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# Radial die-wall pressure as a reliable tool for studying the effect of powder water activity on high speed tableting

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ABSTRACT

The effect of moisture as a function of water activity (Aw) on the compaction process is important to understand particle/water interaction and deformation. Studying powder/moisture interaction under pressure with radial die-wall pressure (RDWP) tool was never done. The aim of our study was to use this tool to study this interaction at high compression pressure and speed. Moreover, the effect of changing ejection cam angle (EA) of the machine on ejection force (EF) was investigated. Also, a new tool for prediction of tablet sticking was proposed. Materials with different deformation behaviors stored at low and high moisture conditions were used. Compaction simulation guided by modeling was applied. High Aw resulted in a low residual die-wall pressure (RDP) for all materials, and a high maximum die-wall pressure (MDP) for plastic materials, $p < 0.05$. This was due to the lubricating and plasticizing effects of water, respectively. However, microcrystalline cellulose showed capping at high Aw and compaction pressure. By increasing compression pressure at high Aw for all materials, effective fall time (EFT) was increased, $p < 0.05$, showing tendency for sticking. Increasing EA caused an increase of friction and EF for powders, $p < 0.05$. RDWP was a useful tool to understand particle/moisture interaction under pressure.



## 1. Introduction

Water activity (Aw) is the active or free part of powder moisture content. By definition, Aw is the relative humidity which is reached at equilibrium for a product in a sealed container and is expressed on a scale of zero to one. Aw is also known as equilibrium relative humidity. Stubberud et al. (1996) recommend studying the effect of moisture as a function of Aw if the degree of powder crystallinity is unknown. They suggest that the presence of moisture in powder during tableting may lead to phase transitions at high temperatures generated by the press machine. Generally moisture affects powder characteristics like flowability and compact hardness, so could later alter the compact disintegration or dissolution profile (Dawoodbahai and Rhodes, 1989). Moisture changes the cohesive/adhesive behavior of powder (Maggi et al., 1999). Moreover, moisture content could change the deformation behavior, bonding type, and area of particles (Mollan and Çelik, 1995; Sebhatu et al., 1994). Effect of moisture on tableting compression cycles was previously is reported by Touré et al. (1980). The presence of moisture in powder for a certain limit is important for compression and consolidation (Rees, 1970; Khan et al., 1981; Armstrong and Patel, 1986; Pilpel and Ingham, 1988; Shukla and Price, 1991a; Garr and Rubinstein, 1992; Pande and Shangraw, 1995). Water is reported to act as a plasticizer for polymers and amorphous powders, increasing molecular mobility, and lowers the glass transition temperature turning the material from a hard to a soft rubbery state (Oksanen and Zografi, 1990; Slade and Levine, 1991; Picker-Freyer and Durig, 2007). Studies on the effect of moisture on compaction are rare and very old and there are almost no studies involving die-wall pressure monitoring. Application of fully instrumented compaction simulators is helpful in understanding the compaction cycle at early stages of development and in monitoring tablet production process as well (Doelker and Massuelle, 2004). Among the forces that could be measured by the sensors in the simulator, the adhesive force radially transmitted to the die-wall. Controlling such a tool is very beneficial to understand particles deformation and interaction with moisture under pressure and speed. Moreover, this parameter was rarely used in compaction research and data regarding this issue are quite old and controversial. Another interesting feature of our study was the capability to change ejection cam angle (EA) by the aid of compaction simulation. No studies at all are found regarding the effect of changing ejection angle on ejection force. This is a major advantage of the simulator used in this study, that the ejection angle cam can be changed to investigate friction and ejection forces. In rotary machines, this angle is fixed to different values, e.g. Korsch: 13°; Fette: 12°. Thus, by Presster the different conditions can be simulated.

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**Table 1**
Average water activity (Aw) values of powders before, during and after compaction.

| | %RH | Temperature (°C) | | | | | Aw | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Before | During | After | Average | SD | Before | During | After | Average | SD |
| MCC | 0 | 26.5 | 29.6 | 28.9 | 28.3 | 1.63 | 0.032 | 0.038 | 0.056 | 0.042 | 0.01 |
| | 90 | 28 | 29.6 | 29.5 | 29.0 | 0.90 | 0.902 | 0.874 | 0.861 | 0.879 | 0.02 |
| Pre-gelatinized starch | 0 | 27.8 | – | 30 | 28.9 | 1.56 | 0.049 | – | 0.067 | 0.058 | 0.01 |
| | 90 | 28.2 | – | 29.7 | 29.0 | 1.06 | 0.888 | – | 0.876 | 0.882 | 0.01 |
| Mannitol | 0 | 28.3 | 28.6 | 30.4 | 29.1 | 1.14 | 0.229 | 0.35 | 0.336 | 0.305 | 0.07 |
| | 90 | 28.9 | 29.4 | 30.2 | 29.5 | 0.66 | 0.888 | 0.853 | 0.851 | 0.864 | 0.02 |
| Lactose | 0 | 28.5 | – | 31.5 | 30.0 | 2.12 | 0.14 | – | 0.328 | 0.234 | 0.13 |
| | 90 | 29.3 | – | 31.4 | 30.4 | 1.48 | 0.729 | – | 0.403 | 0.566 | 0.23 |
| CHPD | 0 | 27.4 | – | 28.8 | 28.1 | 0.99 | 0.167 | – | 0.402 | 0.285 | 0.17 |
| | 90 | 27.9 | – | 28.9 | 28.4 | 0.71 | 0.748 | – | 0.417 | 0.583 | 0.23 |

The aim of our study was to investigate the effect of Aw on compaction of powders through Radial Die Wall Pressure monitoring. Tools for early prediction of powder sticking were also applied. Moreover, the effect of ejection angle change on ejection was studied. Finally these tools were discussed and evaluated for a real application.

## 2. Materials and methods

### 2.1. Materials

Microcrystalline cellulose MCC (Avicel® PH102, FMC Corporation, DE, USA), Directly Compressible Mannitol (Parteck® M200, Merck KGaA, Darmstadt, Germany), Calcium hydrogen phosphate dihydrate CHPD (Emcompress®, JRS Pharma, Rosenberg, Germany), Pre-gelatinized starch (Sta-Rx® 1500, Colorcon, Idstein, Germany), spray dried lactose monohydrate (Flowlac® 100, Meggle, Wasserburg, Germany), and Magnesium stearate (Mg-stearate, supplied by Sandoz AG, Basel, Switzerland).

### 2.2. Powder storage

Powders were stored for six weeks to ensure complete equilibrium in desiccators with two extreme conditions of relative humidity; (0% RH, temperature 19 ± 1.5 °C), and (90 ± 3.2% RH, temperature 20 ± 1 °C) created by a saturated solutions of phosphorus pentoxide and potassium nitrate, respectively (analytical grade, Merck KGaA, Darmstadt, Germany).

