Chapter -5

PHYSICOMECHANICAL AND PHYSICOCHEMICAL CHARACTERIZATIONS OF BIEXPONENTIAL COMPACTION PROCESS OF PARACETAMOL IN THE PRESENCE OF TALCUM-LUBRICATED-MCC
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5.1. Introduction

Tablet manufacturing by direct compression technique appears to be the cost effective, most efficient and interesting approach in the formulation development point of view (Boyapally H et al., 2010). Many active pharmaceutical ingredients are ductile in nature and behave in an elastic manner to be compressed by direct tableting method. Hydrophilic polymers derived from cellulose are suitable for biomedical applications and since long time have been used in pharmaceutical industries.

MCC is a depolymerised non-fibrous novel form of crystalline cellulose powder composed of porous particles and used in many dry formulations, particularly direct compression processes in tableting (Kalita R.D et al., 2013) and (Gryczke A et al., 2011) Silicified microcrystalline cellulose (co-processed blend of 98% MCC and 2% colloidal silicon dioxide) claims better flowability and compressibility compared to MCC alone or physical mixture. Powder composition and/or formulation process parameters determine the final properties of the compacts related to good tensile strength, free from cracks and defects, and drug dissolution (Kachimanis K et al., 2003) and (Santi M et al., 2012).

Design of powder formulation and process parameters are the main contributing factors related to the major practical aspects of powder compaction such as density distribution, consistency, and mechanical properties (Pandeya A et al., 2012) and (Ma H et al., 2010). Modelling can be used to optimize the composition of the powder, so that the tablet formulation can be designed on a rational basis. Although numerous researches have been reported so far, powder compaction process is too complicated to address properly (Mallick S., 2014). Powder compaction process involves die filling, compression using rigid punches and ejection of dense compact from the die. However, particle rearrangement and deformation can be called as the fundamental mechanisms of powder compaction.
process. At the initial rearrangement stage of pharmaceutical powder compression, particle moves without deformation followed by the stage of elastic deformation, plastic flow or fragmentation (Heckel R.W.1961), (Sun C et al., 2001 and Nordstrom J et al., 2009).

Kawakita and co-workers described the powder compression as the volume reduction on tapping process as well as applied pressure. Kuno et al., 1979 described the compression as powder packing process applying tapping only. Kuno developed the monoexponential equation based upon the relationships between the change of apparent density and the number of tapping. Several researchers have utilized Kuno equation and reported “packability” value (k) without illustrating graphical profile to characterize the compaction process (Kawashima Y et al., 1989), (Nokhodchi A., 2008), (Patel S V et al., 2011). Absence of graphical profile lacks actual mechanisms of “packability” scenario.

Paracetamol exhibits poor mechanical performance and cannot be tableted by direct compression technique. In the present work compaction process of paracetamol in the presence of MCC has been characterized (Rojas J et al., 2012) reported comparative functional properties of different polymorphic forms of MCC as direct compression excipient, after mixing and compressing with paracetamol. Talcum is a superior in vitro lubricant compared to magnesium stearate and silicon dioxide. It also improves tablet compression, hardness, friability, appearance and disintegration behaviour (Dawooddbhai et al., 1987).

Lubricating effect of talcum coupled with its crystalline nature may be advantageous over magnesium stearate and sodium lauryl sulfate during the compression of the MCC. MCC compact also showed increase in the strength in comparison to that of SMCC when lubricated with talcum. Paracetamol–MCC blends were lubricated with talcum (0.5–2.0%, wt/wt) and the initial rearrangement stage without deformation and final stage of elastic deformation, plastic flow or fragmentation of the particles were described in the present study.

Biexponential process of compression which involves the change in apparent density under tapping, and pressure has been applied for the powder formulation. The change in apparent density of the biexponential process has been attempted to correlate (level A correlation) with the conventional tabletability after mechanical testing at the same
applied pressure. Fourier transform infrared (FTIR) spectroscopic measurements, morphological investigation, scanning electron microscopy and in vitro dissolution studies were performed for characterizing tablet formulation. This type of characterization of powder formulation for direct tableting has not been reported earlier and is supposed to provide more information on the tableting behaviour.

**Biexponential compressibility**

**Apparent density as a function of number of tapping**

Kuno described a monoexponential relationship between the change in apparent density of a powder bed and number of tapping as:

\[(\rho_t - \rho_n) = (\rho_t - \rho_0) \exp (-kN)\]

- \(\rho_0\) = The apparent density at poured state
- \(\rho_n\) = The apparent density at \(N^{th}\) tapping state
- \(\rho_t\) = The apparent density at equilibrium packed state under tapping;
- \(k\) = The rate of packing process during tapping.

Biexponential equation can describe the packing process of powder material under both tapping and pressure. Two phases of powder packing process under tapping are:

i. Primary rearrangement process,
ii. Secondary rearrangement process and expressed as:

\[(\rho_t - \rho_n) = (\rho_p - \rho_0) \exp (-k_pN) + (\rho_t - \rho_p) \exp (-k_sN)\]

Where,

- \((\rho_p - \rho_0)\) = Density difference due to primary rearrangements of fine discrete particles.
- \((\rho_t - \rho_p)\) = Density difference that gives secondary rearrangement only after achieving primary rearrangement.
\[(\rho_t - \rho_0) = \text{density difference due to the total rearrangement phenomena that is the total compaction achieved after primary rearrangement and secondary rearrangement altogether.}\]

**kp and ks** = constants related to packing rate during primary rearrangement and packing rate during secondary rearrangement respectively.

