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ORIGINAL RESEARCH ARTICLE

Assessing the Impact of Punch Geometries on Tablet Capping Using a Newly Proposed Capping Index

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Abstract

Purpose Increased tablet anisotropy could lead to increased tablet capping propensity. Tooling design variables such as cup depth could serve as a key player for inducing tablet anisotropy.

Methods A new capping index (CI) consisting of the ratio of compact anisotropic index (CAI) and material anisotropic index (MAI) is proposed to evaluate tablet capping propensity as a function of punch cup depth. CAI is the ratio of axial to radial breaking force. MAI is the ratio of axial to radial Young's modulus. The impact of various punch cup depths [flat face, flat face beveled edge, flat face radius edge, standard concave, shallow concave, compound concave, deep concave, and extra deep concave] on the capping propensity of model acetaminophen tablets was studied. Tablets were manufactured at 50, 100, 200, 250, and 300 MPa compression pressure at 20 RPM on different cup depth tools using Natoli NP-RD30 tablet press. A partial least squares model (PLS) was computed to model the impact of the cup depth and compression parameters on the CI.

Results The PLS model exhibited a positive correlation of increased cup depth to the capping index. The finite elemental analysis confirmed that a high capping tendency with increased cup depth is a direct result of non-uniform stress distribution across powder bed.

Conclusions Certainly, a proposed new capping index with multivariate statistical analysis gives guidance in selecting tool design and compression parameters for robust tablets.

Keywords capping index · compact anisotropic index · material anisotropic index · tablet capping · USP <1062>

Introduction

A pharmaceutical compact is manufactured with an axial compression of a radially confined powder blend or granules in a rigid die. Material properties and process parameters are two main components of tablet manufacturing which dictate the unique features of successful or failed compacts [1]. Most pharmaceutical materials used in tableting are anisotropic in nature. Anisotropic materials exhibit different properties in different dimensional planes, as opposed to isotropic materials, which exhibit the same properties in all planes. Pharmaceutical blends have different particle-morphology, −sizes, and preferred deformation and/or fragmentation mechanisms during the consolidation process under the applied compression load [2]. Anisotropic material deformation is also synergized with an adopted tooling geometry for manufacturing tablets. Punch cups that deviate from flat face geometry can cause significant non-uniform distribution of compression pressure on the confined powder bed [3]. As a result of material intrinsic properties and tooling, particles undergo preferred orientation and deformation/fragmentation mechanism in different planes. This induces anisotropy with respect to internal particle bonding and associated mechanical attributes. Furthermore, the resulting compacts display anisotropic recovery due to different magnitude of elastic recovery in the axial and radial direction during the decompression process.

A pharmaceutical material and tablet anisotropy creates a 'heterogeneous internal tablet structure' [4]. This structural heterogeneity is acceptable if the tablet is easy to handle during the manufacturing process and remains efficacious as a drug delivery device. A high amount of mechanical anisotropy

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of compacts can lead to tablet manufacturing problems like capping and lamination [4]. It can also impact tablets' disintegration and dissolution profiles. Altered disintegration and dissolution profiles lead to an undesired release rate of medication in the gastrointestinal tract with a potential impact on the therapeutic response [5]. Thus, reduction in the mechanical anisotropy of compacts could be a key for successful tableting.

As described earlier, 'compact mechanical anisotropy' is a function of material and compact anisotropy. It could be quantified by measuring Young' s modulus and compact strength in both the axial and radial directions. The Young's modulus in parallel (axial) and perpendicular (radial) direction of the compaction gives 'material anisotropy' [4]. The force required for breaking or fracture of compacts in the axial and radial direction gives magnitude of 'compact mechanical anisotropy'. Thus, authors are proposing a new method of computing Capping Index (CI) for identifying the capping behavior of tablets using 'compact mechanical anisotropy'. Tablet capping is a complete removal of the cup portion of a tablet during handling, physical testing, or ejection [6]. The ratio of axial breaking force and radial breaking force of a compact is called 'compact anisotropy index' (Eq. 1). The ratio of axial and radial Young's moduli is called 'material anisotropy index' (Eq. 2). Finally, capping index is calculated as a ratio of compact anisotropy index to material anisotropy index (Eq. 3). This is a unitless number which can be used as an indicator of capping tendency of pharmaceutical formulation.

$$Compact\ Anisotropy\ Index\ (CAI) = \frac{Axial\ Breaking\ Force}{Radial\ Breaking\ Force} \tag{1}$$

$$Material\ Anisotropy\ Index\ (MAI) = \frac{Axial\ Young\ Modulus}{Radial\ Young\ Modulus} \tag{2}$$

$$Capping\ index = \frac{CAI}{MAI} \tag{3}$$

A proposed comprehensive approach could serve as a predictive quantifiable indicator of capping propensity rather than the traditional way of visual observation of capping.

Tablet tooling dimensions such as punch cup geometry play a vital role in the incorporation of anisotropic characteristics to compact and subsequent tablet integrity. Tablet cup shapes vary from a flat face to hemispherical. Deviation of a compact from isotropic properties could lead to potential tableting problems like capping and lamination [7]. The FF punches distributing uniform compression pressure on the powder bed during the powder compression event could impart better material deformation, improve inter-particulate bonding, and reduce compact anisotropy. This could translate into a quasi-equal or equal mechanical strength throughout the tablet structure. A cylindrical geometry conferred by FF punches provide significant challenges during packaging and their consumption by patient due to the sharp edges. These limitations are addressed by modifying punches with a certain cup shape. Convex tablets are more prone to tablet manufacturing problems like capping and lamination than flat face tablets. However, convex shaped tablets are typically preferred by patients due to ease of swallowing throughout the gastrointestinal track [8]. A sharp-edged flat tablet also poses additional manufacturing challenges during coating, packaging, and transportation [9]. Thus, it is imperative to have a certain degree of convexity in the tablet shape regardless of the induced heterogenous tablet structure.