### 2.3. Powder characterization

#### 2.3.1. Water activity

Powder water activity as well as temperature was checked regularly with HygroPalm AW1 and HygroClip water activity station (Rotronic AG, Bassersdorf, Switzerland) before, during, and after compaction, see Table 1.

#### 2.3.2. Apparent particle density

Apparent particle density of powders was measured by AccuPyc 1330 helium pycnometer (Micrometrics, Norcross, GA, US). A weight (2.5 g) of the samples was placed into the sample cell. Values were expressed as the mean of five parallel measurements.

#### 2.3.3. Differential scanning calorimetry (DSC)

DSC was done to check any phase transitions after the powders storage at the two different relative humidity conditions (Perkin Elmer DSC 4000, MA, US). Samples (4–8 mg) were encapsulated in aluminum pans with holes and heated in a temperature range of 0–250 °C with a heating rate 10 °C/min in a nitrogen atmosphere.

### 2.4. Powder compaction

Powder compaction was carried out using a compaction simulator (Pressster™, Metropolitan Computing Corp., NJ, US) simulating the tablet press Korsch PH336 (36 stations). Resolution for force and displacement measurements on Pressster were interpreted as the accuracy of signal voltage measurements (in Volts) multiplied by respective calibration factors of the transducers (in kN/V or mm/V). Absolute Accuracy of the data acquisition board installed on the Presster is ±0.0015% of Full Scale value which is ±10 V. Calibration factors were 5.81 kN/V for upper compression; 5.61 kN/V for lower compression; 1.38 mm/V for upper punch displacement; −1.35 mm/V for lower punch displacement. The sampling rate was 1 kHz.

Unlike hydraulic simulators, for Presster the mechanical replicator, both LVDTs are installed into the same carrier as the die. As the carrier does not support the compression force, the distances among each LVDT and die do not change with the force. The LVDT cores are fastened to the punches in close proximity to the punch tips thus minimizing the influence of the applied force on the measurements. Only punch tips deformation might be taken in consideration. The calculated combined elasticity of 10 mm round punch tips used with the instrumented die is 0.003 mm/kN (0.002 for the lower punch and 0.001 for the upper one). In many cases, the involved error can be considered negligible. The compaction rolls used were 300 mm in diameter. Accordingly, a flat-faced B-tooling with a diameter of 10 mm was used to make tablets of 250 mg in weight. Powder feed was manually done. All powders were mixed with 1% (w/w) Mg stearate as a lubricant. The machine was set to perform compaction pressures of 50 and 300 MPa at the compaction speeds of 0.5 and 2 m/s corresponding to the following dwell times (19, and 4.8 ms), respectively and at the ejection angles of 5 and 15 degrees. Six tablets were compressed at the same experimental conditions and the mean was calculated. Residual die-wall pressure (RDP), maximum die-wall pressure (MDP), work of compression (WC), ejection force (EF), take off force (TO, force required to scrape the formed compact from the lower punch after ejection), and effective fall time (EFT, Time interval between 90% and 10% of the peak on the down slope for force/time compression curve) were measured, see Figs. 1–3. The die-wall pressure reaches a maximum value, MDP, just after the upper and lower punches show maximum compression values, and shows a constant residual value, RDP, after upper and lower punch forces become zero. Axial to radial stress ratio (SR) (MDP to the average of upper and lower compression pressures) was calculated, friction coefficient during ejection FCE

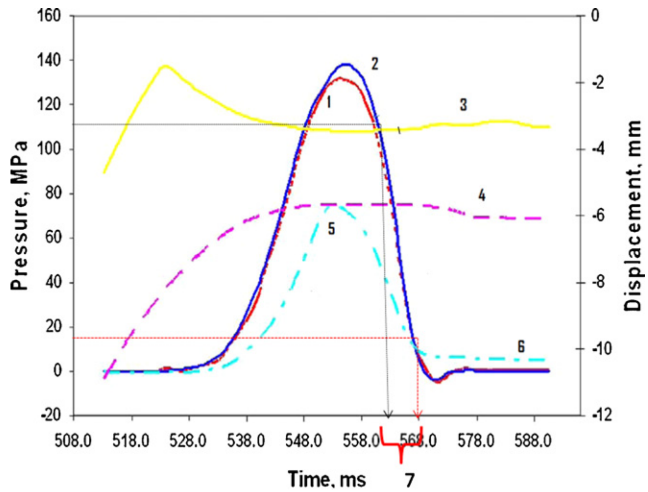


**Fig. 1.** Compression waveform of the Presster™ showing (1) Upper and (2) Lower compression pressures (MPa), (3) Upper and (4) Lower punch displacement (mm) curves, (5) Maximum radial die-wall pressure MDP (MPa), (6) Residual die-wall pressure RDP (MPa), (7) Effective fall time EFT (ms).

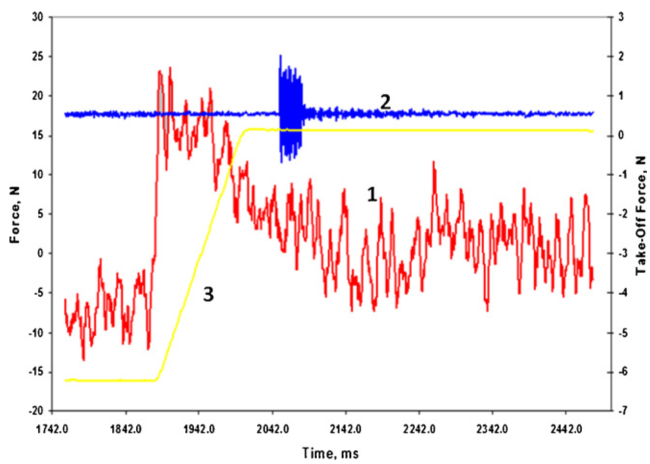


**Fig. 2.** Presster™ software curves of (1) Ejection force EF (N), (2)Take-off force TO (N), and (3) Lower punch displacement.

($\mu_e$) and friction coefficient during compression FCC ($\mu_c$) were also calculated according to Eq. (1) (Hölzer and Sjögren, 1981) and Eq. (2) (Cunningham et al., 2004).

$$\mu_e = \frac{F_e}{F_{r0}} \tag{1}$$

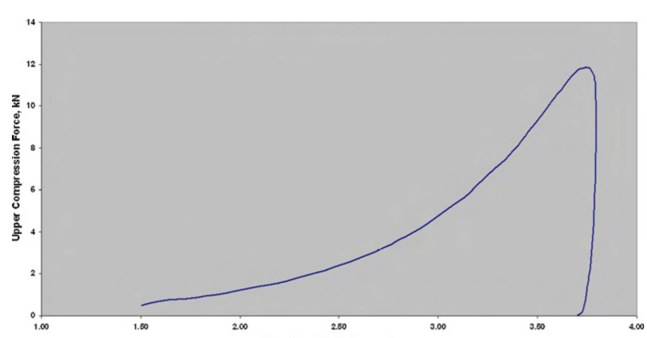


**Fig. 3.** Presster™ Force–displacement curve where the area under the curve corresponds to the total work of compaction WC (J).