Where, \(\rho_p\) = apparent density describing the extent of primary rearrangement of particles of powder bed.

**Apparent density as a function of applied pressure**

Compression phenomenon on applied pressure has been described by the following biphasic equation as:

\[(\rho_t - \rho) = (\rho_t - \rho_0) \exp (-k_r P) + (\rho_t - \rho_r) \exp (-k_b P)\]

Where,

\(\rho_t\) = true density, \(\rho\) = apparent density at the specific applied pressure \(P\),

\(\rho_r\) = apparent density describing the extent of particle rearrangement under pressure,

\((\rho_r - \rho_0) = \text{density difference that describes the theoretical maximal compaction which could be achieved by die filling and particle rearrangement}\)

\((\rho_t - \rho_r) = \text{density difference that indicates plastic deformation and bond formation only}\)

\(kr\) and \(kb\) = packing rate during die filling and particle rearrangement, and packing rate during plastic deformation respectively.
5.2. Experimental

5.2.1. Powder formulation

Paracetamol (crystalline powder: Tejani Life Lines, Cuttack, India); MCC (Avicel PH 101 nominal mean particle size 50 μm: Lupin Pharmaceuticals, Mumbai, India) and Talcum (≥99% through #200mesh, Himedia, Mumbai, India) were used in this study. Paracetamol blended with MCC as major excipient in the weight ratios of 1:1, 2:1, 3:1 and 4:1 by geometric mixing process without trituration. Different degrees of lubrication (0.5, 1.0, 1.5 and 2.0 wt/wt.%)) were also done to prepare a total of sixteen dry powder formulations and tabulated in Table 5.1. Particle size analysis of bulk commercial paracetamol, and formulated powder mixtures was done by sieve analysis method using mesh: 44, 60, 85, 100, 120, 150 and 170.

5.2.2. Assessment of compressibility by tapping

The compressibility of the powder samples was investigated by pouring gently into a measuring cylinder and tapped using a bulk density measurement apparatus (Koshiash Instruments, India). Initially, the bulk density or poured density (minimum density) was determined from the volume of the loose powder bed by visual estimation. The tap density was also determined by tapping the same cylinder up to 250 taps or until the volume did not change significantly. Reported results were the mean of six separate experiments. Helium pycnometer (Pycno 30, Smart Instruments, India) was used to determine the true density of each powder material without replication. All the compressibility parameters of \((\rho_p - \rho_o)\), \((\rho_t - \rho_p)\), \(\rho_p\), \(k_p\) and \(k_s\) under tapping related to apparent density were obtained by biphasic linear plots of \(\ln(\rho_t - \rho_n)\) versus \(N\).

5.2.3. Assessment of compressibility by pressure

All powder formulations were compressed using a Hydraulic pellet press (Techno search Instruments, Maharashtra, India) over a compression pressure of 24.5 to 343.2 MPa. A 10 mm diameter die and flat faced punch were used for compact preparation. Sample materials for each compact were weighed accurately (400 mg) on an analytical balance and poured manually into the die. Compacts for each load were prepared with a dwelling time under load of 60 s. During compression in the laboratory ambient condition (~27 °C, ~60%
maximum upper punch pressure was recorded for each compact. A digital micrometer (Mitutoyo, Japan) was used for measuring the thickness of freshly produced tablets. Apparent density, porosity and degree of volume reduction were calculated from these thickness data. \( (\rho_r - \rho_o), (\rho_T - \rho_r), \rho_r \) and \( k_p \) were estimated from the graphical plot of dense compact of \( \ln (\rho_T - \rho) \) versus \( P \).

5.2.4. Mechanical testing of the compact

**Tensile strength (Ts)**

Mechanical strength of the compact is commonly measured by its tensile strength. It is evaluated from the force required to fracture a tablet diametrically in a compression test. The tablet crushing force \( (F) \) was evaluated using a digital hardness tester (Model: HT-50P, Campbell electronics, India) within one minute after compacts were prepared. The tensile strength \( (Ts) \) was calculated using Eq. (1).

\[
Ts = \frac{2F}{\pi dH}
\]  (5.1)

Where, \( d \) is tablet diameter, and \( H \) is tablet thickness. This Equation is only valid to round flat-faced tablets when tablets fail in tension by splitting cleanly into halves diametrically under compression. Only tablets that failed in tension were used. Tablets which did not fail under diametrical compression were excluded from the test.

5.3. Physicochemical characterization

The compacts were prepared at 0.5 ton pressure with a dwelling time of 30 s and used for Fourier transform infrared (FTIR) spectroscopic measurements, morphological investigation, scanning electron microscopy and in vitro dissolution studies.

5.3.1. FTIR Spectroscopy

FTIR spectroscopic measurements were performed using FTIR spectrometer (FTIR-4100 type A, Jasco, Tokyo, Japan) using KBr pellet method. The crushed powder of compacts was scanned from 4000–400 cm\(^{-1}\). All spectra were collected through a scan of 80 accumulations at a resolution of 4 cm\(^{-1}\) and scanning speed of 2 mm/s at ambient
temperature of 18°C. For data acquisition and holding Spectral Manager for Windows software (Jasco, Tokyo, Japan) was used.

5.3.2. Morphological investigation

Morphological investigation of the tablet surface, and particulate arrangement in microscopic level were performed using intex camera respectively.