A punch cup endows a desired convex shape to a manufactured compact. An adoption of concave punches causes a deviation from the cylindrical tablet geometry. Punches with a non-flat cup shape distribute uneven compression pressure, which significantly impacts the tablet mechanics [10]. The initial contact of concave cup punches with the flat surface of the powder bed is established around the outer periphery. It causes local densification of this area. The densification of the tablet center occurs only after the full contact of the top punch with the top surface of the powder. This event occurs at the end of compaction. Moreover, punch travel is inadequate for a sufficient increment in the local density. Uneven compression pressure distribution impairs the material deformation under the applied compression load (Fig. S1). It induces a differential compaction with inhomogeneous density distribution across the tablet microstructure [10]. These tablets might have the same average densities, but they could have dramatically different internal porosity distribution across the tablet body. The overall impact of these events translates into enhanced compact anisotropy leading to weaker or defective tablets. One of the prominent tablet defects associated with punch cup depth is tablet capping [11]. Thus, cup design induced tablet mechanics analysis is important to select and optimize desired tool design. Clearly, punches with different degree of concavity could serve as a suitable parameter to test our proposed capping index parameter.

The aim of the study was to understand the effect of punches with different cup depths (Fig. 1) on tablet capping using a newly proposed capping index parameter. A model acetaminophen (APAP) formulation was selected for study by compressing the formulation blend at a different compression pressure to keep material properties as a constant variable to evaluate utility of new capping index. Additionally, the impact of punch cup depth on the USP <1062> profile (Fig. S2) of model APAP formulation was tested. Compressibility, tabletability, compactibility, and manufacturability are four components of USP<1062> tablet compression characterization [12]. A bench-top compaction tester was used to measure the anisotropic properties of materials and compacts for computing the capping index. A qualitative and quantitative multivariate statistical model was developed to understand the main effects

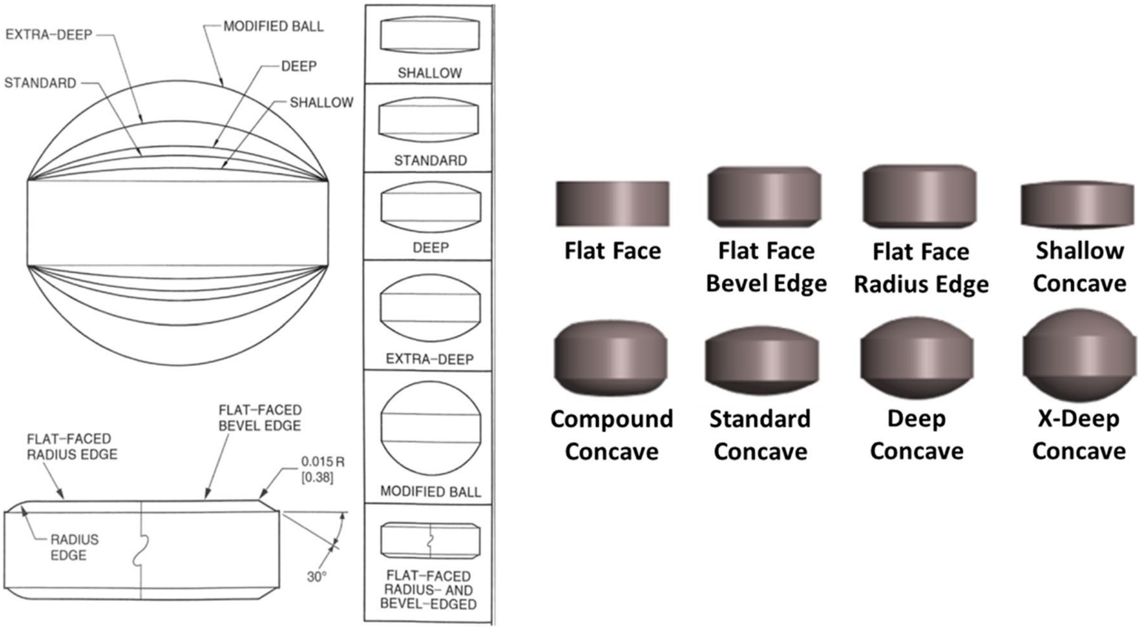

Fig. 1 Tablets with various cup depth.

of punch cup type and process parameters on mechanical anisotropy and capping propensity of tablets. A predictive PLS model was developed to predict the capping index of tablets with regard to different tool geometry.

Materials

Acetaminophen (APAP) was used as a model drug in this study. APAP powder (Lot# 2CH0035) was purchased from Spectrum Chemical Mfg. Corp., New Brunswick, NJ. Microcrystalline Cellulose (MCC) (Vivapur® 102, Lot# V102C20K16) was gifted from JRS Pharma LP, Patterson, NY. Copovidone (Kollidon® VA 64 Fine, Lot# 08335556P0) was procured from BASF Corporation, Florham Park, NJ. A hydrophilic fumed silica (Aerosil® 200, Lot# 308110200) was received from Evonik Corporation USA, Parsippany, NJ. Magnesium Stearate (MgSt) [Parteck® LUB MST, Lot# K50105163822] was received from EMD Millipore Corporation, Billerica, MA. All materials were used as received. All compression tooling was designed and provided by Natoli Engineering Company Inc., Saint Charles, MO.

Methods

Particle Size Measurement

Particle size distributions of individual materials were analyzed using a laser diffraction particle size analyzer (Mastersizer 3000, Malvern Instruments Ltd., Westborough, MA). Approximately 0.5 g of material was used for each analysis. All measurements were done in triplicate. Data is reported in Table I.