**Table 2**
Experimental design generated by STAVEX® 5.0 to study the effect of powder water activity (Aw) and machine's ejection cam angle (EA) on radial die-wall pressure at high/low compression pressure and speed.

| Run | Compression pressure (MPa) | Compression speed (m/s) | Aw (%) | EA (degrees) |
|---|---|---|---|---|
| 1 | 50 | 0.5 | 0 | 5 |
| 2 | 50 | 2 | 90 | 5 |
| 3 | 50 | 2 | 0 | 15 |
| 4 | 50 | 0.5 | 90 | 15 |
| 5 | 300 | 2 | 0 | 5 |
| 6 | 300 | 0.5 | 90 | 5 |
| 7 | 300 | 0.5 | 0 | 15 |
| 8 | 300 | 2 | 90 | 15 |
| 9 | 300 | 0.5 | 0 | 5 |
| 10 | 300 | 2 | 90 | 5 |
| 11 | 300 | 2 | 0 | 15 |
| 12 | 300 | 0.5 | 90 | 15 |
| 13 | 50 | 2 | 0 | 5 |
| 14 | 50 | 0.5 | 90 | 5 |
| 15 | 50 | 0.5 | 0 | 15 |
| 16 | 50 | 2 | 90 | 15 |

where $F_e$ is the ejection force and $F_{r0}$ is the residual die-wall force.

$$\mu_c = \frac{D}{4H}\frac{F_U}{\text{MDF}}\left(\frac{F_L}{F_U}\right)^{\text{LPD}/H} \ln\frac{F_L}{F_U} \tag{2}$$

Eq. (2) was developed by Cunningham and coworkers but was modified by us to fit to the dynamics of the Presster™.

Where $F_U$ and $F_L$ are the upper and lower compression forces, MDF is the maximum die-wall force, LPD is the lower punch displacement, $D$ is the die diameter and $H$ is the compaction height.

### 2.5. Compact characterization

#### 2.5.1. Radial tensile strength (RTS)

Crushing strength of a compact was determined by pressing it diametrically on a Pharmatron tablet tester (model 8D, Dr Schleuniger Pharmatron Inc, Solothurn, Switzerland). Radial tensile strength $\sigma$ (MPa) was calculated according to:

$$\sigma = \frac{2F}{\pi d h} \tag{3}$$

where $F$ is the force required to cause failure in tension (N), $d$ is the compact diameter (mm), $h$ is the compact thickness (mm) and $\pi$ is a constant equals 3.1416. Compacts dimensions were measured using a micrometer with a precision of 0.01 mm (Mitutoyo, Japan).

#### 2.5.2. Porosity

Compact porosity was calculated from compact's apparent density and dimensions.

#### 2.5.3. Elastic recovery (% $ER_0$)

The % $ER_0$ for a compact was calculated from "zero pressure thickness" that could be seen from the force vs. thickness plot, and "minimum punch gap" (thickness at maximum compression), features of Presster® software.

#### 2.5.4. Differential scanning calorimetry

A mass from the compact was snatched by a spatula and measured after compaction as mentioned above.

### 2.6. Data interpretation

To study the effect of different compaction variables, runs were generated according to an experimental design using STAVEX® 5.0 (Aicos, Switzerland) applying a 2-level full-factorial design, two blocks, unforced, modeling mode, Table 2. Compaction pressure,

**Table 3**
Apparent particle density and DSC parameters of the investigated materials.

| Powder | Apparent particle density ± SD | RH (%) | Peak temperature (°C) ± SD | Delta *H* (J/g) ± SD |
|---|---|---|---|---|
| MCC | 1.58 ± 0.0019 | 0 | 76.58 ± 1.65 | 168.08 ± 13.22 |
| | | 90 | 76.68 ± 4.80 | 193.72 ± 16.90 |
| Pre-gelatinized starch | 1.49 ± 0.0006 | 0 | 89.48 ± 3.01 | 237.05 ± 0.00 |
| | | 90 | 83.73 ± 0.00 | 247.81 ± 0.00 |
| Mannitol | 1.51 ± 0.0007 | 0 | 168.73 ± 0.36 | 249.67 ± 6.49 |
| | | 90 | 168.49 ± 0.10 | 243.41 ± 1.07 |
| Lactose | 1.54 ± 0.0012 | 0 | 145.63 ± 0.43 | 166.56 ± 24.59 |
| | | 90 | 146.86 ± 0.11 | 175.79 ± 29.43 |
| CHPD | 2.48 ± 0.0016 | 0 | 192.9 ± 1.32 | 392.79 ± 9.29 |
| | | 90 | 194.54 ± 1.67 | 388.73 ± 21.55 |

speed, Aw, and EA (2-Level) were the factors. RDP, MDP, SR, EF, FCE, FCC, TO, EFT, WC, RTS, $ER_0$, and porosity were the responses. Least squares analysis was applied for the fitted model. The model was evaluated in terms of statistical significance using analysis of variance (ANOVA) at a level of significance $p < 0.05$.

## 3. Results and discussion

### 3.1. Apparent particle density and differential scanning calorimetry

Table 3 shows the values of apparent particle density for powders used and DSC parameters. The apparent particle density values for all powders were in the same range except for CHPD, which had the highest density. Regarding DSC, powders showed almost the same thermograms at 0 and 90% RH where peak temperature and Delta H did not significantly change. Also for compacts, the same result was found at low/high speeds and compression pressures (results not shown). These results indicated no phase change due to moisture. Mannitol, lactose, and CHPD powders showed relatively high Aw before, during and after compaction regarding to the powder storage at 0% RH. Previous study showed that these powders were the least sensitive to moisture (Sangekar et al., 1972).

### 3.2. Effect of Aw on residual die-wall pressure

By increasing compaction pressure and Aw, RDP was reduced for all powders, $p < 0.00001$, Table 4; except for pre-gelatinized starch where increasing compression pressure/speed at high Aw caused an increase in RDP, $p < 0.003$. Fig. 4 shows the effect of Aw on RDP for MCC where RDP was significantly reduced by increasing Aw. The reduction of RDP could be attributed to lubrication effect of water where adsorbed moisture reduces particle surface energy, hence adhesion to die-wall. Similar results were reported before (Rees and Shotton, 1971; Staniforth et al., 1988; Nokhodchi et al., 1995a; Ahlneck and Alderborn, 1989a). However for pre-gelatinized starch, the increase of RDP at high speed/compression pressure is related to the increase in radial relaxation for pre-gelatinized starch compacts at these conditions by increasing Aw due to reduced interparticulate friction and interaction.