5.3.3. Scanning Electron Microscope (SEM)

Compacts were radially broken into halves and the broken face was visualized by a Scanning electron microscope (JSM-6390, JEOL and Tokyo, Japan). The dried samples were sputtered with gold and scanned at room temperature using an accelerated voltage of 10/20 kV.

5.3.4. Preparation of standard curve and In – Vitro dissolution study

Accurately weighed 100mg of drug dissolved in pH 5.8 phosphate buffer in a 100 ml volumetric flask. Different aliquots for desired concentrations (5, 10, 15, 20, 25 and 30 µg/ml.) were taken from the stock solution in to different 100ml of volumetric flasks and the volumes were made with the buffer solution. The absorbance of these concentrations was analyzed at 243 nm. This process was repeated in triplicate. The mean absorbance and concentration was plotted in X and Y axis respectively. The conformity of linearity between concentration and absorbance was established by regression analysis utilising Microsoft Excel.

The compacts were also used for in vitro dissolution testing in 900 ml of pH 5.8 phosphate buffer using USP dissolution apparatus (Paddle type: Electrolab, dissolution tester USP, TDT06L, India) at a paddle speed of 50 rpm for 30 min at 37 ± 0.5 °C. Samples were withdrawn at 5, 10, 15, 20, 25 and 30 min through 0.45µ membrane filter and spectrophotometrically analyzed the content of paracetamol at 243 nm after suitable dilution. The percent of paracetamol dissolved was reported as an average of four measurements with standard deviation.
5.4. Results

Table 5.1. Characteristics of compaction of talcum-lubricated-MCC particles containing paracetamol as a model drug under tapping and applied pressure.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Group</th>
<th>Paracetamol MCC</th>
<th>Talcum</th>
<th>Particle size (μm)</th>
<th>Ln (ρt−ρn) versus N</th>
<th>ln(ρt−ρ) versus P</th>
<th>r² of primary packing stage</th>
<th>r² of secondary packing stage</th>
<th>pₚ (mean ± sd, n = 4)</th>
<th>Tₚ</th>
<th>r² of dense Compaction</th>
<th>pr (mean ± sd, n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>–</td>
<td>15</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>P1M1T0.5</td>
<td>I</td>
<td>1:1</td>
<td>6</td>
<td>6</td>
<td>0.5</td>
<td>0.06</td>
<td>~250</td>
<td>~150</td>
<td>~125</td>
<td>0.966</td>
<td>0.927</td>
<td>0.316 ± 0.025</td>
</tr>
<tr>
<td>P1M1T1.0</td>
<td></td>
<td>1:1</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>0.12</td>
<td>~180</td>
<td>~105</td>
<td>~90</td>
<td>0.991</td>
<td>0.992</td>
<td>0.379 ± 0.008</td>
</tr>
<tr>
<td>P1M1T1.5</td>
<td></td>
<td>1:1</td>
<td>6</td>
<td>6</td>
<td>1.5</td>
<td>0.18</td>
<td>~180</td>
<td>~105</td>
<td>~90</td>
<td>0.982</td>
<td>0.924</td>
<td>0.404 ± 0.018</td>
</tr>
<tr>
<td>P1M1T2.0</td>
<td></td>
<td>1:1</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>0.24</td>
<td>~180</td>
<td>~105</td>
<td>~90</td>
<td>0.974</td>
<td>0.996</td>
<td>0.386 ± 0.001</td>
</tr>
<tr>
<td>P2M1T0.5</td>
<td>II</td>
<td>2:1</td>
<td>6</td>
<td>3</td>
<td>0.5</td>
<td>0.045</td>
<td>~250</td>
<td>~125</td>
<td>~90</td>
<td>0.966</td>
<td>0.938</td>
<td>0.377 ± 0.029</td>
</tr>
<tr>
<td>P2M1T1.0</td>
<td></td>
<td>2:1</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>0.09</td>
<td>~250</td>
<td>~125</td>
<td>~90</td>
<td>0.991</td>
<td>0.973</td>
<td>0.372 ± 0.019</td>
</tr>
<tr>
<td>P2M1T2.0</td>
<td></td>
<td>2:1</td>
<td>6</td>
<td>3</td>
<td>1.5</td>
<td>0.135</td>
<td>~250</td>
<td>~125</td>
<td>~90</td>
<td>0.99</td>
<td>0.973</td>
<td>0.404 ± 0.027</td>
</tr>
<tr>
<td>P2M1T2.0</td>
<td></td>
<td>2:1</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>0.18</td>
<td>~250</td>
<td>~125</td>
<td>~90</td>
<td>0.988</td>
<td>0.943</td>
<td>0.409 ± 0.007</td>
</tr>
<tr>
<td>P2M1T0.5</td>
<td>III</td>
<td>3:1</td>
<td>6</td>
<td>2</td>
<td>0.5</td>
<td>0.04</td>
<td>~250</td>
<td>~125</td>
<td>~105</td>
<td>0.99</td>
<td>0.961</td>
<td>0.355 ± 0.010</td>
</tr>
<tr>
<td>P3M1T0.5</td>
<td></td>
<td>3:1</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>0.08</td>
<td>~250</td>
<td>~125</td>
<td>~105</td>
<td>0.996</td>
<td>0.981</td>
<td>0.389 ± 0.014</td>
</tr>
<tr>
<td>P3M1T1.0</td>
<td></td>
<td>3:1</td>
<td>6</td>
<td>2</td>
<td>1.5</td>
<td>0.12</td>
<td>~250</td>
<td>~125</td>
<td>~105</td>
<td>0.965</td>
<td>0.931</td>
<td>0.388 ± 0.026</td>
</tr>
<tr>
<td>P3M1T2.0</td>
<td></td>
<td>3:1</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>0.16</td>
<td>~250</td>
<td>~125</td>
<td>~105</td>
<td>0.984</td>
<td>0.953</td>
<td>0.397 ± 0.024</td>
</tr>
<tr>
<td>P4M1T0.5</td>
<td>IV</td>
<td>4:1</td>
<td>8</td>
<td>2</td>
<td>0.5</td>
<td>0.05</td>
<td>~250</td>
<td>~125</td>
<td>~105</td>
<td>0.988</td>
<td>0.982</td>
<td>0.357 ± 0.016</td>
</tr>
<tr>
<td>P4M1T1.0</td>
<td></td>
<td>4:1</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>0.1</td>
<td>~250</td>
<td>~125</td>
<td>~105</td>
<td>0.993</td>
<td>0.934</td>
<td>0.385 ± 0.009</td>
</tr>
<tr>
<td>P4M1T1.5</td>
<td></td>
<td>4:1</td>
<td>8</td>
<td>2</td>
<td>1.5</td>
<td>0.15</td>
<td>~250</td>
<td>~125</td>
<td>~105</td>
<td>0.967</td>
<td>0.942</td>
<td>0.381 ± 0.024</td>
</tr>
<tr>
<td>P4M1T2.0</td>
<td></td>
<td>4:1</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>0.2</td>
<td>~250</td>
<td>~125</td>
<td>~105</td>
<td>0.993</td>
<td>0.973</td>
<td>0.419 ± 0.020</td>
</tr>
</tbody>
</table>