Preparation of Formulation

The composition of APAP model formulation is listed in Table II. APAP, MCC, and copovidone were sieved (mesh size #30) individually. These materials were added into V-blender (Globe Pharma Inc., New Brunswick, NJ) in the same order and blended for 10 min at 15 rpm. This blend was mixed with hydrophilic fumed silica (mesh size # 60) for 10 mins at 15 rpm. The entire blend was lubricated with MgSt (mesh size # 60) for 3 mins at 15 rpm in a V-blender. The final blend was discharged into a polyethylene bag for further study.

Pycnometric Density Measurement

The pycnometric density of the model formulation was determined using a helium displacement pycnometer (AccuPyc™ II 1340, Micromeritics GmbH, Neuss, Germany). The

Table I Particle Size Distribution

Material	D_{10} (µm)	D_{50} (µm)	D_{90} (µm)
APAP	7.04 ± 0.28	43.1 ± 1.49	236 ± 16.7
MCC	51.6 ± 0.71	152 ± 2.12	293 ± 2.17
Copovidone	9.70 ± 0.21	30.1 ± 0.57	67.6 ± 1.71
Silica	7.55 ± 0.24	17.43 ± 0.32	37.40 ± 1.31
MgSt	2.31 ± 0.02	6.51 ± 0.07	23.7 ± 0.79

Table II Formulation Composition

Material	%w/w
Acetaminophen	50.0
Microcrystalline Cellulose	43.0
Copovidone	5.0
Silica	1.0
Magnesium Stearate	1.0

sample holder was filled up to 3/4th volume with the powder. The net weight of the filled powder was determined using an analytical balance (Model EBL 164e, Adam Equipment, Oxford, CT). The powder was purged with five repetitive cycles. A mean of these measurements was taken as the pycnometric density. The pycnometric density measurement was done in triplicate.

Impact of Punch Cup Dimensions on the USP <1062> Profile

The impact of various punch cup dimensions on the USP <1062> profiles (tabletability, compressibility, compactibility, and manufacturability) were generated for the APAP model formulation using punches with various cup dimensions listed in Table III. All tablets were manufactured using Natoli NP-RD30 4 station B/D rotary tablet press. A force feeder was used to ensure proper die filling of the powder. Each tool was 10.0 mm in diameter. The APAP model formulation was compressed using 100, 150, 200, 250, and 300 MPa compression pressure at 20 rpm turret speed. Approximately 100 tablets were manufactured at each compression pressure for further studies. Tablet weight was measured immediately after tablet production (Model EBL 164e, Adam Equipment, Oxford, CT). Tablet thickness and diameter were measured 24 h after production using digital vernier caliper to provide sufficient time for possible viscoelastic recovery associated with APAP tablet (Model: CD-6” ASX, Mitutoyo Corporation, Kanagawa, Japan). Tablet breaking force was measured with a breaking force tester (Model: PTB 511E, Pharma Test, Hainburg, Germany). Tablet mechanical strength (TMS) (MPa) was calculated using Eq. 4 [13].

Table III Various Punch Cup Dimensions

Tool	Cup Depth (mm)	Cup Volume (mm^3)*	Cup Area (mm^2)*
Flat Face (FF)	0.00	0.00	0.00
Flat Faced Bevel Edge (FFBE)	0.38	26.12	81.41
Flat Faced Radial Edge (FFRE)	0.38	24.95	80.83
Shallow Concave (SHCC)	0.41	16.14	79.07
Compound Concave (CCC)	0.89	43.79	83.09
Standard Concave (SCC)	0.94	37.35	81.32
Deep Concave (DCC)	1.30	50.18	83.85
X-Deep Concave (XDCC)	1.91	72.54	89.94

*Based on 10 mm Diameter punch

$$TMS = \frac{2F}{\pi Dt} \tag{4}$$

Where, F is the breaking force (N), D is the diameter (mm), and t is the thickness (mm). Equation 4 is true for flat face (FF) tablets only. Pitt and Newton (1988) have established the empirical relationship for computing TMS from a breaking force of convex tablets (Eq. 5) [14]. This equation was used for determining TMS of convex tablets.

$$TMS = \frac{10F}{\pi D^2}\left(2.84\frac{t}{D} - 0.126\frac{t}{W} + 3.15\frac{W}{D} + 0.01\right)^{-1} \tag{5}$$

Where, F is the breaking force (N), D is the diameter (mm), t is the thickness (mm), and W is the thickness (mm) of the band.

Solid fraction (SF) of the tablet was determined using Eq. 6 [15].

$$Solid\ Fraction = \frac{Apparent\ Density}{Particle\ Density} \tag{6}$$

Where, *Apparent Density* is tablet out-of-die density and *Particle Density* is a pycnometric density.

Capping Index (CI)

These measurements were determined by breaking tablets in axial and radial directions as shown in Fig. 2. Gamlen Bench Top Compaction Tester (Model: D1000, Gamlen Instruments, Beckenham, United Kingdom) was used to break these tablets. Tablets were broken at the speed of 0.33 m/s. Axial and radial breaking force were determined from the force-displacement data collected from the Gamlen Bench Top Compaction Tester. The first drop in the force was considered as the breaking force of the tablet. The force-displacement plot was converted to stress-strain plot to determine the axial and radial Young’s modulus [16]. The slope of stress vs strain plot was calculated and used as the Youngs modulus. Each measurement was done in triplicate and mean was calculated. Capping index (CI) was determined using Eq. 3.

A high capping index value indicates a greater propensity for capping of the compact at the applied compression conditions, while a low capping index indicates a lower propensity for capping of the compact at the same compression conditions.

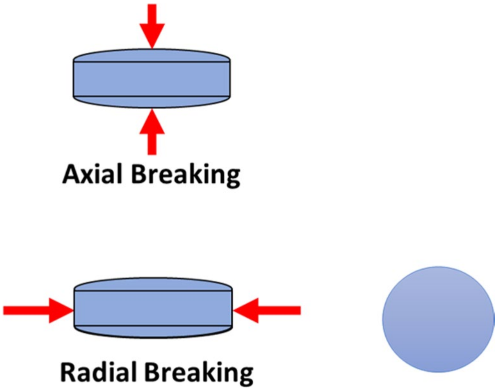

Fig. 2 Schematic of axial and radial tablet breaking test.