### 3.3. Effect of Aw on maximum die-wall pressure

By increasing compaction pressure and Aw, MDP was increased for plastic powders: MCC, pre-gelatinized starch, and mannitol, $p < 0.007$; Table 5. Fig. 5 shows the increase of MDP for MCC by increasing Aw. Regarding brittle powders; MDP was reduced for lactose, $p < 0.05$, and no effect in case of CHPD. The increase of MDP was due to the increased plasticity of the powders by moisture. At high Aw, compression pressure caused an increase in MDP

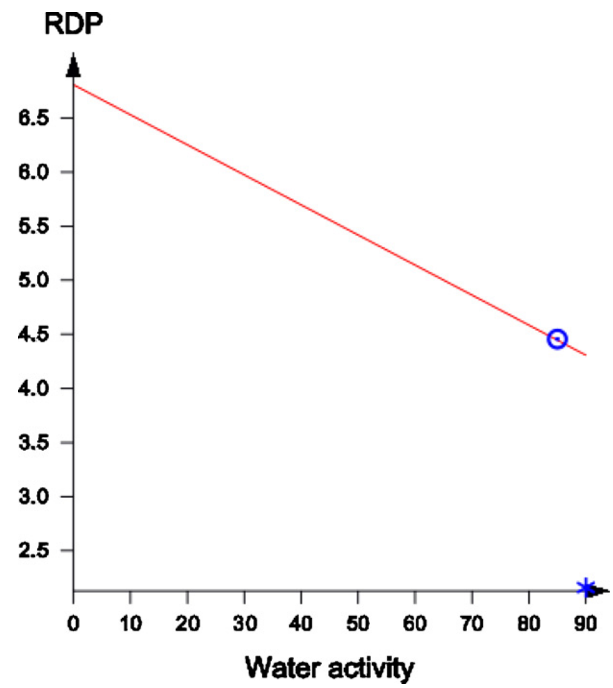


**Fig. 4.** Effect of water activity (%) on RDP (MPa) for MCC.

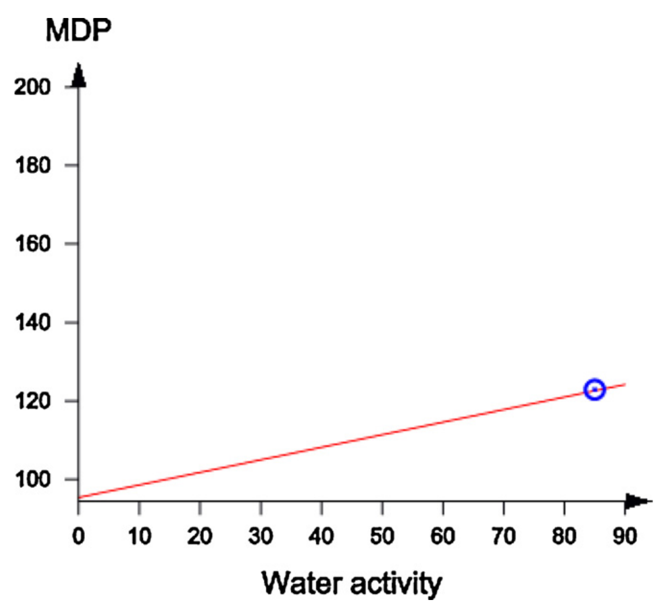


**Fig. 5.** Effect of water activity (%) on MDP (MPa) for MCC.

**Table 4**
Models suggested for RDP of different materials showing the investigated variables, compression pressure (C), speed (S), water activity (W), ejection angle (E) and their interactions.

| MCC | Pre-gelatinized starch | Mannitol | Lactose | CHPD |
|---|---|---|---|---|
| $R_c^2 = 0.9920$ | $R_c^2 = 0.9345$ | $R_c^2 = 0.9955$ | $R_c^2 = 0.9993$ | $R_c^2 = 0.9993$ |
| RDP = +4.238 | RDP = +2.506 | RDP = +1.624 | RDP = +1.510 | RDP = −0.1307 |
| +0.01709 C | +0.01069 C | +0.1272 C | +0.1015 C | +0.1033 C |
| −0.1600 S | −0.9317 S | −2.210 S | −0.7210 S | −0.5098 S |
| −0.02324 W | −0.04182 W | −0.01309 W | +7.222E−05 W | −0.005669 W |
| +0.03500 E | +9.111E−05 C.W | −0.0003599 C.W | −0.005013 C.S | −0.006487 C.S |
| −0.001000 C.S | +0.02070 S.W | +0.01531 S.W | −9.644E−05 C.W | −8.633E−05 C.W |
| −2.622E−05 C.W | | | | +0.004500 S.W |
| −0.02800 S.E | | | | |

$R_c^2$ is the corrected goodness of fit.

for MCC and pre-gelatinized starch, $p < 0.00001$, due to plasticity enhancement and a decrease in MDP for lactose, $p < 0.002$ due to the prevalence of its brittle nature and creation of new surfaces continuously that fail to adhere to the die-wall. On the other hand, increasing speed at high Aw led to the increase of MDP for pre-gelatinized starch which could be explained similar to the effect on RDP. Obiorah and Shotton (1976) reported that moisture caused a slight increase of MDP for paracetamol and phenacetin. Nokhodchi et al. (1995b) reported that moisture improves plastic deformation for ibuprofen compacts. It was found that water acts as a plasticizer that increases molecular mobility and increases compressibility of powders (Khan and Pilpel, 1987; Lemagnen and Larroute, 1988; Slade and Levine, 1993; Stubberud et al., 1996; Sebhatu et al., 1997; Van der Voort Maarschalk et al., 1997; Steendam et al., 2001; Zhang et al., 2003). Moisture was reported to facilitate powder compression by reduction of interparticulate friction (Coelho and Harnby, 1978; Ahlneck and Alderborn, 1989a). Moreover, moisture was also reported to increase the rearrangement and slippage of particles and reducing interparticulate interactions (Nokhodchi et al., 1996; Malamataris et al., 1994; Garr and Rubinstein, 1992). In our study, CHPD and mannitol are crystalline in nature, while pre-gelatinized starch, MCC and lactose have both crystalline and amorphous fractions (Gunsel and Lachman, 1963; Pilpel and Ingham, 1988; Ahlneck and Alderborn, 1989b; Van der Voort Maarschalk et al., 1997; Salameh and Taylor, 2006). Moisture increased the fluidity and molecular mobility of crystalline powders and changed hard, glassy, amorphous powders to a soft, rubbery state, so the net result was an improvement in compressibility and high radial relaxation in response to applied axial pressure.