P – Paracetamol Pure Drug
Table 5.2. Tabletability characteristics and its correlation with $\ln (\rho_T - \rho)$ versus P model of particles in the pressure range of 24.5 to 343.2 MPa.

W. The tabletability coefficient estimated from the slope of tensile strength (MPa) versus applied pressure (MPa) plot.

a. Correlation coefficient of tabletability (tensile strength versus applied pressure).

b. Area under the tensile strength versus applied pressure curve; value in the parentheses indicates ratio of AUTCi /AUTC min.

c. Linear relationship describes how changes in $\ln (\rho_T - \rho)$ can be predicted from the changes in tensile strength at an applied pressure.

d. Correlation coefficient between $\ln (\rho_T - \rho)$ and tensile strength at the same applied pressure in the range of 24.5 to 343.2 MPa.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Group</th>
<th>$r^2$</th>
<th>W. mean $\pm(\times 10^5)$</th>
<th>AUC$^b$ mean $\pm$sd</th>
<th>Regression equation$^c$</th>
<th>$R^d$ (%)</th>
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</thead>
<tbody>
<tr>
<td>P1MIT0.5</td>
<td>I</td>
<td>0.993</td>
<td>1.13$\pm$0.101</td>
<td>4.617$\pm$0.211(3.09)</td>
<td>Y=-173.74X+0.23</td>
<td>0.961</td>
</tr>
<tr>
<td>P1MIT1.0</td>
<td></td>
<td>0.992</td>
<td>2.00$\pm$0.182</td>
<td>4.615$\pm$0.315(3.08)</td>
<td>Y=-12.64X-1.97</td>
<td>0.990</td>
</tr>
<tr>
<td>P1MIT1.5</td>
<td></td>
<td>0.949</td>
<td>1.16$\pm$0.105</td>
<td>4.929$\pm$0.292(3.29)</td>
<td>Y=-8.22X-1.91</td>
<td>0.936</td>
</tr>
<tr>
<td>P1MIT2.0</td>
<td></td>
<td>0.957</td>
<td>0.68$\pm$0.071</td>
<td>5.001$\pm$0.413(3.34)</td>
<td>Y=-16.71X-1.87</td>
<td>0.977</td>
</tr>
<tr>
<td>P2MIT0.5</td>
<td>II</td>
<td>0.982</td>
<td>1.26$\pm$0.111</td>
<td>4.069$\pm$0.327(2.72)</td>
<td>Y=-19.04X-2.32</td>
<td>0.986</td>
</tr>
<tr>
<td>P2MIT1.0</td>
<td></td>
<td>0.978</td>
<td>1.07$\pm$0.102</td>
<td>3.821$\pm$0.219(2.55)</td>
<td>Y=-171.2X-0.65</td>
<td>0.973</td>
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<tr>
<td>P2MIT1.5</td>
<td></td>
<td>0.983</td>
<td>0.72$\pm$0.058</td>
<td>4.295$\pm$0.501(2.87)</td>
<td>Y=-53.94X-1.68</td>
<td>0.988</td>
</tr>
<tr>
<td>P2MIT2.0</td>
<td></td>
<td>0.991</td>
<td>1.32$\pm$0.150</td>
<td>3.542$\pm$0.298(2.37)</td>
<td>Y=-29.38X-2.22</td>
<td>0.991</td>
</tr>
<tr>
<td>P3MIT0.5</td>
<td>III</td>
<td>0.984</td>
<td>1.40$\pm$0.112</td>
<td>2.701$\pm$0.219(1.80)</td>
<td>Y=-33.27X-2.36</td>
<td>0.957</td>
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<td>0.975</td>
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<td>3.19$\pm$0.192(2.13)</td>
<td>Y=-53.13X-2.19</td>
<td>0.993</td>
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<tr>
<td>P3MIT1.5</td>
<td></td>
<td>0.968</td>
<td>0.98$\pm$0.088</td>
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<tr>
<td>P3MIT2.0</td>
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<td>0.964</td>
<td>0.61$\pm$0.081</td>
<td>2.813$\pm$0.276(1.88)</td>
<td>Y=-283.13X+0.05</td>
<td>0.957</td>
</tr>
<tr>
<td>P4MIT0.5</td>
<td>IV</td>
<td>0.988</td>
<td>0.29$\pm$0.031</td>
<td>1.724$\pm$0.201(1.15)</td>
<td>Y=-364.66X-1.39</td>
<td>0.972</td>
</tr>
<tr>
<td>P4MIT1.0</td>
<td></td>
<td>0.985</td>
<td>0.34$\pm$0.017</td>
<td>1.496$\pm$0.121(1.00)</td>
<td>Y=-150.93X-2.68</td>
<td>0.971</td>
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<td>P4MIT1.5</td>
<td></td>
<td>0.995</td>
<td>0.63$\pm$0.044</td>
<td>1.756$\pm$0.189(1.17)</td>
<td>Y=-71.29X-2.65</td>
<td>0.978</td>
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<tr>
<td>P4MIT2.0</td>
<td></td>
<td>0.956</td>
<td>0.29$\pm$0.021</td>
<td>1.864$\pm$0.102(1.24)</td>
<td>Y=-619X-0.0764</td>
