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INVESTIGATING THE IMPACT OF MANUFACTURING AND FORMULATION FACTORS ON THE COMPACTABILITY OF ACETAMINOPHEN TABLETS USING HECKEL AND MULTIVARIATE ANALYSIS

J. S. Saddik, K. Chaturvedi and R. H. Dave *

Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Division of Pharmaceutical Sciences, Long Island University, Brooklyn, NY-11201, USA.

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Correspondence to Author:
R. H. Dave

Professor and Division Director, Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Division of Pharmaceutical Sciences, Long Island University, Brooklyn, NY-11201, USA.

E-mail: rutesh.dave@liu.edu

ABSTRACT: The present work evaluates the impact of alterable manufacturing and formulation factors on the physicomechanical properties of Acetaminophen (APAP); a poorly compressible Active Pharmaceutical Ingredient (API). By varying the amount of APAP and particle size of Microcrystalline Cellulose (MCC), six different formulations were prepared. These formulations were compressed into tablets at different compression pressures and speeds. The porosity of the tablets was evaluated through "out-of-die" Heckel analysis. Furthermore, the qualitative and quantitative relationships of (i) Percentage of APAP, (ii) Compression pressures, (iii) Compression speeds, and (iv) Particle size of MCC with tablet porosity were evaluated by principle component analysis (PCA) and principle component regression (PCR). Heckel analysis revealed that increasing the ratio of APAP to MCC in the formulation adds its compressibility when the MCC particle size is similar to that of APAP. While, using large MCC particle size increases the compressibility due to fragmentation of particles, using MCC of small particle size increases the compressibility to a higher extend. The PCA indicated that the percentage of APAP, compression pressure and particle size of MCC are all correlated negatively to tablet porosity. Furthermore, the PCR quantified these correlations to show that tablet porosity was predominantly dependent on compression pressure followed by MCC particle size, APAP percentage, and compression speed in descending order. This work provides an insight into the collective impact of manufacturing and formulation factors on the mechanical properties of tablets, which can help developing an optimized multivariate function to ensure tablet quality of poorly compressible APIs.

INTRODUCTION: In pharmaceutical industry, tablets are produced by applying pressure to powder which in turn solidifies inside a die forming a tablet. Looking close rat this process, two steps happen when pressure is applied to powder. Firstly, a reduction in volume of the powder and secondly, a formation of compact mass which is the tablet. Compressibility is the ability of the powder to be reduced in volume under pressure, while compactability is the ability of powder to build a holding form of a certain strength under pressure [1].

Compressibility and compactability of pharmaceutical powders play a very important role in the process of tableting [2]. For example, achieving the desired hardness of a tablet can be predicted easily once the compressibility and compactability of the

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powder forming that tablet is understood. Also, the least pressure that is needed to be applied to a powder to form an intact tablet can be known by studying compressibility and compactability of powders. Unfortunately, till this day, tablet manufacturing science lacks a universal compression equation that can enable understanding and predicting compression of powders into tablets [3]. The reason behind this is that the process of compressing powders into tablets depends on many formulation and manufacturing factors [4].

The formulation factors that contribute to compressibility and compactability of powders involves: (i) Particle size of Active Pharmaceutical ingredient (API) [5], (ii) Particle size of the excipients [6], (iii) Tableting material behavior under pressure [7] and (iv) Drug load in the formulation. Two of these factors are usually unalterable, the particle size of the API, and the powder behavior under pressure. Although, one can change the excipients used in the formulation and thus change the overall material behavior of the formulation, the powder behavior under pressure is considered as an unchangeable factor. The reason is that the based on its behavior under pressure. For example, if the API deforms elastically under compression pressure, the filler that will be added to this API should deform plastically under working pressure to avoid common tableting problems such as tablet sticking, capping, *etc*. On the other hand, the manufacturing factors contributing to compressibility and compactability of powders involve: (i) Compression force [8] and (ii) Compression speed [9]. Both these factors are alterable and can be changed to achieve the desired quality of tablets. Understanding how all these factors work together and contribute to the quality of the formed tablets would help in understanding and predicting the powder compression process, which is a key step in the science of tablet manufacturing. The authors are aware that powder processing through dry, wet or melt granulation also affects the compressibility and compactability [10], but in this article, the focus is only on the direct compression process.

A substantial amount of work has been dedicated to understanding the compressibility of powders in the past, especially due to the application of this process in a variety of industries like metals, ceramics, catalyst, food, and pharmaceuticals. Many models were developed to describe and provide a better understanding of powder densification. The most successful and commonly used compression models in pharmaceutical industry are ones developed by Heckel [11], and Kawakita [12]. Although, not all of these models were developed for pharmaceutical powders, in particular, these equations have been modified or shown to work well with pharmaceutical powders. For the purposes of this paper, only Heckel analysis will be discussed and used.

Heckel model describes compressibility and compactability of powder as a factor of reduction in porosity of powder as the pressure applied increases [13]. Heckel equation assumes that the compression of powders can be described by a first-order reaction, where pores are reactants, and densification of bulk powder is the product. Based on this assumption, a first-order reaction equation can be written:

$$dD / dP = K(1-D) \quad \text{.....Eq (1)}$$

Where, P is pressure applied, D is the solid fraction (*i.e.* the relative density), 1 – D is the void fraction (*i.e.* the tablet porosity, ε) and K is a material constant that represents the influence of pressure on reducing the volume of the powder. The reciprocal of K (1/K) is called the yield pressure which is the least pressure applied to the material for it to start plastic deformation forming a compact. Integrating equation (1) for relative density changing from D0 (initial relative density) to D (final relative density) as the pressure increases from zero to P yields the following equation:

$$\text{Ln } \{1/(1-D)\} = KP \quad \text{.....Eq (2)}$$

Since, Ln {1/(1-D)} *vs*. P curves obtained were not observed to be linear for a range of metal powders, Heckel modified the equation by introducing a new parameter B11:

$$\text{Ln } \{1/(\varepsilon)\} = KP + B \quad \text{.....Eq (3)}$$

The constant B is the material constant that describes the movement and the arrangement of powder particles at a low pressure where no significant inter particulate bonding is observed Heckel plot is a linear relationship between porosity and the natural logarithm of the reciprocal of the porosity.

