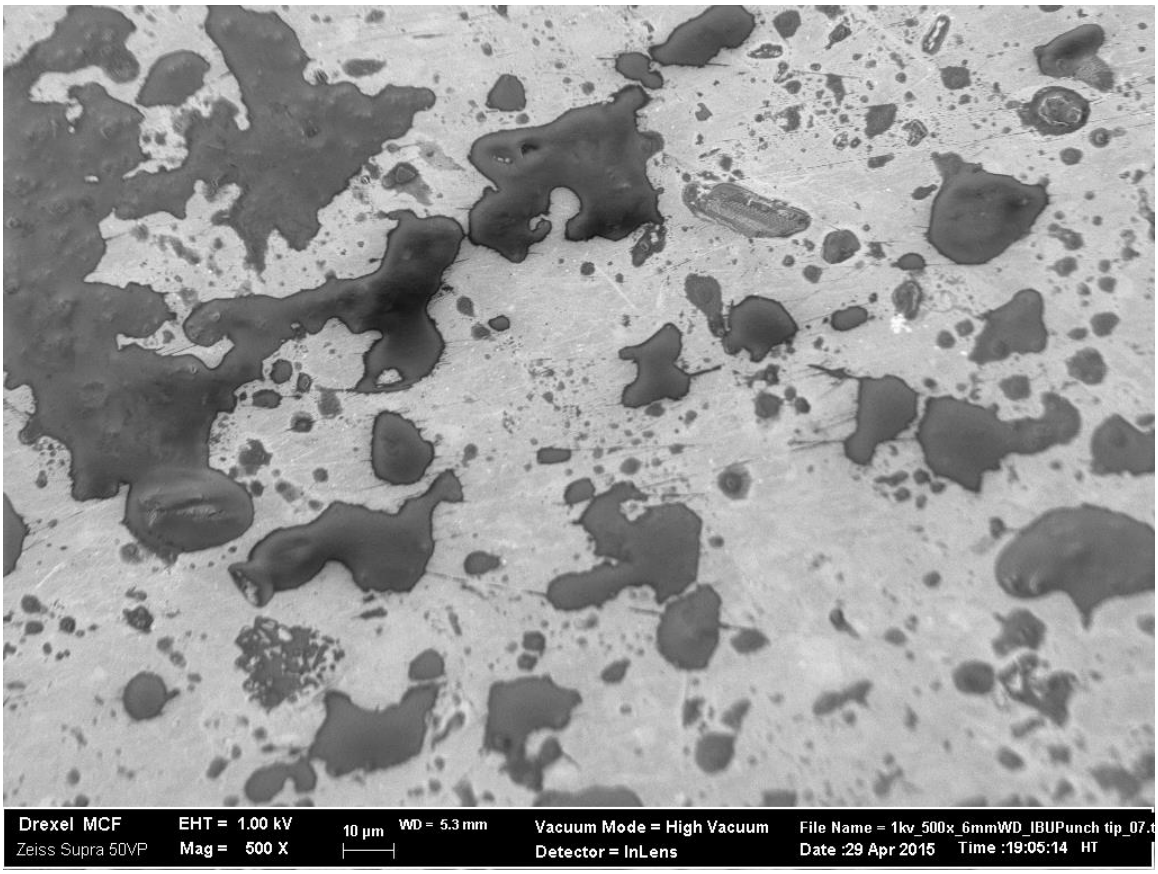



SEM image of Ibuprofen captured at 1kV.




A zoomed in inset image showing the surface texture of ibuprofen.

## Appendix G: Effect of solvent on sticking

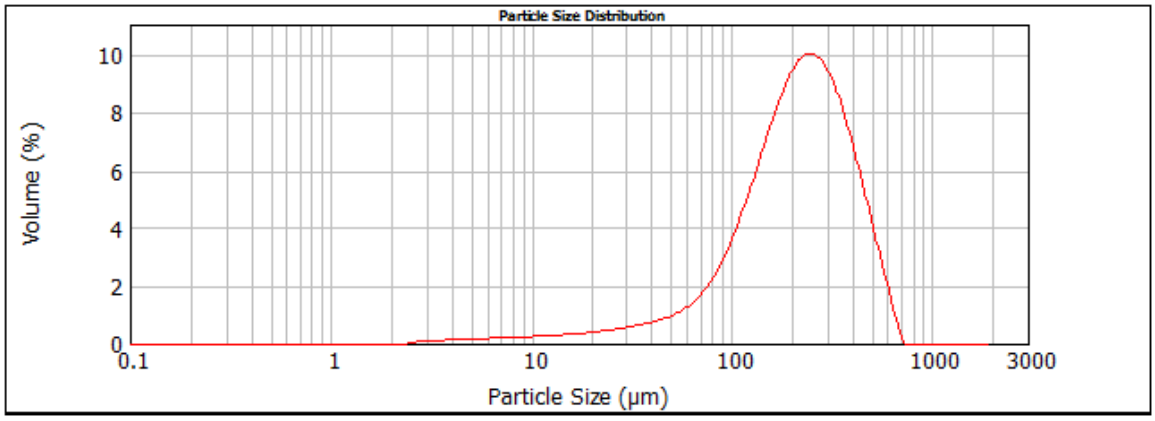



Appearance of ibuprofen on punch tip after cleaning tip with methanol.

## Appendix H: Sticking in 100% ibuprofen

Appearance of the tablet surface of 100% ibuprofen affected by sticking. A 10mm flat faced punch was used to produce 5 tablets to a relative density of 0.92. Shown here is a photograph of tablet #3.

**Appendix I: Particle size of Acetylsalicylic Acid**




x10: 74µm, x50: 216µm, x90: 427µm

## Appendix J: List of Acronyms.

AFM – Atomic Force Microscopy
API – Active Pharmaceutical Ingredient
ASA – Acetylsalicylic Acid
CNIB – Chromium Nitride Ion Bombarded
DSC – Differential Scanning Calorimetry
FEM – Finite Element Method
FFRE – Flat Face Radius Edge
HPLC – High Performance Liquid Chromatography
IBU – Ibuprofen
IR – Infrared Spectroscopy
MCC – Microcrystalline Cellulose
MgSt – Magnesium stearate
MIC – Micronized
PEG – Polyethylene Glycol
PSA – Particle Size Analysis
PTFE – Polytetrafluoroethylene (Teflon®)
R&D – Research and Development
RH – Relative Humidity
SC – Standard Cup
SCR – Scrapper Force
SEM – Scanning Electron Microscope
TSR – Tablet Surface Roughness