Finite Element Analysis (FEA) of Tablet Punches

Force distribution on different cup geometry was identified by FE analysis. The FE analysis was performed using SolidWorks simulation software (Waltham, MA, USA). S7 steel material was modeled for punch simulation with a yield strength of 1896 MPA (275 ksi). A 15.7 kN force was applied equivalent to 200 MPa for 10 mm diameter round tablet punches. Von Mises yield criterion model was used to generate stress plot.

Multivariate Statistical Analysis

A qualitative principal component analysis (PCA) was performed (Unscrambler® 10.4.1, Trondheim, Norway) to understand correlations between various X-variables such as axial YM, radial YM, axial BF, radial BF, material anisotropy index, compact anisotropy index, and capping index. These correlations were observed with PCA loadings plots. Additionally, PCA was used to decode grouping of various punch geometries with regard to these X-variables. The groupings were decoded with PCA scores plot. A total of three PCs were used to explain 98% variance in the data. The first two PCs explained 79% variance in the data (Fig. 4). The details of PCA method and result interpretations could be found in our previous publications [17, 18].

The data set was divided into calibration and validation set for a quantitative analysis with partial least square calibration model (PLS). The calibration and validation data set were composed of 32 and 8 data points, respectively. A quantitative PLS was computed (Unscrambler® 10.4.1, Trondheim, Norway) to understand the effect of punch cup depths and compression conditions on capping index (CI) using calibration data set. The X-variables used in the statistical analysis were punch cups, cup depths, cup volume, compression pressure, ejection force and solid fraction. The response variable was capping index (CI). The independent and dependent variables were weighted with their standard deviation (1/SD) to normalize the data. This was done to avoid the influence of their design range and response values on the developed models. A full cross validation coupled with Jack-Knifing method was used to quantify statistical significance of regression models [19]. The impact of category matrix that is CPE types was separated by coding them as “split-category” variables. These variables were coded as 0 and 1 during the analysis. The statistical significance of the model was measured at $\alpha < 0.05$. A predictive performance of PLS model was tested with an independent validation data set (Fig. S4).

Results and Discussion

USP <1062> Tablet Compression Characterization

The USP<1062> tablet compression characterization profile of model APAP tablets manufactured with different tooling geometry is shown in Fig. 3.

A powder having maximum solid fractions at lowest or given compression pressure is known to have a better compressibility profile. The compressibility profile (Fig. 3A) APAP tablets with a different punch geometry did not exhibit a plateau in the studied compression pressure range. It precludes the possibility of powder over compression. APAP tablets made with all punch designs showed an increase in the solid fraction correlating to an increase in the compression pressure. Tablets having a cylindrical geometry (FF punch) achieved the highest solid fraction as compared to the other studied punch geometries. These tablets achieved the maximum solid fraction of 0.90 at the 300 MPa compression pressure as compared to other punch geometries. As mentioned earlier, a maximum solid fraction with a cylindrical geometry could be attributed to the uniform density distribution within the tablet microstructure due to improved material deformation and or fragmentation. It would be interesting to see the effect of a wider range of compression pressure on solid fraction and strength of tablets. Cylindrical tablets manufactured with FF punch could pose better resistance against tablet capping [20]. The difference in the solid fractions of APAP tablets manufactured with FFBE, FFRE, SCC, SHCC, and CCC punch was statistically insignificant. The lowest solid fraction was achieved by APAP tablets produced with XDCC and DCC punch (Table S1). This could be attributed to non-uniform translation of compression pressure on the powder bed with an increment in the punch cup volume [Fig. S1(B)], which could provide maximum density gradients across the tablet microstructure as compared to the other punch designs.

The compactibility profile [Fig. 3B] [10] portrays a how a given solid fraction translates into tablet mechanical integrity. Figure 3B indicates that the solid fractions achieved by