Since, compressibility and compactability behavior of a tablet formulation is of great importance for the quality of tablets produced, it is essential to understand the effect of formulation and manufacturing factors on this behavior. Changeable factors like excipients particle size, the applied pressure, tablet press turret speed (dwell time) and drug load in the formation have a great impact on quality of produced tablets. The aim of this work is to focus on these factors and their effects on the compressibility and compactability of tablet formulations. The effect of all these factors on the porosity of the produced tablets are studying through Heckel analysis. Furthermore, a multi-variate method is used to model the collected data to explain and quantify the effect of these factors on the physical and mechanical properties of produced tablets.

MATERIALS AND METHODS:

Materials: The materials used in this study were Acetaminophen (APAP) USP Powder from Letco Medical LLC, Micro-crystalline Cellulose (MCC) as Avicel PH-101, 102 and 105 from DuPont Nutrition & Health, Sodium Starch Glycolate (SSG) from JRS Pharma, and USP grade Magnesium Stearate (Mg.St) from Sigma-Aldrich.

Methods:

Preparation of Six Dry Blend Formulations: Powder blends of six different formulations were prepared using V-blender (Maxiblend, GlobePharma Inc, New Brunswick, NJ). The final blend size of each formulation was 1 Kg. **Table 1** shows the percentage weight by weight of each ingredient in the final blend of each formulation. For blending, formulation respective amount of APAP and Avicel was sifted using sieve #16 and then transferred to V-blender where it was blended for 7 min at 20 rpm. Then SSG was sieved through sieve #16 and transferred to V-blender, and blended with APAP & MCC for 5 min at 20 rpm. Finally, Mg. st was added to that blend after sifting it through sieve #25 and blended for 2 min at 20 rpm.

TABLE 1: LIST OF MATERIALS AND THEIR LOADS (IN PERCENTAGE WEIGHT BY WEIGHT (% w/w)) IN THE SIX FORMULATIONS

Materials	Formulation 1	Formulation 2	Formulation 3	Formulation 4	Formulation 5	Formulation 6
APAP	20	40	20	40	20	40
MCC 101	77	57	-	-	-	-
MCC 102	-	-	77	57	-	-
MCC 105	-	-	-	-	77	57
SSG	2.5	2.5	2.5	2.5	2.5	2.5
Mg. St	0.5	0.5	0.5	0.5	0.5	0.5

Powder Characterization:

Particle Size Measurement: Particle size distributions were determined using a laser diffraction particle size analyzer (Mastersizer 3000, Malvern Instruments, Westborough, MA). Small amounts of the sample from bulk APAP, MCC 101, MCC 102, and MCC 105 (0.5g ± 0.1g) were used for the analysis. Reported values are the mean of three runs for each material.

Powder Density Measurement: True densities of all the formulations were determined in triplicate by Helium Pycnometer (Ultrapyc 1200e, Quantachrome Instruments, Boynton Beach, FL) at ambient conditions. On the other hand, Bulk density was calculated for each formulation by weighing 100 ml of powder and then dividing that weight by 100 ml.

Preparation of Tablets: Tablets were compressed using Riva Piccola tablet press equipped with standard flat-faced, domed head punches with a tip diameter of 10 mm. Each blend was compressed at five different compression pressures, 50, 100, 150, 200 & 250 MPa. At each compression pressure, 200 tablets were collected at four different turret speeds, 20, 40, 60 & 80 rpm. The target weight of each individual tablet was set to be300 mg by adjusting fill cam. Tablets collected were stored in an airtight container until further use.

Tablets Physical Measurements: Tablet physicals, thickness, and diameter, were measured using an electronic caliper (0.01 mm, CD-6" ASX; Mitutoyo Corporation, Sakado, Japan). Tablet porosity was measured using the following equations [14]:

$$\text{Tablet Density} = \text{Tablet mass (g)}/\text{Tablet volume (cm}^3\text{)} \quad \text{...Eq (4)}$$

$$\text{Tablet porosity } (\varepsilon) = 1 - \text{Tablet density (g/cm}^3\text{)} / \text{Powder true density (g/cm}^3\text{)} \quad \text{…Eq (5)}$$

Each data point in the Heckel plots reported in this study is an average of 20 tablet analysis.

Multivariate Statistical Analysis: The qualitative and quantitative relationship of different manufacturing and formulation factors with 'out of die' tablet porosity was evaluated through PCA and PCR using the multivariate algorithms in the Unscrambler × 10.4 software (CAMO Software AS, Trondheim, Norway). To induce variability in the data, individual values were used for the PCA and PCR modeling. PCA modeling was used to qualitatively identify the main factors affecting tablet porosity. On the other hand, PCR was used to quantify the impact of these factors on tablet porosity. In PCR, the X-variables were: (i) Percentage of APAP to MCC in the formulation, (ii) Tablet press turret speed (which corresponds to dwell time), (iii) Compression pressure, and (iv) Particle size of MCC used in the formulation. The Y-variable was the 'out of die' porosity. The PCR coefficient of uncertainty was estimated with cross-validation and jack-Knifing method [15]. All the variables and the responses were weighted and scaled by dividing with their standard deviation before PCA and PCR algorithms were performed. In addition, the statistically significant differences in tablet porosity were quantified. Tablet porosities having a p-value of less than 0.05 were considered statistically different for each other.