<td>0.956</td>
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</tbody>
</table>
Fig. 5.1: Biexponential plots of Ln (ρ_r− ρ_n) versus N of pure paracetamol and powder formulations: (a) Paracetamol/MCC ratio 1:1; (b) paracetamol/MCC ratio 2:1; (c) paracetamol/MCC ratio 3:1; and (d) paracetamol/MCC ratio 4:1.
Fig. 5.2: Effect of MCC on primary and secondary particle packing rate under tapping (b) density difference due to compaction by total particle rearrangement and apparent density describing the extent of primary rearrangement of particle under tapping and (c) density difference due to compaction by primary, secondary rearrangement of particle under tapping.
Fig. 5.3. Profiles of $\ln (\rho_T - \rho)$ versus $P$ of dense compact of all powder formulations: (a) Paracetamol/MCC ratio 1:1, paracetamol could not be tableted without MCC (insert picture); (b) Paracetamol/MCC ratio 2:1; (c) Paracetamol/MCC ratio 3:1; and (d) Paracetamol/MCC ratio 4:1.
Fig. 5.4.(a) Effect of MCC on rate of particle packing under pressure for dense compaction; (b) density difference due to compaction by particle rearrangement together with plastic deformation, and apparent density describing the extent of particle rearrangement under pressure; and (c) density difference due to compaction by particle rearrangement ($\rho_r - \rho_o$), and plastic deformation ($\rho_T - \rho_r$) under pressure
Fig. 5.5: Tabletability profiles of Group I (a); Group II (b); Group III (c) Group IV (d); and relationship between \( \ln (\rho T - \rho) \) of dense compact and tensile strength at the same applied pressure range of 24.5 to 343.2 MPa of Group I (e); Group II (f); Group III (g); and Group IV (h).
Fig. 5.6: FTIR spectra of pure paracetamol and the crushed powder of compacts of P1M1T1.0, P3M1T1.0, and P4M1T1.0 formulations.
Fig. 5.7: Compact morphology by Intex camera: paracetamol pure drug failed to be tableted alone: cracked tablet (A) and laminated layers (B); tablet compressed (P1M1T1.0): absence of crack on the flat face (C) and side wall (D); tablet compressed (P4M1T1.0): presence of uneven porous surface (E, F); surface view of the laminated tablet of pure paracetamol (G); and good tablet (P1M1T1.0) (H);
Fig. 5.8: Scanning electron microscopy of pure crystalline paracetamol, physical mixture (pm) of P1M1T1.0, broken face of radially halved tablets (P4M1T1.0 and P1M1T1.0).
Fig. 5.9: A: Absorption maxima of paracetamol, B: Standard curve of paracetamol.
C: In vitro dissolution study of tablets of Group I; Group II; Group III; and Group IV in phosphate buffer pH 5.8.
5.5. Discussion

5.5.1. Particle size distribution

Amongst the various factors particle size plays a great role in interparticulate bonding of the tablets. (Ahmad M J et al., 2012). Influence of particle size on the direct compression of ibuprofen has been studied systematically recently. Particle size distribution of bulk paracetamol, and formulated powder mixtures was determined and the respective $D_{90}$, $D_{50}$ and $D_{10} \, (\mu m)$ of all the samples has been reported in Table 5.1. Major difference in particle size distribution has not been noticed between pure paracetamol and dry powder formulations of Groups II, III and IV of paracetamol/Avicel ratios 2:1, 3:1 and 4:1 ($D_{90}$ and $D_{50}$ values are 250 and 125 $\mu m$ respectively). Nominal $D_{90}$ and $D_{50}$ of Group I formulations of paracetamol/MCC ratio 1:1 have been decreased to 180 and 105$\mu m$ respectively due to the presence of maximum amount of MCC which was most fine in nature. Presence of talcum in the range of 0.5–2.0% did not affect the nominal $D_{90}$ and $D_{50}$ of the formulations.