### 3.4. Effect of Aw on stress ratio

By increasing compaction pressure and Aw, stress transmission through powder bed was increased for all powders (except CHPD, no effect), $p < 0.01$, which was attributed to the increase of plasticity for these powders as mentioned for MDP. Fig. 6 shows the effect of Aw on SR for pre-gelatinized starch where SR significantly increases by increasing Aw. Increasing compression pressure at high Aw increased SR for MCC, $p < 0.0001$, and reduced SR for lactose and pre-gelatinized starch, $p < 0.0003$, because of the increase of fragmentation for the first and limited MDP increase relative for the applied high axial pressure for the later. However at high Aw, speed increased SR for pre-gelatinized starch, $p < 0.0001$, due to enhancing the plastic component over the elastic component where elastic recovery was reduced, as would be mentioned later. Moisture content within powder was reported to improve axial pressure transmission through powder bed due to improvement of densification (Jaffe and Foss, 1959; Rees and Hersey, 1972) and due to hydrodynamic lubrication (Garr and Rubinstein, 1992).

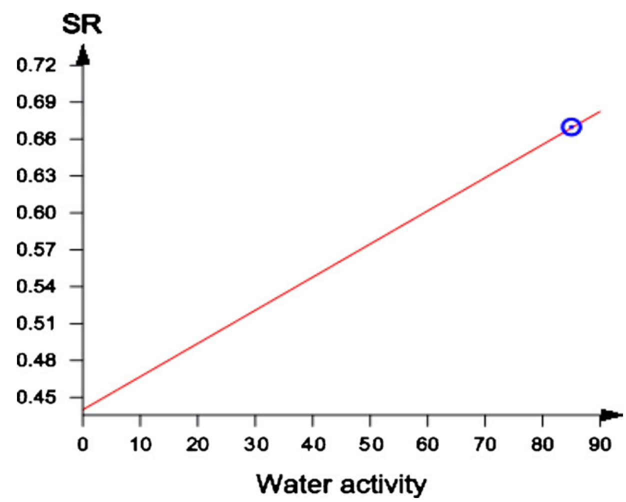


**Fig. 6.** Effect of water activity (%) on SR for pre-gelatinized starch.

**Table 5**
Models suggested for MDP of different materials showing the investigated variables, compression pressure (C), speed (S), water activity (W), ejection angle (E) and their interactions.

| MCC | Pre-gelatinized starch | Mannitol | Lactose | CHPD |
|---|---|---|---|---|
| $R_c^2 = 0.9999$ | $R_c^2 = 0.9992$ | $R_c^2 = 0.9998$ | $R_c^2 = 0.9996$ | $R_c^2 = 0.9983$ |
| MDP = | MDP = | MDP = | MDP = | MDP = |
| −4.375 | −5.849 | −6.316 | −5.388 | −3.199 |
| +0.6259 C | +0.6405 C | +0.6916 C | +0.6212 C | +0.5414 C |
| −3.537 S | −6.779 S | −5.545 S | −5.860 S | −5.174 S |
| −0.05876 W | −0.05649 W | +0.007078 W | +0.008540 W | −0.04548 W |
| −0.1013 E | −0.02116 C.S | 0.3446 E | −0.0003048 C.W | +0.02957 C.S |
| −0.02009 C.S | +0.002442 C.W | −0.02357 C.S | +0.01943 S.W | +0.0002599 C.W |
| +0.002168 C.W | +0.06774 S.W | +9.622E−05 C.W | | |
| | | +0.2757 S.E | | |

$R_c^2$ is the corrected goodness of fit.

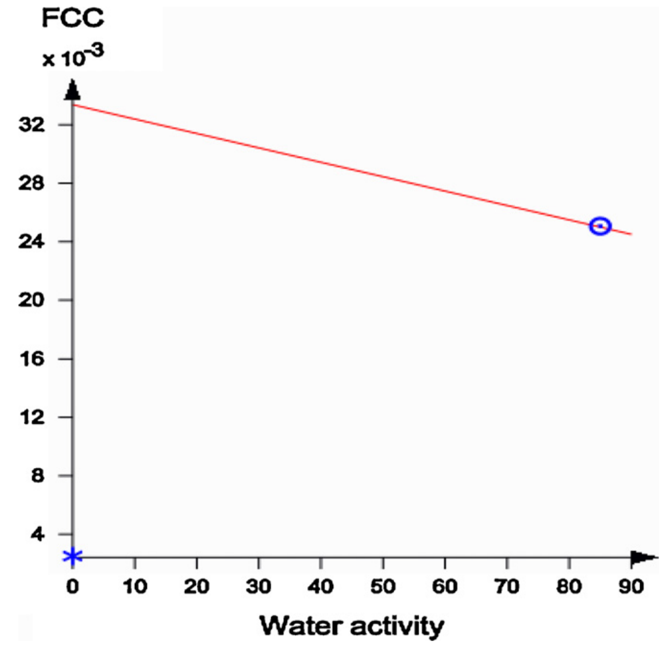


**Fig. 7.** Effect of water activity (%) on FCC for MCC.

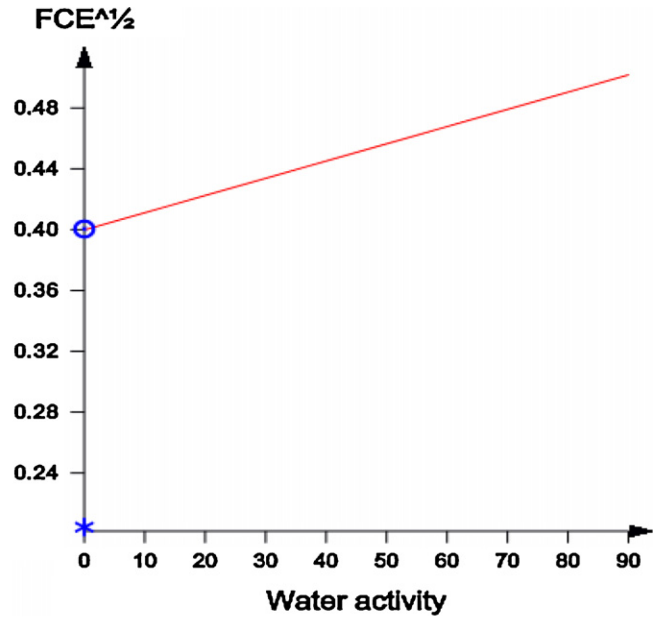


**Fig. 8.** Effect of water activity (%) on FCE for mannitol.

### 3.5. Effect of Aw on ejection force

By increasing compaction pressure and Aw, EF was reduced for MCC, lactose, and CHPD, $p < 0.0005$, due to lubrication effect as mentioned with RDP. No effect was found for pre-gelatinized starch, and mannitol. Increasing compression pressure at high Aw reduced EF for mannitol and CHPD due to the lubrication effect of moisture, $p < 0.003$. Nokhodchi et al. (1995a) reported that an increase in moisture resulted in reduction of EF for ibuprofen compacts. This was due to reduction of particle adhesion to die-wall by the water film on the particle surface.