RESULTS AND DISCUSSION:

Particle Size Measurement: Powder particle size and its distribution have an impact on the physical and mechanical properties of tablets; they are compressed into [16]. APAP and the three grades of MCC used in this study were subjected to particle size analysis **Fig. 1**. Median particle size (d50) was used to compare the particle size of the samples. MCC 102 was observed to have the largest particle size compared to the other MCC grades, while MCC 105 was observed to have the smallest particle size of all. The d50 of MCC 101, 102, and 103 was 64.3, 182, and 21.5µm, respectively. The supplier of the different grades of MCC reported that the d50 of MCC 101, 102, and 105 was 50, 100, and 205 µm, respectively. Furthermore, thed50 of APAP was found to be 61.1 (approximately similar to that of MCC 101) with a wide particle size distribution range.

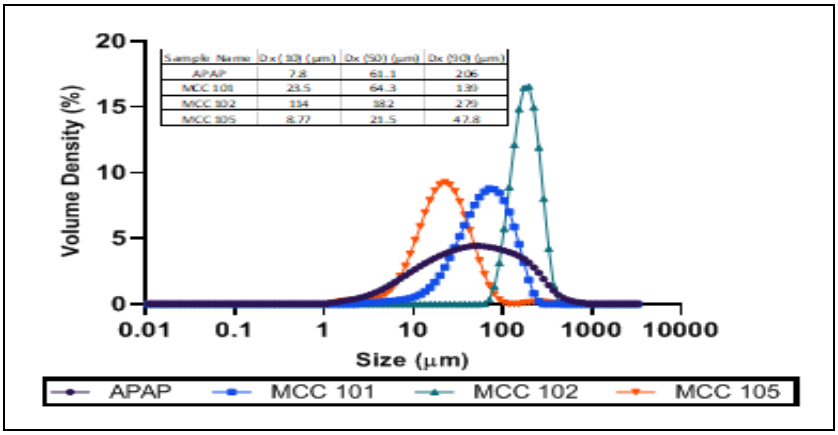

FIG. 1: PARTICLE SIZE MEASUREMENT AND DISTRIBUTION OF APAP, MCC 101, MCC 102, AND MCC 105

Heckel Analysis: By overlaying Heckel plots of formulation 1 **Fig. 2A** at different turret speed, we observed that the tablets compressed at 20 and 40 rpm had shown significantly different porosity compared with tablets compressed at 60 and 80 rpm. No significant difference in tablet porosities was observed between tablets compressed at 20 and 40 rpm as well as tablets compressed at 60 and 80 rpm. The difference in the porosity of tablets compressed at low rpms (20 and 40 rpm) and tablets compressed at high rpms (60 and 80 rpm) can be explained by the dwell time effect. At dwell time, the force exerted by the upper and lower punch is perpendicular on the power bed since dwell time corresponds to contact time between the compaction roll and the flat region of the punch head [17]. Decreasing the dwell time (increasing turret speed) corresponds to a significant increase in the ratios of plastic to elastic energies. This means that at low dwell time, less elastic deformation of materials takes place compared to high dwell time [18]. This explains the difference in the porosity of tablets compressed at low rpms compared to those compressed at high rpms.

In addition, the difference in porosity between tablets compressed at low rpms and those compressed at high rpms resulted in a trend that caused a difference in the slope of the linear portion of the Heckel plot (the portion between 150 to 250MPa). As a result, the yield pressure calculated for tablets compressed at low rpm was lower than the yield pressure calculated for tablets compressed at high rpm. The yield pressures of formulation 1 powder compressed at low and high rpms are 135 and 167 MPa, respectively. This implies that the onset of plastic deformation occurs at lower pressures when the tablet press is operated at low rpms.