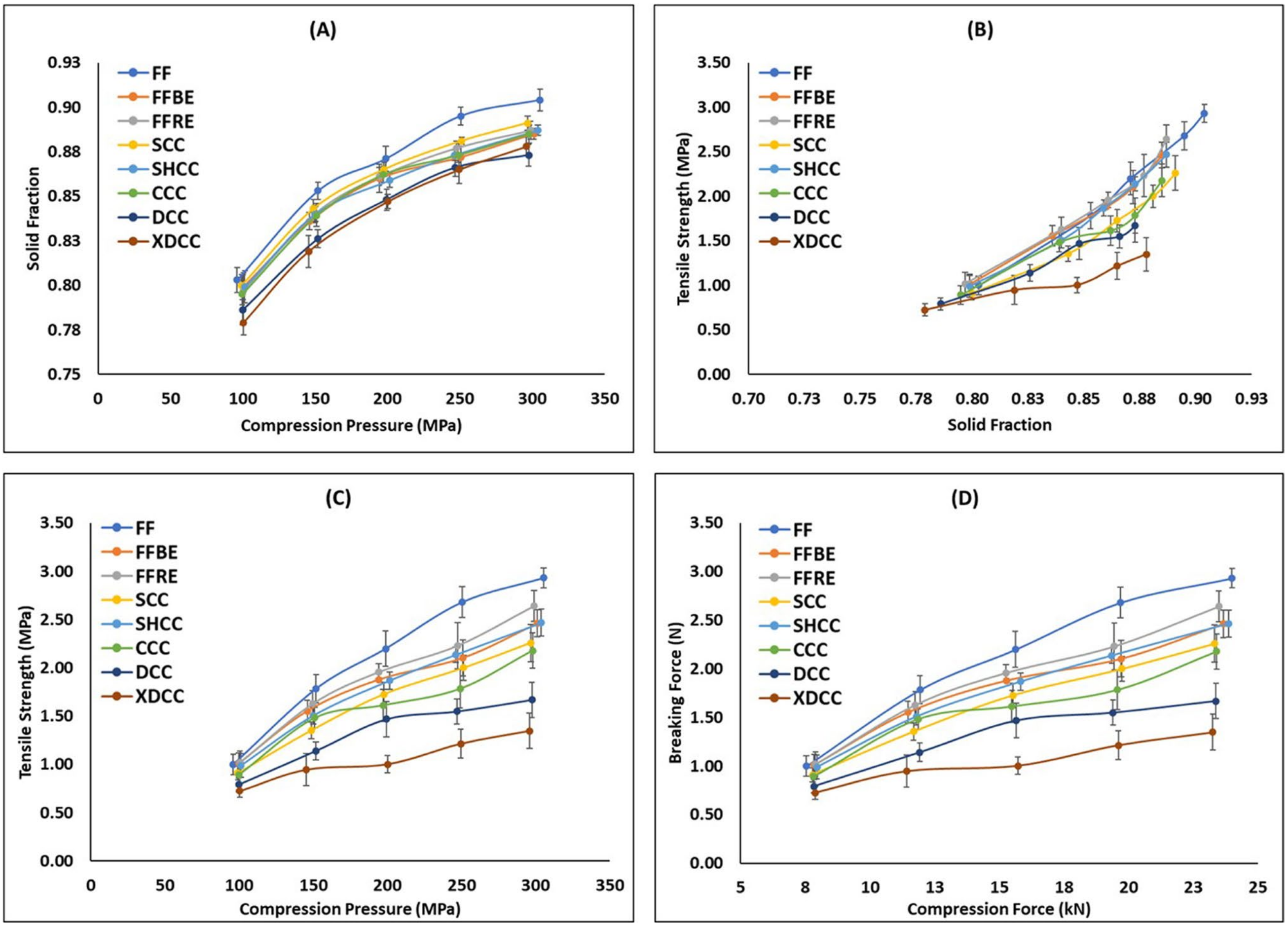

Fig. 3 USP <1062> Tablet Characterization Profile (**A**) Compressibility, (**B**) Compactibility, (**C**) Tabletability, and (**D**) Manufacturability [N = 3]. [flat face (FF), flat face bevel edge (FFBE), flat face radial edge (FFRE), standard concave (SCC), shallow concave (SHCC), compound concave (CCC), deep concave (DCC), and x-deep concave (XDCC)]

XDCC punches have the least mechanical integrity of all punch geometries. This punch geometry achieved the least solid fraction as compared to others without losing mechanical integrity. As cup depth was reduced, the solid fraction of the resulting tablets increased accordingly. Flat punches exhibited the highest mechanical integrity for a given solid fraction due to reduced compact anisotropy. It confirms a hindered translation of uniform compression pressure on the powder bed with increased deviation from cylindrical geometry [Fig. S1(B)] by increasing the cup volume of the punch design [10].

Compressibility and compactibility of a formulation translate into its tabletability. As expected, cylindrically designed APAP tablets exhibited a better tabletability (Fig. 3C) and subsequent manufacturability (Fig. 3D). The highest deviation from a cylindrical design (XDCC) produced the weakest tablets for a given solid fraction. All other punch types showed an increase in tablet strength with an increase in compression pressure. Clearly, the same formulation could produce weaker or stronger tablets based on how far the tooling design deviates from cylindrical geometry. These findings further corroborate the importance of uniform translation of the compression stress on the powder bed during tableting to avoid or reduce density gradients across the tablet microstructure. Such induced low-density areas within the tablet structure create weaker zones responsible for various tooling-associated tableting problems [11]. Tablets produced with DCC and XDCC punches at compression pressures 200, 250, and 300 MPa showed 100% capping during the tablet breaking force test. The following descending rank order for compaction of the APAP model formulation was observed with regard to studied punch designs:

FF > FFRE > FFBE > SHCC > CCC > SCC > DCC > XDCC

Capping Index (CI)

A tablet's Young's modulus and breaking force in both axial and radial directions are main comprehensive meso-descriptors of the compact indicating, respectively, directional