5.5.2. Characteristics of compressibility by tapping

Biexponential linear plots of $\ln (\rho_t - \rho_n)$ versus $N$ of pure paracetamol and all formulations of 1:1, 2:1, 3:1 and 4:1 ratios (paracetamol/MCC in Groups I, II, III and IV respectively) have been illustrated in Fig.5.1 a–d. All the profiles of change of density under tapping exhibited biphasic linear regions and were found to fit well with the biexponential Eq. (2) ($r^2$ values 0.924 to 0.996). The one linear region could be described as the one major steps of particle rearrangement process viz, (i) primary rearrangement and (ii) secondary rearrangement. Density difference ($\rho_t - \rho_n$) values of dry powder formulations of Groups I, II, and III containing paracetamol mostly have been increased up to 100th tapping compared to paracetamol alone (Fig.5.1 a, b, and c) whereas, ($\rho_t - \rho_n$) values of Group IV formulations have been increased up to 15th tapping only and then gradually decreased as the tapping continued (Fig.5.1d).

The graphical profiles indicated a gradual decreasing trend in the area in between the curves (ABC) of formulation and pure paracetamol from Group I to Group III. Formulations of Group IV have failed to show significant positive ABC after 15th tapping.
rather, it was increased negatively. The change in apparent density under tapping \((\rho_t - \rho_n)\)
was actually related to the compression ability of powder bed. Hence, above results
indicated the fact that as the MCC amount decreased, compressibility of the powder
formulation decreased and the compressibility became least when paracetamol/MCC ratio
was 4:1. Moreover, Fig. 5.1(a–d) also indicated that higher concentration of talcum in the
formulation supported the improvement of compressibility of the powder Fig.5.2 described
the effect of MCC on particle packing rates and particle rearrangements under tapping
process.

The particle packing rates \((k_p\) and \(k_s\)) as a function of drug loading in the powder
formulation were shown in Fig.5.2a. Column chart indicated that the primary
rearrangement packing rate \((k_p)\) was higher than the packing rate during secondary
rearrangement \((k_s)\) in all powder samples with a great difference. That means primary
packing rate was significantly faster than secondary packing rate during the tapping process
due to fast release of loose air pockets in the powder bed during primary rearrangement of
particles. Both \(k_p\) and \(k_s\) of pure paracetamol were smaller compared to most of the
formulations. Group IV formulations of paracetamol/MCC ratio 4:1 have shown somewhat
higher values than other formulations. Packing rate or, exponential decrease in density
difference per unit tapping could not be correlated directly with the compressibility rather it
may be called as the mechanism of packing process during tapping. Influence of drug
loading on density difference due to total particle rearrangement or total packing \((\rho_t - \rho_o)\)
and apparent density describing the extent of primary rearrangement of particles under
tapping have been illustrated in Fig 5.2b. In fact, difference in apparent density due to
tapping has a direct relation with the compactibility of the powder material.

Hence, on the basis of tapping experiment again we can say paracetamol
compactibility has been increased in all MCC based dry powder formulations and least
improvement was observed in Group IV formulations containing least amount of MCC
comparing to paracetamol alone. Apparent density after primary rearrangement of all the
formulations has also increased. The drug loading effect on density difference due to
tapping by primary \((\rho_p-\rho_o)\) and secondary rearrangements \((\rho_t-\rho_o)\) has been shown in
Fig.5.2c. In this figure \((\rho_p-\rho_o)\) was always more than \((\rho_t-\rho_o)\) means compaction was more
in the first step of packing rather than the second step during tapping process. Transitional
tapping between primary and secondary packing phase ($T_p$) was noticed to be 35–40 tapping. The $r^2$ of $\ln (\rho_t - \rho_n)$ versus $N$ plots, $\rho_p$ and $T_p$ values were reported in Table 5.1.

5.5.3. Characteristics of compressibility by pressure

Plots of $\ln (\rho_t - \rho_n)$ versus $P$ of dense compact of all powder formulations of Group I, II, III and IV were depicted in Fig.5.3 (a–d). All the powder formulations have been compressed and compact was produced due to plastic flow of the composite particulate powder bed. This step was known as plastic deformation or dense compaction.

Pure paracetamol powder could not be compacted into tablet due to its poor compressibility and excessive elastic recovery and the lamination of tablets after compression has been shown in the inset of Fig.5.3a. All the profiles of dense compaction exhibited linear relationship between $\ln (\rho_T - \rho)$ and $P$ and produced $r^2$ between 0.929–0.994. Difference in apparent density ($\rho_T - \rho$) values of Group I were in the greatly higher level compared to other Groups of dry powder formulations. Majority of ($\rho_T - \rho$) points of Group II were higher rather than Group III where as, Group IV has exhibited majorly lower values than rest of the Groups. Therefore, compressibility by pressure can be categorized in the decreasing order as: Group I N Group II N Group III N Group IV. More number of ($\rho_T - \rho$) points were in the higher level in the formulations of talcum content 1.5 to 2.0% compared to 0.5 to 1.0%. On the basis of this result it could be assumed that talcum in the range of 1.5 to 2.0% increased compressibility in each group.