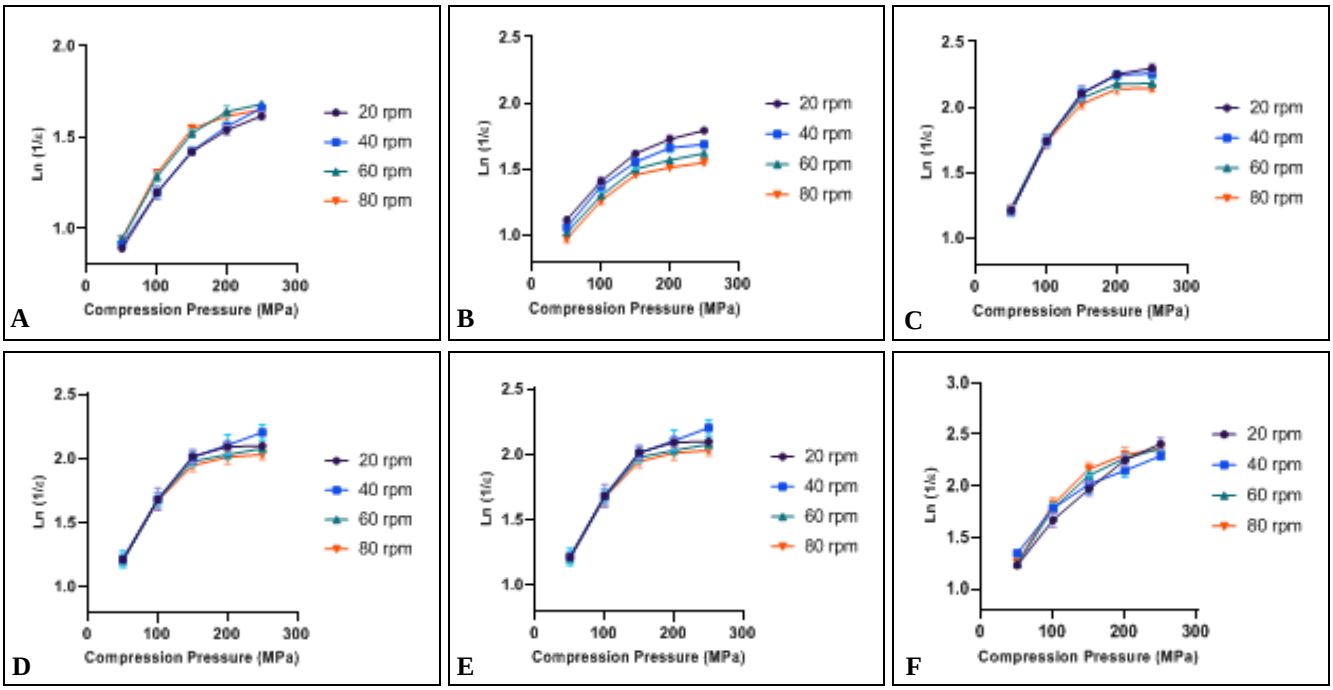

FIG. 2: HECKEL PLOTS OF: (A) FORMULATION 1, (B) FORMULATION 2, (C) FORMULATION 3, (D) FORMULATION 4, (E) FORMULATION 5, AND (F) FORMULATION 6 AT DIFFERENT TURRET SPEEDS

The same analysis was applied to the Heckel plots of tablets compressed at different turret speeds using formulation 2 blend **Fig. 2B**. The only difference between formulation 1 and 2 was the ratio of filler to API. In formulation 2, this ratio was decreased by reducing the percentage of MCC 101 and an increasing percentage of API in the formulation. There was a significant difference in the porosity of tablets compressed under different pressures at different turret speeds. It was observed that as the turret speed of the press increases, Heckel plot of the tablets produced reaches the linear portion faster and with a shallower slope. The shallower the slope, the higher the yield pressure calculated. The yield pressures of tablets compressed from formulation 2 blend at 20, 40, 60, and 80 rpm are 134, 175, 188 and 250 MPa, respectively. This means that formulation 2 powder requires higher pressure to undergo deformation as the turret speed increases. The decrease in the porosity of tablets as the rpm increases can only be explained by a certain type of interparticulate bond that is dwell time-dependent. There are three main interparticulate bonds that can form within the powder particles in the blends used in this study: (i) APAP-APAP bonds, (ii) MCC-MCC bonds, and (iii) APAP-MCC bonds. Many studies have investigated the poor compression properties of APAP since the APAP-APAP bond is weak and cannot hold the powder together to form a tablet [19-21]. On the contrary, MCC-MCC and APAP-MCC bonds are strong bonds and are responsible for the strength of the tablets produced. In formulation 1, the ratio of MCC to APAP is high since the amount of MCC in the blend is approximately double the amount of APAP. This led us to the conclusion that the predominant bonds responsible for the compactability of tablets made from formulation 1 are MCC-MCC bonds. In formulation 2, the ratio of MCC to APAP is approximately a 1:1 ratio, which implies that the predominate interparticulate bonds responsible for the compactibility behavior of the powders are MCC-APAP bonds. Since the only difference between formulation 1 and 2 is the

ratio of MCC 101 to APAP, overlays of Heckel plots of tablets produced at each rpm of these formulations were constructed **Fig. 3**. From these overlays, it was observed that at 20 rpm, tablets made from formulation 2 have lower porosity than tablets made from formulation 1. At 40 rpm, tablets of formulation 2 still had lower porosity than tablets of formulation 1, but the difference in the porosities is less than that of tablets produced at 20 rpm. At 60 rpm, tablets of formulation 1 and 2 have approximately same porosity. Lastly, at 80 rpm, the tablets of formulation 1 have lower porosity than tablets of formulation 2. Based on the above observations, it was hypothesized that MCC-APAP interparticulate bond gives superior strength to tablets than MCC-MCC interparticulate bond, and its formation is dwelled time-dependent, unlike the MCC-MCC bond. This hypothesis explains the difference in the porosity of tablets produced from formulation 1 and 2 at different turret speeds. In addition, this hypothesis was supported by multivariant analysis.