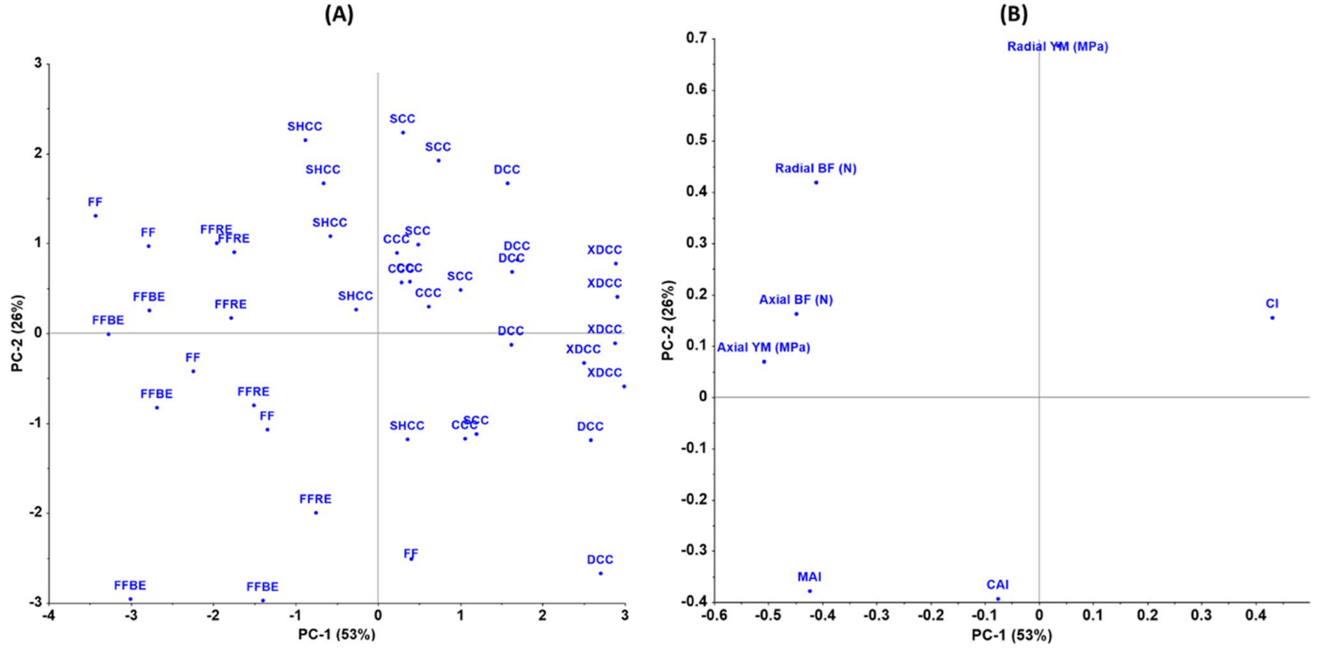

Fig. 4 The principal component analysis (**A**) scores plot and (**B**) loadings plot of different punch cup depths tooling. The first two components explain 79% of the variance in the data. [flat face (FF), flat face bevel edge (FFBE), flat face radial edge (FFRE), standard concave (SCC), shallow concave (SHCC), compound concave (CCC), deep concave (DCC), and x-deep concave (XDCC)]

material properties and mechanical integrity. These are the constituents of the proposed unitless capping index (Fig. 2). A compact having high capping index is an indicator of enhanced compact anisotropy. Therefore, qualitative PCA correlations (Fig. 4) were established between axial YM, radial YM, axial BF, radial BF, material anisotropy index, compact anisotropy index, and capping index. The current study model is based on few variables and a limited sample size, as this is the first study in this series. The developed 'proof of concept' of the capping index will be challenged with other additional variables like tablet thickness and multiple formulations to get a better trained model for predicting the capping index. PCA scores (Fig. 4A) and loadings plot (Fig. 4B) showed a positive correlation of FFBE, FFRE and majority of FF and SHCC tablets with axial YM, axial BF, radial BF, material anisotropy index and compact anisotropy index along PC1. These tablets showed a negative correlation with the capping index. It indicates that these compacts have reduced material and compact anisotropy which translates as a decreased capping tendency. SCC, SHCC, CCC, DCC, and XDCC tablets exhibited negative correlations with axial YM, axial BF, radial BF, material anisotropy index, and compact anisotropy index along PC1. These tablets showed a positive correlation with capping index along PC1. Certainly, these correlations confirmed that increased material and compact anisotropy due to punch geometry could be a potential cause of tableting problems like capping.

Additionally, a separate bivariate analysis of capping index with regard to applied compression pressure for different punch geometries of APAP model formulations was performed. Cylindrical tablets produced with FF punch displayed the lowest CI at all studied compression pressures (Fig. 5). Tablets having the highest deviation from a cylindrical geometry (XDCC) exhibited the highest CI at all compression pressures. An increase in the punch cup depth and cup volume has a positive impact on the tablet capping index. This trend is consistent with that observed in the USP<1062> profile of the APAP formulation and PCA. Thus, it validated that the proposed comprehensive CI parameter could be used to evaluate tablet capping tendency with regard to material properties and tooling designs. The capping index of cylindrical tablets decreased with an increase in the compression pressure. However, an opposite trend was observed with APAP tablets having increased deviation from the cylindrical geometry. It suggests that an increase in the compression pressure (a key process parameter) could not improve mechanical integrity of the tablet if it has an extreme deviation from the cylindrical geometry.

Quantitative PLS Analysis

After validation of the proposed capping index with the USP<1062> profiling and PCA, a predictive capping index model was computed with a multivariate statistical analytical tool. A quantitative partial least squares (PLS) regression method was used to quantify capping index as a function of several process parameters. Various process parameters

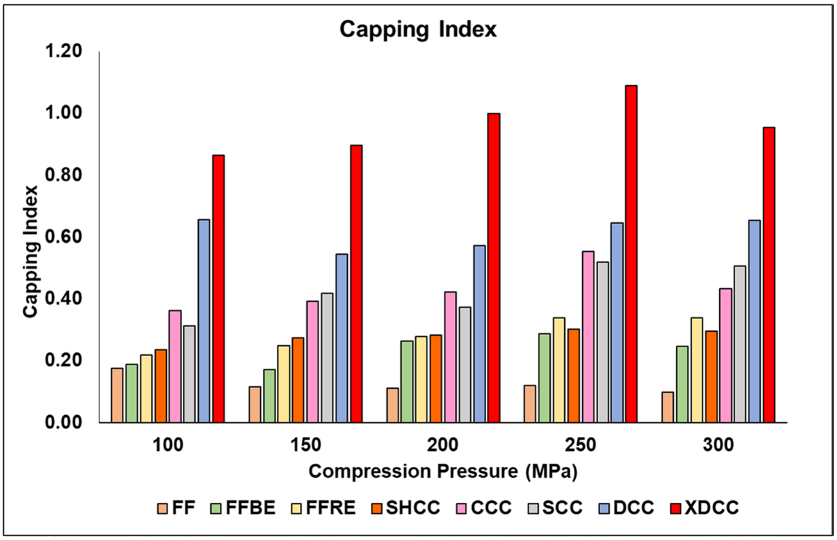

Fig. 5 Capping Index plot of different punch cup depth tools at different compression pressure (MPa). [flat face (FF), flat face bevel edge (FFBE), flat face radial edge (FFRE), standard concave (SCC), shallow concave (SHCC), compound concave (CCC), deep concave (DCC), and x-deep concave (XDCC)]