### 3.6. Effect of Aw on friction coefficient during compaction (FCC) and friction coefficient during ejection (FCE)

By increasing compaction pressure and Aw, friction coefficient during compression FCC was reduced for MCC (Fig. 7) and pre-gelatinized starch, $p < 0.0001$, due to die-lubrication effect by moisture and reduction of particulate friction. However, in case of mannitol; FCC was increased. This could be due to the low sensitivity of mannitol to moisture (Yoshinari et al., 2003). No effect was found on lactose and CHPD due to their brittle nature. Regarding friction during ejection, by increasing compaction pressure and Aw; FCE was reduced for MCC, lactose, and CHPD, $p < 0.02$, Table 6; but increased in case of mannitol, $p < 0.008$, Fig. 8. This is explained similar to the effect of Aw on FCC. Similar results were reported by Shotton and Rees (1966).

### 3.7. Effect of Aw on takeoff force (TO) and effective fall time (sticking prediction tools)

By increasing compaction pressure and Aw, TO force was enhanced only for pre-gelatinized starch (Fig. 9), and CHPD, $p < 0.008$, leading to higher tendency of sticking while TO force was reduced for lactose, $p < 0.03$. Moisture could act as a triggering agent to activate the surface of particles for adhesion. On the other hand, lactose showed a reduced TO force by increasing moisture due to smoother surface in comparison to CHPD (Rowe et al., 2006). TO force has been previously used as a prediction tool for sticking, however not sensitive enough to differentiate between the powders quantitatively (Wang et al., 2004). Moisture was reported to be directly related to sticking (Otsuka, 1998; Shimada et al., 2003). Pre-gelatinized starch was reported to show inherent sticking tendency by increasing moisture (Waimer et al., 1999). In our study, we propose a new sticking prediction tool; EFT which is derived from the decompression time. A delay or an increase in EFT means upper punch sticking to the compact surface which requires more time for separation during decompression phase. We found that by increasing compression pressure at high Aw; all the powders showed an increase in EFT, $p < 0.01$, showing tendency for sticking at these extreme conditions. Fig. 10 shows the effect of increasing Aw and compression pressure on pre-gelatinized starch where EFT is significantly increased (contour lines increase from 9 to 11 ms or from blue to red zone). However by increasing Aw at low pressure, EFT was decreased for MCC, pre-gelatinized starch, and CHPD, $p < 0.002$, due to water lubrication effect, Table 7. Gen-

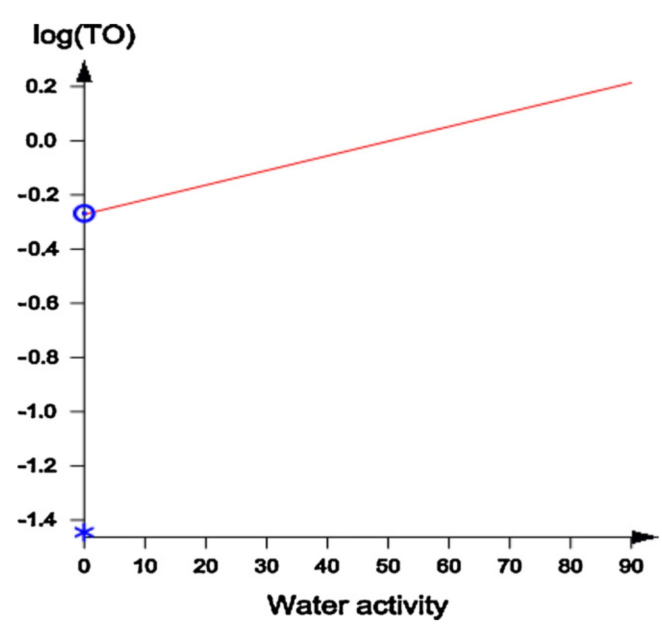


**Fig. 9.** Effect of water activity (%) on TO (N) for pre-gelatinized starch.

**Table 6**
Models suggested for FCE of different materials showing the investigated variables, compression pressure (C), speed (S), water activity (W), ejection angle (E) and their interactions.

| MCC | Pre-gelatinized starch | Mannitol | Lactose | CHPD |
|---|---|---|---|---|
| $R_c^2 = 0.9777$ | $R_c^2 = 0.9834$ | $R_c^2 = 0.8953$ | $R_c^2 = 0.9896$ | $R_c^2 = 0.9017$ |
| $FCE^{0.5}$ = +0.3665 | Log FCE = −4.449 | $FCE^{0.5}$ = −0.01505 | $FCE^{0.5}$ = + 0.2660 | $-FCE^{-2}$ = −211.0 |
| −0.0004691 C | +0.0002374 C | +0.001137 C | +0.0001084 C | +0.3262 C |
| +0.02018 S | +1.355 S | +0.2461 S | +0.09317 S | +54.13 S |
| −0.002483 W | +0.01515 W | +0.003165 W | −0.0006807 W | −0.5372 W |
| −0.0006197 E | +0.05859 E | +0.01333 E | +0.007598 E | +7.613 E |
| −0.0001056 C.S | −0.002470 C.S | −0.0007125 C.S | −0.0002198 C.S | −0.1313 C.S |
| +0.0005806 S.W | −4.350E−05 C.W | −1.161E−05 C.W | +2.621E−06 C.W | −0.01622 C.E |
| +0.009095 S.E | −0.006034 S.W | −3.949E−05 C.E | −1.216E−05 C.E | +0.2531 S.W |
| +8.088E−05 W.E | +0.03466 S.E | | +0.001998 S.E | |

$R_c^2$ is the corrected goodness of fit.