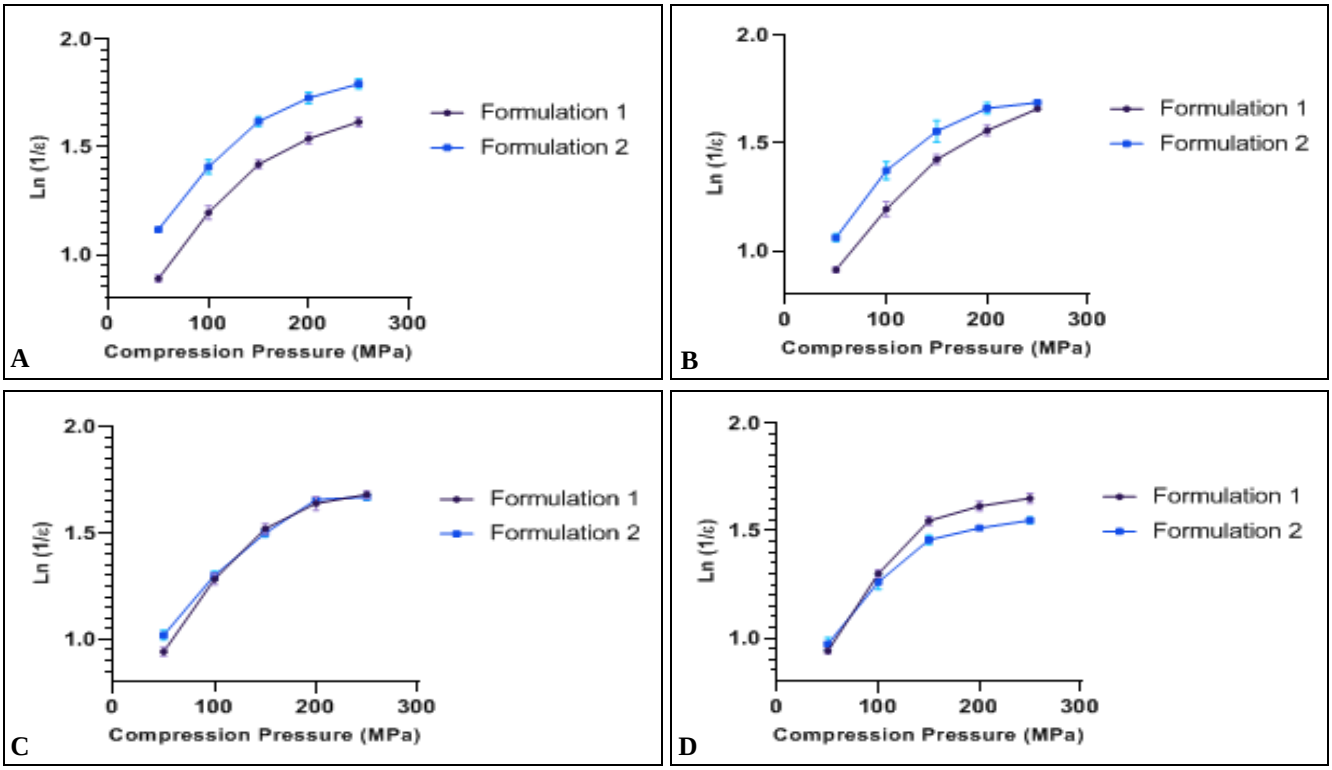

FIG. 3: LAYOUT OF FORMULATION 1 & 2 HECKEL PLOTS AT: (A) 20 RPM, (B) 40 RPM, (C) 60 RPM, AND (D) 80 RPM TURRET SPEEDS

Heckel plots of tablets compressed at different turret speeds using formulation 3 are shown in **Fig. 2C**. Tablets compressed at lower rpms were found to be harder and have less porosity than tablets compressed at higher rpms. The difference in the porosity appears only in the linear portion of Heckel plot which is between 150 and 250 MPa. The reason for this difference in porosity is the dwell time. The longer the dwell time, the longer time is permitted for particles to have close contact with each other and to establish interparticulate bonds with each other and so produce harder tablets with less porosity. At 20 rpm, where dwell time is the longest, the porosity of tablets compressed at 150, 200 and 250 are 0.122 (±0.019), 0.105 (±0.008), and 0.100 (±0.027) respectively compared to 0.132 (±0.022), 0.118 (±0.015) and 0.120 (±0.024) for tablets compressed at 80 rpm. The yield pressure calculated from Heckel plot shows lower pressure is needed to cause plastic deformation of powder when compressed at lower rpm. With increasing rpm, the yield pressure increases. This is because, with a longer dwell time, particles are under pressure for more time, which allows for plastic deformation. By comparing Heckel plots of formulation 3 with those of formulation 1, it was observed that formulation 3 tablets are harder and have lower porosities than tablets of formulation 1. Formulation 3 contains MCC 102 instead of MCC 101 that was used in formulation 1 as a filler. MCC 102 has larger particle size than MCC 101 as shown in **Fig. 1**.

MCC is known to be a plastic/semi-brittle material that fragments during tableting [22-24]. With larger particle size of MCC, fragmentation and breakage to smaller particles occur, which results in a wide range of particle sizes. In this system, small particles fill the voids present between large particles inside the tablet, thereby reducing tablet porosity. This reduction in tablet porosity results in tougher and harder tablets.

Fig. 2D shows Heckel plots of tablets produced at different turret speed using formulation 4. Heckel plots of formulation 4 show the same trend as the Heckel plots of formulation 3 at different rpms. This, as mentioned before, is explained by the dwell time and how it affects the porosity and hardness of tablets. Compared with the tablets made from formulation 3, tablets produced from formulation 4 are more porous and more fragile at each rpm. Overlay of Heckel plots of tablets produced of formulation 3 and 4 at each rpm was constructed **Fig. 4**. The trend observed from these overlays was different from the trend observed from overlays of Heckel plots of tablets produced of formulations1 and 2 of these rpms. It was expected to observe the same trend in Heckel plots of formulations 3 and 4 at each rpm as that observed from Heckel plots of tablets made from formulations 1 and 2 since, in both formulation pairs, the difference between formulations was the ratio of MCC to APAP. As mentioned before, tablets made from formulation 2 showed lower porosity than that produced from formulation 1 at low rpm. As the rpm increases, the porosity of tablets of formulation 2 increases and exceeds the porosity of tablets of formulation 1 at 80 rpm.

It was noticed that the compressibility and compactability of tablets of formulation 3 & 4 are superior to that of formulation 1 & 2. This is due to the breakdown and fragmentation of MCC 102. In addition, the fragmentation of MCC 102 results in an increase in the ratio of MCC to APAP in formulation 4. As a result, a comparison of the Heckel plots of formulations 3 and 4 does not show the same trend as that seen between formulations 1 and 2 at different turret speeds.