such as punch cup shape cup depth, cup volume, compression pressure, ejection force, and solid fraction were designated as 'X-variables'. A capping index was considered as a Y-variable. A PLS model demonstrates a predictive quantitative relation between X-variable and Y- variable. One of the limitations of the current statistical model is limited sample size and not taking consideration of important variables (tablet thickness, compression speed etc.). It could create an impact on final prediction of model. Some statistically insignificant variables are kept in the model, as these are main variables. Additionally, regression coefficient (R^2) values of PLS model at calibration stage and validation stage, RMSEC and RMSEP values were dropping when these important design variables were taken out of the model. An error bar of X-variable not passing through the origin is considered as a statistically significant variable. An X-variable having an error bar above the origin with a positive regression coefficient shows a positive impact on the Y-variable and vice versa. Details of PLS modeling will be found in our previously published articles [1]. Interactions and square effects of main variables are not added in the model to avoid unnecessary complexity.

The current PLS model used three PCs to evaluate the data. The R^2 values of PLS model at calibration stage and validation stage were 0.9772 and 0.9601, respectively. The root mean square error (RMSE) values of PLS model at calibration stage and validation stage were 0.0370 and 0.0504, respectively (Fig. 6). The deviation between measured and predicted values obtained from the PLS model were plotted with error bars (Fig. 7).

Impact of Punch Geometry on the Capping Index

Punch types such as FFBE, FFRE, and SHCC exhibited a statistically significant negative impact on the capping index. FF, SCC, and CCC punch designs showed a statistically insignificant impact on the capping index. However, they have negative correlation with the capping index if we ignore error bars associated with these variables. These results insinuate that a perfect cylindrical geometry and subsequent slight deviation from it could be tolerated without compromising the tablet mechanical integrity. Tablets manufactured with such punch designs could be less prone to various late stage tableting problems such as capping and lamination due to reduced material and compact anisotropy.

An extreme deviation from the cylindrical design such as XDCC displayed a statistically significant positive impact on the capping index. DCC having a substantial deviation with a cylindrical punch design showed an insignificant impact on the capping index, but it has a positive trend on this variable. Tablets manufactured with such designs could possess higher anisotropy. Such tablets might have considerable challenges to maintain their mechanical integrity regardless of material properties.

Other design variables like cup depth and cup volume responsible for deviation from the tablet cylindrical geometry exhibited statistically significant positive impacts on the capping index. These results further delineate their role in compromising tablet mechanical integrity during late stage commercial manufacturing. As seen in Fig. S3, a deviation from cylindrical geometry leads to a rise in the central thickness of the tablet for a given solid fraction. Perfectly cylindrical tablets exhibited the least central thickness, while XDCC displayed the highest thickness. Tablets produced with XDCC punch geometry exhibited ~50% rise in the central thickness for same solid fraction of APAP as compared to FF. These central areas experience delayed and least amount of compression force during the compression cycle, which could be responsible for inducing anisotropy in the compact. This imparts a high porosity to the central region, making it a weaker region of the tablet. The edges of these

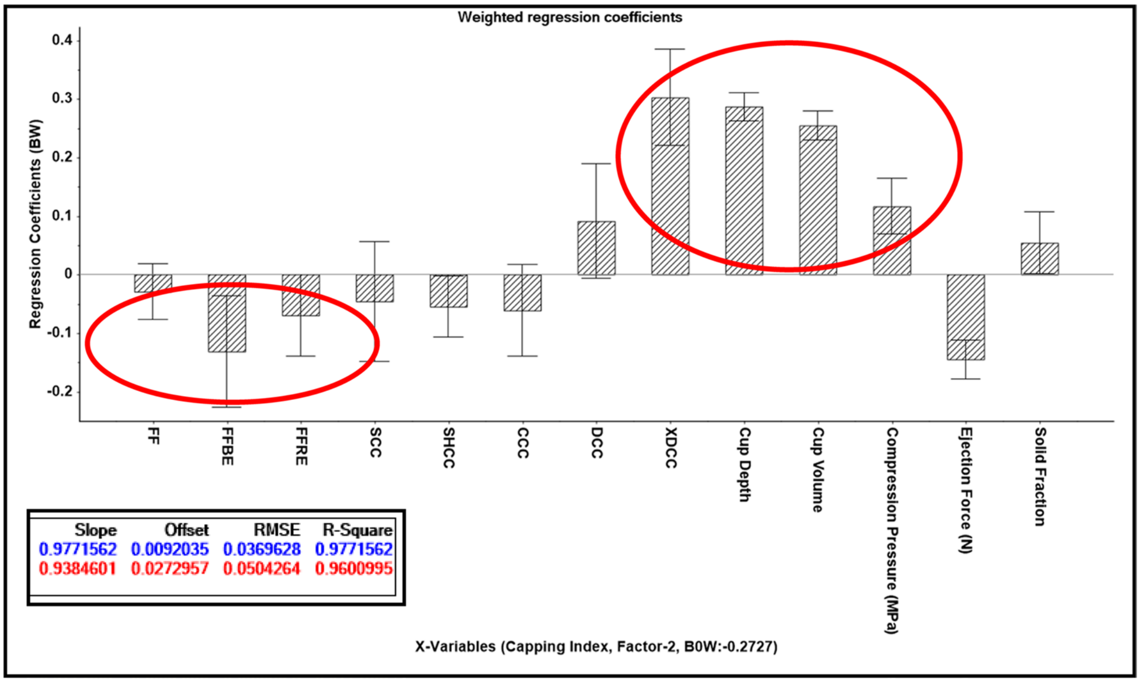

Fig. 6 Partial Least Square Regression plot indicating impact of all x-variables [flat face (FF), flat face bevel edge (FFBE), flat face radial edge (FFRE), standard concave (SCC), shallow concave (SHCC), compound concave (CCC), deep concave (DCC), x-deep concave (XDCC), cup depth, cup volume, compression pressure, ejection force, and solid fraction] on the Y-variable (Capping index). Significance of the model was measured using the Jack-Knifing method and corresponds to $p < 0.05$