Effect of MCC on rate of particle packing, particle rearrangements and plastic deformation under pressure for dense compaction of all formulations has been exhibited in the column chart of Fig. 5.4 a–c. Particle packing under pressure ($k_b$) has been shown in the column chart of Fig.5.4 (a). As seen in case of tapping, rate of packing under pressure or, exponential decrease in density difference per unit pressure could not be correlated directly with the compression ability of the powder materials. No direct relation between $k_b$ and drug loading, and talcum content in the formulations could be established. Only formulations P1M1T0.5, P2M1T1.0, P3M1T1.5, P3M1T2.0, P4M1T0.5 and P4M1T2.0 have shown faster value ($-k_b$) in between 1.0*10^3 to 2.0*10^3 compared to other formulations (nearly 0.5*10^3 and less).
Column chart in Fig. 5.4 (b) showed the effect of drug loading on density difference due to compaction by particle rearrangement and plastic deformation altogether under applied pressure (ρ_T − ρ_0). The column chart also exhibited apparent density describing the extent of particle rearrangement under pressure (p_r) as the function of drug loading in the MCC based dry powder formulation and the actual values were tabulated in Table 5.1.

Group I formulations have significantly greater p_r than Group IV. Fig. 5.4 b indicated that (ρ_T − ρ_0) column heights of Group I formulations were greatest compared to others, and heights gradually decreased through II, III and IV and also there was an increasing trend of height with increasing content of talcum. The results indicated that compressibility decreased with the increase of drug loading in the MCC-based formulation. Moreover, talcum also supported increased compressibility with its increased content in the formulation. The formulation P1M1T2.0 has shown greatest height of (ρ_T − ρ_o) indicating maximum compressibility due to minimum drug loading and maximum content of talcum.

The density, ρ_r was the transitional apparent density in between loose powder bed and dense compact (tablet formation). Group I formulations have shown significantly higher values in both (ρ_T − ρ_o) and ρ_r compared to Group IV. Under applied pressure density difference due to compaction by particle rearrangement (ρ_r − ρ_o) and density difference due to compaction by plastic deformation (ρ_T − ρ_r) influenced by drug loading have been depicted in Fig. 5.4C. Density difference due to compaction by particle rearrangement was significantly very higher compared to compaction by plastic deformation in all the powder formulations. Compaction by plastic deformation has been gradually decreased with gradual increase of drug loading in the powder formulations. While, significant difference was clearly observed between formulations of Group I and IV. As the talcum content varied 0.5–2.0% in each Group (I, II, III and IV) (ρ_r − ρ_o) and (ρ_T − ρ_r) values did not vary greatly in the same group.

MCC is an extremely valuable tableting agent in the pharmaceutical industry particularly in direct-compression processes. Lepek et al. reported that Avicel PH 101 was useful for direct-compression and even more than 50% caused substantial problems in the tableting process of crystalline telmisartan whereas, compression process functioned much better with the tablet blends made from the amorphous form. It was observed in some published article that 30% and 40% of Avicel PH 102 did not improve the compression of
Ludipress (composed of Lactose monohydrate, Povidone K30 and Crospovidone) and the mixtures were not compressible continuously.

Several efforts have been reported earlier for preparation of paracetamol tablet by direct compression technique. Incorporation of 25% dibasic calcium phosphate dihydrate and 75% wt/wt MCC in paracetamol formulations has shown greater resistance to capping, and compacts containing 25% wt/wt of MCC alone produced tablets with double the tensile strength. During compaction, particles come closer to each other and densification takes place and bond formation between particles occurs. Formation of solid bridges, intermolecular forces (Van - der Waals forces and hydrogen bonds) and mechanical interlocking are supposed to be the bonding mechanisms.

5.5.4. Tabletability characteristics and its correlation with Ln ($\rho_T - \rho$)

Evaluation of compacts of the different powder formulations was then performed. Tabletability is the ability of a powder bed to be transformed into a compact of specific mechanical strength under the influence of compaction pressure. The strength of the compacts is influenced by the compressibility characteristic of the powder formulations. Stronger compacts are produced with highly compressible powder which enables the particles to come closer to each other and enhances interparticulate bonding.

Tabletability can be estimated by using linear regression of the plot of radial tensile strength versus compression pressure. Tabletability profiles of the sixteen powder formulation have been exhibited in Fig. 5 a–d. Coefficient of tabletability can be estimated from the slope of the linear region of the plot. Quantification of tabletability can be measured from the area under the tensile strength versus compression pressure curve in a definite pressure range when compact is formed. It was observed that the compacts were more mechanically stronger when the formulation contained more amount of MCC, whereas, weak compacts of less tensile strength were produced when paracetamol amount was increased. Tabletability coefficient and area under the tensile strength versus applied pressure curve (AUTC) of all the formulations have been reported in Table 5.2. All tabletability profiles have shown good linearity (r values: 0.949 to 0.995). An increasing trend of tabletability coefficient (w) was noticed in the powder containing more amount of MCC (P1M1T1.0) has shown a maximum mean value of 2.00 and a minimum value of 0.29 has been shown by both P4M1T0.5 and P4M1T2.0). AUTC values (MPa$^2$) have
gradually been decreased with the gradual increase of paracetamol and consequent decrease of MCC amount. Group I mean values ranged from 4.615 to 5.001 and Group IV ranged from 1.496 to 1.864.