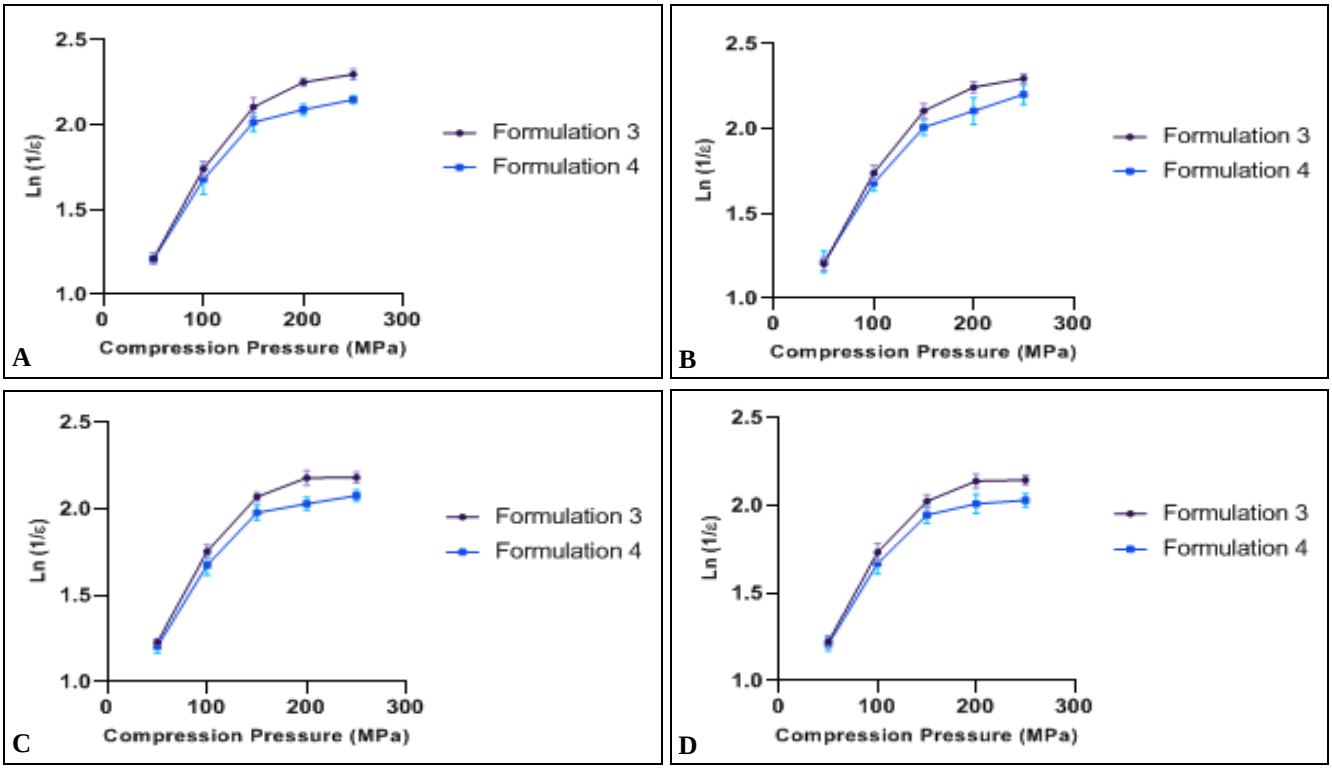

FIG. 4: LAYOUT OF FORMULATION 3 & 4 HECKEL PLOTS AT: (A) 20 RPM, (B) 40 RPM, (C) 60 RPM, AND (D) 80 RPM TURRET SPEEDS

MCC 105 was chosen as the filler for formulations 5 & 6 because its particle size is small. The particle size of MCC 105 is 21.5µm, which is smaller than those of MCC 101 & 102. The overlay of Heckel plot of tablets compressed from formulations 5& 6 at different rpms **Fig. 2E** & **2F** revealed that MCC

105 increases compressibility and compactability of tablets more than tablets made from formulation 1, 2, 3 & 4. This is due to particles of MCC filling the voids between bigger particles in the blend and therefore helps in achieving more compact tablets with lower porosity upon compression. Formulation 5 tablets which were compressed at different rpm at the same compression pressure, showed no significant difference in their porosities. The effect of dwell time is not observed here because the increased compressibility achieved by small particle size of MCC 105 overcomes the reduction in compressibility that occurs upon increasing turret speed (reducing the dwell time). But the effect of dwell time was observed in the yield pressure calculated from Heckel plot. Yield pressure of powder compressed at lower rpm is lower than that of powder compressed at higher rpm. This can be explained, as mentioned before, by more interparticulate bonds forming between particles at lower rpm since the powder is under maximum pressure from punches for a longer time, which increases the contact time between particles and therefore gives more time for interparticulate bond formation. The opposite happens at higher rpms where the powder is under maximum pressure for less time and thus, less contact time provides for interparticulate bonds.

In addition, Heckel plot of formulation 6 was compared with Heckel plot of formulation 5 at each rpm **Fig. 5**. It is important to mention that the difference between formulations 5 and 6 is that formulation 6 has lower ratio of MCC 105 to APAP. We observed that the trend of Heckel plot of tablets compressed from formulation 6 at different pressures and rpms overlap Heckel plots of formulation 5 tablets compressed under same respective conditions. The effect of ratio of MCC to APAP seen between formulation 1 and 2 was not observed here between formulation 5 and 6. This is probably because MCC 105 particle size is really small, which results in high ratio of MCC particles to APAP particles in both formulations 5 and 6.