**Table 7**
Models suggested for EFT of different materials showing the investigated variables, compression pressure (C), speed (S), water activity (W), ejection angle (E) and their interactions.

| MCC | Pre-gelatinized starch | Mannitol | Lactose | CHPD |
|---|---|---|---|---|
| $R_c^2 = 0.9971$ | $R_c^2 = 0.9952$ | $R_c^2 = 0.9994$ | $R_c^2 = 0.9999$ | $R_c^2 = 0.9994$ |
| EFT = +17.48 | EFT = +18.38 | EFT = +16.17 | Log EFT = +2.700 | $-EFT^{-1}$ = −0.03703 |
| +0.01006 C | +0.009367 C | +0.01250 C | +0.001534 C | +6.015E−05 C |
| −5.938 S | −6.533 S | −5.607 S | −0.6524 S | −0.08860 S |
| −0.01366 W | −0.03457 W | −0.001494 W | +0.0001612 W | −0.0001131 W |
| −0.005073 C.S | −0.004733 C.S | +0.01513 E | −0.001822 E | +1.902E−05 C.S |
| +4.033E−05 C.W | +6.333E−05 C.W | −0.005567 C.S | −0.0002159 C.S | +3.904E−07 C.W |
| | +0.009704 S.W | +2.100E−05 C.W | −0.0001290 W.W | |
| | | −0.0003361 W.E | +0.0006587 S.E | |

$R_c^2$ is the corrected goodness of fit.

erally, speed decreases decompression time, however, interaction of speed and Aw increased EFT for pregelatinized starch, $p < 0.007$ showing sticking tendency for this excipient and decreased EFT for lactose, $p < 0.01$, due to its weak sensitivity for moisture and smooth surface as mentioned before.

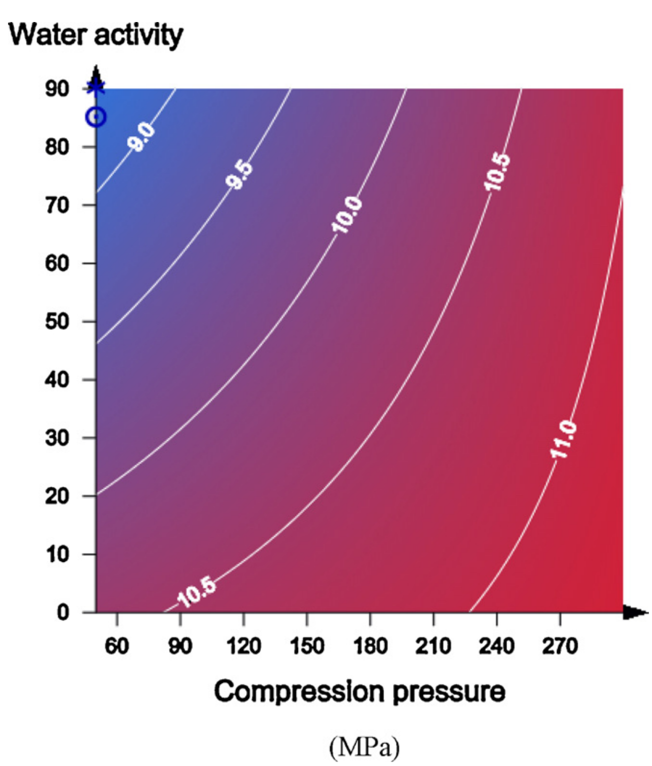


**Fig. 10.** Effect of water activity (%) on EFT (ms) for pre-gelatinized starch.

### 3.8. Effect of Aw on elastic recovery ($ER_0$) and radial tensile strength (RTS)

By increasing Aw, elastic recovery was reduced in case of MCC and pre-gelatinized starch, $p < 0.001$, Fig. 11. The presence of moisture led to the formation of strong hydrogen bonds for plastic materials and reduced $ER_0$. This was in accordance with the results of Khan et al. (1981) and Garr and Rubinstein (1992). Nokhodchi et al. (1995a) reported that moisture reduced elas-

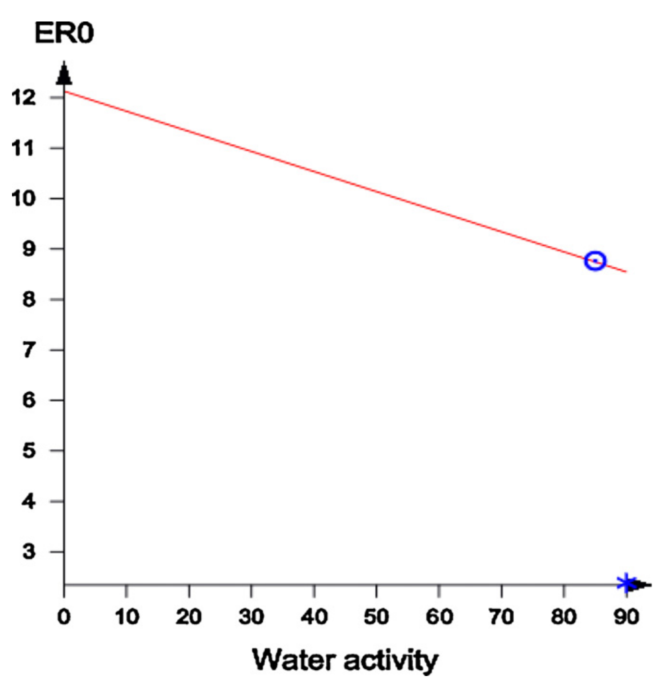


**Fig. 11.** Effect of water activity (%) on $ER_0$ (%) for pre-gelatinized starch.

**Table 8**
Models suggested for WC of different materials showing the investigated variables, compression pressure (C), speed (S), water activity (W), ejection angle (E) and their interactions.

| MCC | Pre-gelatinized starch | Mannitol | Lactose | CHPD |
|---|---|---|---|---|
| $R_c^2 = 0.9995$ | $R_c^2 = 0.9997$ | $R_c^2 = 0.9987$ | $R_c^2 = 0.9993$ | $R_c^2 = 0.9995$ |
| Log WC = +0.8383 | Log WC = −0.5093 | Log WC = +0.1007 | Log WC = +0.09358 | Log WC = −0.6882 |
| +0.005123 C | +0.008918 C | +0.006538 C | +0.005842 C | +0.006673 C |
| +0.02135 S | −0.03285 S | +0.02108 S | −0.07683 S | +0.03636 S |
| −0.005224 W | +0.003392 W | −0.003238 W | −0.004082 W | −0.001105 W |
| +0.0002347 C.S | −0.001987 E | −0.005200 E | +0.003252 E | +0.000437 C.S |
| −3.925E−06 C.W | +0.0003420 C.S | +0.0002148 C.S | +0.0007068 C.S | +2.712E−06 C.W |
| | −3.322E−05 C.W | +6.943E−06 C.W | +6.507E−06 C.W | |
| | +1.135E−05 C.E | +0.004160 S.E | −1.858E−05 C.E | |
| | +0.0006000 S.W | | | |

$R_c^2$ is the corrected goodness of fit.