Presence of talcum has not shown significant variability in a particular group. The optimum amount of talcum for improved AUTC was found in P1M1T2.0 (5.001 ± 0.413), P2M1T1.5 (4.295 ± 0.501), P3M1T1.5 (3.253 ± 0.321) and P4M1T2.0 (1.864 ± 0.102). The ratio of AUTC of an individual formulation to that of the one having minimum value (AUTC min) mentioned in the parentheses (Table 5.2) gave the idea of relative increase of the value. On the basis of that tabletability has been improved more than three fold in Group I formulations. To establish Level A correlation between compaction process Ln($\rho_T - \rho$) versus P) and conventional tabletability, a plot of Ln($\rho_T - \rho$) versus tensile strength has been produced at the same applied pressure range of 24.5 to 343.2 MPa (Fig. 5 e–h). A point-to-point linear relationship (r values 0.936 to 0.993) between Ln($\rho_T - \rho$) and tensile strength proves a “Level A” correlation between the compaction process and tabletability. Regression equation of the linear relationship has also been shown in Table 5.2 which describes how changes in Ln($\rho_T - \rho$) can be predicted from the changes in tensile strength at an applied pressure.

5.5.5. Analysis of FTIR, compact morphology and in vitro dissolution

Physicochemical characteristics of the powders and the compacts of talcum-lubricated-MCC containing paracetamol have been depicted in Fig.5.6. FTIR spectrum of crystalline paracetamol in Fig. 5.6 was described as follows: 3318 cm$^{-1}$ assigned as the N–H stretching vibration; 3150 cm$^{-1}$ indicated the hydrogen bonded OH stretching vibration plus other combination bands; 1654 cm$^{-1}$: the C = O stretching vibration; 1562 cm$^{-1}$: the N–H in-plane bending; 1610, 1509 and 1436 cm$^{-1}$: the aromatic ring mode; 1324 cm$^{-1}$: the O–H bending vibration and 1225–1250 cm$^{-1}$: the C–O and/or C–N stretching vibrations, respectively.

The above representative FTIR bands did not decrease its peak intensity and also did not shift significantly in the formulation mixture, since the atoms or molecules occupied the fixed site with very little vibrational motion in the solid state. Peak at 3150 cm$^{-1}$ shifted and intensity at 1654 cm$^{-1}$ decreased only very slightly due to the presence of MCC. A short-term milling can influence the shape of FTIR spectra of cellulose and the changes
have been mainly associated with a decrease in crystalline intensity of cellulose. Crystallinity of cellulosic materials was measured by the ratio of absorptivity at ~1372 cm\(^{-1}\) (C–H bending) to that at~2901 cm\(^{-1}\) (CH2 and CH stretching). In the spectra of P1M1T1.0, P3M1T1.0, and P4M1T1.0, particularly the peaks at 1372 cm\(^{-1}\) and 2901 cm\(^{-1}\) of MCC have been affected.

This result indicated that the crystallinity of both paracetamol and MCC has been affected in the compaction process. Moreover, intermolecular forces such as Van der Waals forces and hydrogen bonds might be the confirmatory assumptions responsible for the mechanical strength of the compact of the formulation due to the presence of MCC.

The morphological characterization of the formulated powdered has been depicted in Fig.5.7. Cracked tablet and laminated layers were formed when paracetamol was attempted to be compressed alone (A, B). Tablet free of cracks and no lamination has been produced when P1M1T1.0 was compressed (C, D). Tablet containing slightly uneven porous surface was noticed when P4M1T1.0 was compressed (E, F). Surface view of the laminated tablet of pure paracetamol clearly showed appearance of numerous empty pores in between drug crystals (G) even after compaction, whereas, P1M1T1.0 produced smoothed surface and absence of pores (H). Solid bridges formation and mechanical interlocking confirmed the assumption to be the other bonding mechanisms.

Scanning electron microscopy study presented in Fig.5.8 revealed the distinct crystalline nature of paracetamol while the presence of excipients were clearly observed in the physical mixture (pm) of P1M1T1.0. The halved tablet broken face of P4M1T1.0 indicated loosely packing of paracetamol particle in the excipients matrix with numerous pores compared to tightly packing of particles with significantly less porosity in P1M1T1.0. These observations again supported the fact that the solid bridge formation and mechanical interlocking were more intensified as the MCC amount increased in the formulation.

The absorption maxima (243nm) and the standard curve has been depicted in Figure no 5.9(A and B) respectively. Drug dissolution Figure no 5.9 (C) was found faster as the MCC loading increased and the mean percent dissolution (n = 4) can be categorized as: Group I (95.2–102.9) N Group II (94.6–101.9) N Group III (83.0–92.9) N Group IV (72.5–
80.9). MCC played an important role in the process of disintegration and made the consequent dissolution faster as its loading in the tablet formulation was increased.

### 5.6. Conclusions

- Difference in apparent density due to both tapping and pressure has a direct relation with the compactibility of the powder material.
- Primary rearrangement packing rate was faster compared to secondary rearrangement packing rate in all powder formulations with a great difference as understood by tapping experiment.
- Density difference due to compaction under pressure by particle rearrangement was very high compared to compaction by plastic deformation in all the powder formulations.
- Apparent density has been increased in all MCC based dry powder formulations and least improvement was observed in Group IV formulations containing least amount of MCC compared to paracetamol alone.
- Compressibility and mechanical strength increased with the increase of MCC loading in the powder formulation.
- A “level A” correlation has been established between compaction process and tabletability.
- Drug dissolution was found faster as MCC loading increased in the tablet formulation.