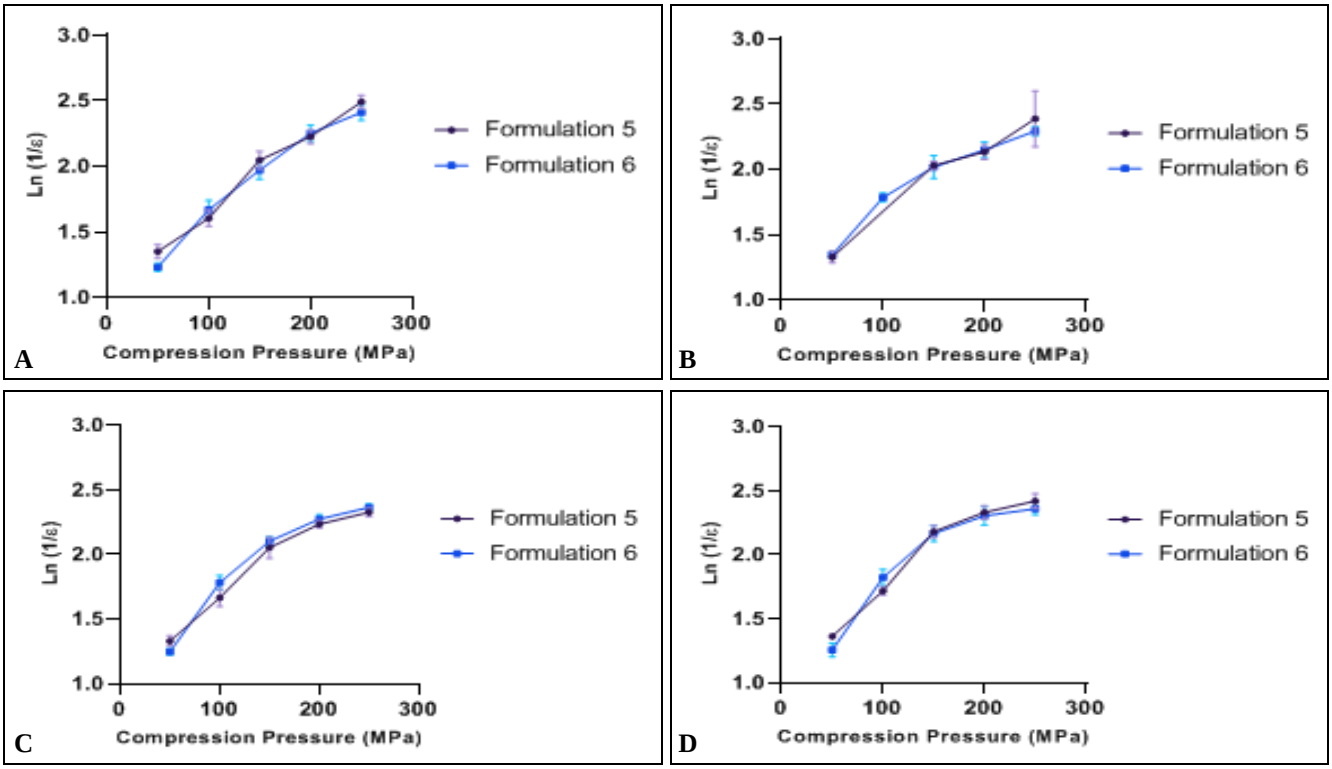

FIG. 5: LAYOUT OF FORMULATION 5 & 6 HECKEL PLOTS AT: (A) 20 RPM, (B) 40 RPM, (C) 60 RPM, AND (D) 80 RPM TURRET SPEEDS

Multivariate Statistical Analysis:

Qualitative Analysis: The data was qualitatively analyzed through PCA modeling. Five Principle Components (PCs) were used in the modeling to explain 100% variation in the data. The first and second PCs explained 57% of the variation in the data. Every PCA model is characterized by two sets of attributes, Loadings, and Scores. **Fig. 6** represents the PCA loading and score plot. The PCA loading plot describes the data structure in

terms of variable correlations and contributions, while PCA score plot visualizes sample groupings, patterns, differences, and similarities. This means that the loading plot describes the contribution of variables responsible for sample patterns, groupings, differences and similarities shown in the score plot. Thus, these two plots cannot be interpreted without each other to reveal the qualitative relationship within the data.

The PCA loading plot shows the correlations and contributions of: (i) percentage of APAP in the formulation, (ii) Tablet press turret speed (RPM), (ii) Particle size of MCC used in the formulation, and (iv) Compression pressure on the quality of tablets produced represented in tablet porosity. The samples and variables located on the same side of the PC in the loading plot are positively correlated, while these located on different sides of PC are negatively correlated. A negative correlation of both particle size of MCC and compression pressure was identified to the tablet porosity along PC1. The percentage of APAP in the formulation also was negatively correlated to tablet porosity through PC2. The tablet press turret speed (RPM) was not correlated to tablet porosity since it was very close to the center of the loading plot. Further, the PCA score plot showed two distinct groups along the PC2. These two groups are distinct from each other based on the percentage of APAP, and since the formulations used in this paper contain either 20% or 40% of APAP, the score plot shows two distinct groups. Group 1 is the group of data containing 40% APAP, while Group 2 shows the data containing 20% APAP.

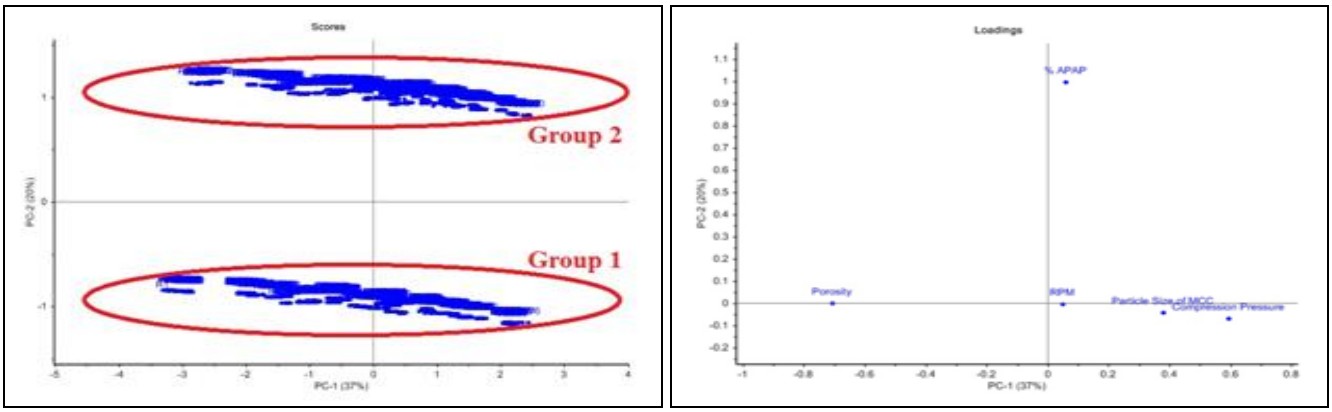

FIG. 6: PRINCIPLE COMPONENT ANALYSIS SCORE AND LOADING PLOT. A TOTAL OF FIVE PC EXPLAINED THE 100% VARIANCE IN THE DATA. THE FIRST TWO PCS ACCOUNTS FOR 57% OF THE VARIANCE IN THE DATA