tic energy for ibuprofen compacts by increasing Van der Waal's forces and reducing separation between particles. On the other hand, elastic recovery was increased for lactose by increasing Aw, $p < 0.0001$, due to water multilayer formation on particle surface leading to an increase of the distance between particles and to a reduction of particles attraction or bonding. This was further confirmed by the reduced RTS for lactose compacts, $p < 0.0001$, Fig. 12. Lerk et al. (1983) reported that removal of water of crystallization from α-lactose monohydrate resulted in higher tablet strength. Shukla and Price (1991b) reported a reduced RTS on increasing water content for lactose. Moisture was reported to reduce bonding between paracetamol particles (Khan et al., 1981; Li and Peck, 1990; Malamataris et al., 1991). By increasing compression pressure/speed at high Aw, $ER_0$ was increased for MCC. At these conditions, MCC compacts showed capping and lamination. Increasing speed caused shorter dwell time available for particle bonding, hence higher elastic recovery. These results are in accordance with those reported by McKenna and McCafferty (1982), Garr and Rubinstein (1992), Nokhodchi et al. (1995a). In our study pre-gelatinized starch failed to form compacts at low Aw and low pressure which indicated the importance of moisture up to certain limits for successful compaction. This is in accordance with Zografi and Kontny (1986), who reported that poor starch compacts were formed because of low moisture.

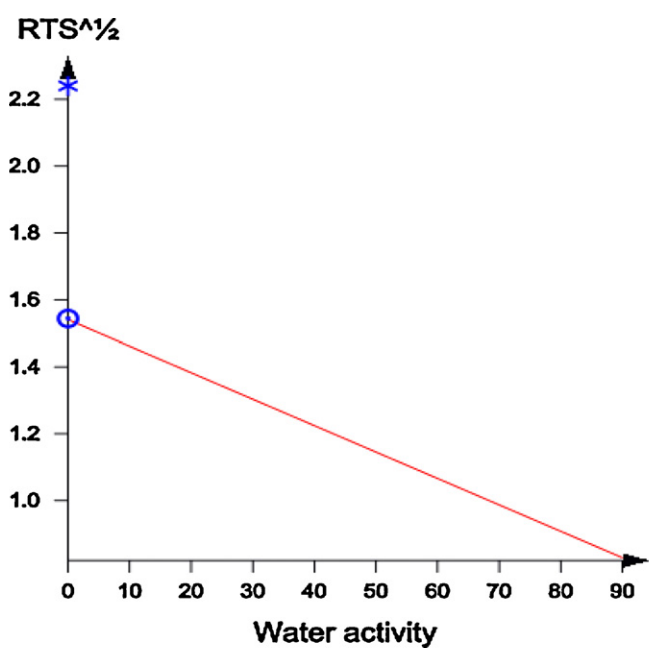


**Fig. 12.** Effect of water activity (%) on RTS (MPa) for lactose.

### 3.9. Effect of Aw on work of compaction (WC)

By increasing Aw, WC was reduced for all powders, $p < 0.0001$, Table 8; due to plasticizing effect of water by reduction of interparticulate friction and ease of particles slippage and arrangement, hence facilitated compressibility. Moisture content was reported to decrease plastic energy of compaction (Esezobo and Pilpel, 1976; Nokhodchi et al., 1995a, 1996; Shukla and Price, 1991a; Van der Voort Maarschalk et al., 1997).

### 3.10. Effect of Aw on porosity

By increasing Aw, porosity of the compacts was reduced for mannitol, lactose, and CHPD, $p < 0.005$, and no effect was found for other powders. This could be explained by the condensation of water in the capillary region of powder bed at the area of contact between particles increasing the cohesion by liquid bridges. Such phenomenon was explained previously by Hiestand (1966). Armstrong et al. (1988), reported reduction in porosity by increasing moisture for CHPD tablets. Garr and Rubinstein (1992) reported that moisture increases the relative density of powder bed under compaction and Ahlneck and Alderborn (1989a) reported that high moisture reduced porosity. However at high compression pressures, porosity was increased for mannitol and lactose, $p < 0.0003$, due to pressure effect where water is squeezed off the pores creating a porous structure. On the other hand, porosity was reduced for CHPD by increasing compression pressure at high Aw, $p < 0.007$, due to its brittle nature and creation of new particles occupying the pores.

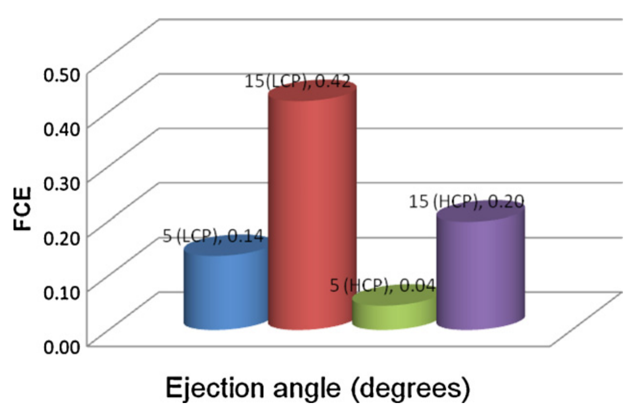


**Fig. 13.** Effect of ejection angle change on FCE for MCC at high speed and water activity (LCP = Low compression pressure; HCP = High compression pressure) (RSE = 0.01).

### 3.11. Effect of Aw on ejection angle

Not ever studied before, increasing the angle of ejection cam, enhanced the values of EF and FCE, $p < 0.0001$, for all the powders (except mannitol, no effect). Thus, it is advised to adjust the EA to a minimum during compaction. Fig. 13 shows the effect of changing EA from 5 to 15 degrees on FCE for MCC powder at high speed/Aw and both low and high compression pressures where friction was increased.

## 4. Conclusion

Aw or free moisture could give an estimate of the bound water in powder.

Moisture could change the deformation behavior of particles. Radial die-wall monitoring was a useful tool to investigate particle/moisture interaction regarding cohesion and adhesion. Low RDP values induced by moisture showed low tendency for the particles to adhere to die-wall due to lubrication which was further confirmed by reduced other related compaction parameters like EF and friction coefficients. High MDP values induced by moisture plasticizing effects showed the ease of compressibility and good axial pressure transmission through powder bed. Moisture reduced elastic recovery due to decreased interparticulate interaction, reduced porosity due to filling of pores by water, and reduced tensile strength due to weakening of bonding. Moisture increased TO force due to activation of particle surface for bonding and reduced EFT due to lubrication effect. As a new reliable tool to detect sticking, EFT showed an increased value (delay in decompression) at high moisture and compression pressure. Regarding ejection, it is advised to keep the angle of ejection to a minimum during compaction in order to avoid the increase of EF and friction which could shorten the tablet machine and tooling life span.

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