tablets serve as highest density zones [10]. This could be attributed to the non-uniform stress distribution by concave punches as compared to the flat face punch (Fig. S1). Concave punches exert more compression pressure on the edges compared to the center point of tablet. Such variation in the stress distribution on the powder bed could impair material deformation and/or fragmentation under the compression load [21]. This could be responsible for material anisotropy under the compression load. Material deformation and/or fragmentation are key elements of inter-particulate bonding to impart compactness, reduced compact anisotropy, and desired strength to the tablet [22]. These series of events eventually translate into weaker compact formation, which are susceptible for tablet capping during the decompression phase or tablet ejection from the die [23]. Such weak central regions are rising exponentially with deviation from the cylindrical geometry.

Impact of Process Parameters

The compression pressure showed a positive impact on the capping index. Certainly, an increment in the compression pressure during tablet manufacture will not reduce the tablet capping rather it could aggravate the capping issue. This could be attributed to the saturation of compressibility, compactibility, and tabletability of the formulation, which is profiled with USP < 1062>. APAP formulation USP <1062> profile (Fig. 3) clearly revealed that the APAP formulation is approaching or close to its saturation limits with regard to the USP <1062> parameters depending on the adopted punch geometry. After exhaustion of formulation compressibility, compactibility, and tabletability, it is not possible to increase the tablet mechanical strength. In such cases, an excessive application of the compression pressure could reduce the interparticle bonding leading to a potential capping.

Ejection force demonstrated a negative impact on the capping index. It means that tablets having high ejection force during the decompression phase will pose less capping

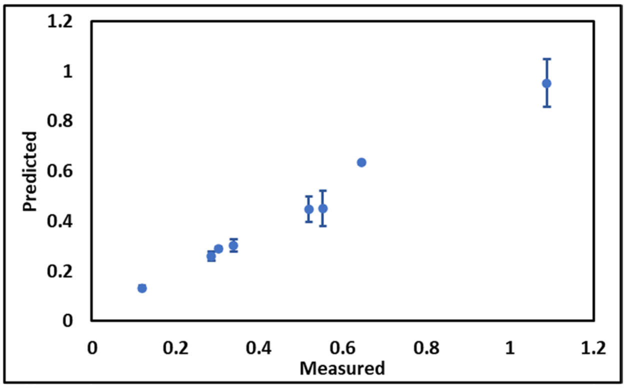

Fig. 7 Deviation between measured and predicted values of capping index plotted using error bars

tendency. A model APAP formulation is known for its intrinsic capping tendency [24, 25] due to its predominantly elastic nature. However, material properties are a constant variable in the present study. The band thickness in the tablet decreases with increase in the punch cup depth [26]. In the present study, as observed with USP < 1062>, perfectly cylindrical tablets manufactured with FF punch were stronger as compared to tablets deviating from the cylindrical geometry. Such cylindrical tablets due to large band thickness will have more die-wall friction as compared to concave tablets [27]. Thus, cylindrical tablets will require a high ejection force due to a high die-wall friction and tablet strength as compared to concave tablets. This could explain the negative impact of ejection force in the capping index.

Finally, solid fraction displayed a significantly positive impact on the capping index. It implies that increase in the solid fraction could lead to increased capping tendency of the formulation. This effect could be explained with the compressibility and compactibility components of the USP <1062> profile (Fig. 3). The maximum theoretically possible solid fraction would be 1 for any tablet. An increase in the solid fraction leads to reduction in the space between the particles required for compression. As solid fraction reaches above 0.9, there is very limited space between the particles. It could trigger over-compression. Powder over-compression is known for breaking interparticle bonds rather than making them. Thus, over-compression triggered with increase in the solid fraction could lead to weaker tablets prone to capping [23].

Prediction Performance of Optimized PLS Model

A predictive performance of an optimized capping index PLS model was tested on an independent data set. Fig. S4 shows the relationship between experimentally measured and predicted capping index values. The deviation of predicted values from optimized PLS models for capping index for eight independent data points were < 5.0%. The regression coefficient (R^2) between predicted and experimental value was 0.94205. These results could reveal a better predictive performance of optimized capping index PLS model.

Conclusions

The present study demonstrated the utility of the proposed comprehensive capping index based on the material and mechanical anisotropy of compacts to evaluate the capping tendency of an APAP model formulation with regard to selected tool design.

Deviation from flat face punch geometry translated into a significant increase in the central tablet thickness for the same solid fraction of APAP. A rise in the central thickness was directly proportional to the cup depth and volume. The central thickness is a function of varying density gradient due to nonuniform distribution of compression pressure observed in the FEM analysis. Such high porosity weaker regions could be responsible for increased compact mechanical anisotropy and subsequent tablet capping. XDCC punches having an extreme deviation from the flat punch geometry displayed the least tablet mechanical strength and accommodation of solid fraction as compared to other punches. FE analysis corroborated uniform distribution of pressure on the powder bed with flat faced punches. These tablets showed the least capping index at all compression pressures.

PLS multivariate model showed statistically significant negative impact of FFBE, FFRE, and SHCC on the capping index. XDCC punch, cup depth, and cup volume showed statistically significant positive impact on the capping index. These findings confirmed that an increase in cup depth and volume in the punch geometry translates to increased mechanical anisotropy. It eventually leads to a higher capping propensity as compared to tablets compacted with less punch concavity. A formulation capping index is a function of tablet thickness, compression pressure, and cup depth.

Though these findings are based on a limited data set, the findings of the present study confirmed that proposed capping index could serve as an indicator for aiding proper tool design to control final compact structural integrity.

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Declarations

Conflict of Interest None.

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