Quantitative Analysis: To quantify the relationships between the manufacturing and formulation factors (X-variables) with the resulting tablet porosity (Y-variable) PCR modeling was performed on the data. Four PCs were used that explained 100% and 69% variance of X- and Y-variables, respectively. PC1 and PC2 explained 50% and 66% of X- and Y-variables, respectively. The root means square error (RMSE) for both calibration and prediction stage were 0.046, while the coefficient of determination (R2) was 0.69. Based on the PCR model, tablet porosity can be given by the following raw coefficient equation:

Tablet porosity = 2.6041 - 0.0006 (%APAP) - 0.0008 (CP) - 0.0002(RPM) - 0.022(MCC Particle size)…….Eq (6)

Statistically insignificant variables are variables with a 95% confidence interval bars crossing the zero line. The statistical significance of this model was determined at $p < 0.05$. All the variables showed a negative impact on the tablet porosity **Fig. 7**. The variable with the highest impact was identified to be the compression pressure. As the compression pressure increases, the produced tablets are harder due to lower porosity. The reason behind compression pressure having the highest impact on tablet porosity among the other variable is that the major component in the formulations used in this study was MCC. Since MCC is a plastic/semi-brittle material, increasing the compression pressure causes more plastic deformation and/or fragmentation of MCC particles, which in turn increases the strength (lowers porosity) of tablets produced, as explained before by Heckel analysis. Furthermore, the fragmentation of MCC explains the negative impact of MCC particle size

on the tablet porosity. As the MCC particle size increases, fragmentation is more likely to happen to result in a broad range of particle sizes. The broader range of particle sizes, the less porous the tablets produced because the different size particles will fill the voids in the powder bed giving strength to tablets produced.

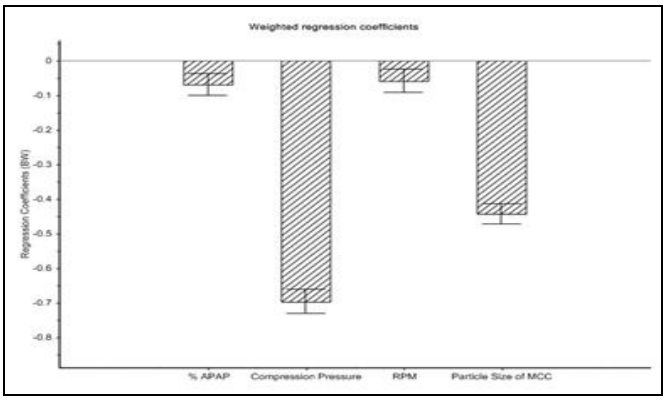

FIG. 7: THE PRINCIPLE REGRESSION ANALYSIS PLOT INDICATING WEIGHTED REGRESSION COEFFICIENT OF X-VARIABLES (PERCENTAGE OF APAP IN FORMULATION, COMPRESSION PRESSURE, TABLET PRESS TURRET SPEED, AND MICROCRYSTALLINE CELLULOSE PARTICLE SIZE) ON THE Y-VARIABLES (TABLET POROSITY). THE STATISTICAL SIGNIFICANCE (α = 0.05) OF THE MODEL WAS DETERMINED BY CROSS VALIDATION

The percentage of APAP in the formulation had also shown negative effect on the porosity of tablets produced. It was expected that increasing the amount of APAP in the formulation would result in an increase in the tablet porosities due to the poor compressibility behavior of APAP. However, the opposite effect was observed through Heckel analysis and PCR modeling. This effect can be explained by the interparticulate bonds formed between powder particles under pressure and are responsible for the intactness of the produced tablets. Increasing the APAP amount in the formulation results in interparticulate APAP-MCC bond to be the predominant bond in the produced tablets (compared to MCC-MCC and APAP-APAP bonds). APAP-MCC bonds are believed to add the strength of tablets produced more than MCC-MCC and APAP-APAP bonds. Therefore, this PCR model identifies percentage of APAP as a variable that have a negative impact on tablet porosity.

The effect of the turret speed on tablet porosity could not be interpreted through PCA model because it was very close to the center in the loading plot. It was expected that the turret speed would show an insignificant impact on the tablet porosity in the PCR model. However, the turret speed had shown a negative effect on the tablet porosity through this PCR model. The impact of turret speed on tablet porosity was the least among all the other variables studied. The reason for this negative impact is the elastic deformation behavior of APAP under pressure. Increasing the turret speed (reducing dwell time) result in more elastic deformation of elastic materials with less elastic recovery. This is the reason that APAP tablets exhibit capping more prominently when compressed at lower turret speeds [25].

CONCLUSION: The present study demonstrated the impact of alterable manufacturing (compression pressure and speed) and formulation factors (drug load in the formulation, the particle size of excipients) on the tablet porosity of poorly compressible API; Acetaminophen. Heckel and multivariate statistical analysis revealed that all these factors have a negative effect on tablet porosity and, therefore, on the overall quality of tablets produced. This negative effect of all these factors on the tablet porosity was quantified using a PCR model, which revealed that tablet porosity is predominantly dependent on compression pressure followed by MCC particle size, APAP percentage, and compression speed in descending order. In addition, a predictive equation was developed *via* PCR to predict the porosity of APAP tablets as a function of compression pressure, MCC particle size, APAP percentage in the formulation, and compression speed. The above work gives an insight into the collective impact of the alterable manufacturing and formulation factors on the mechanical quality of poorly compressible API tablets.

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