The effect of starch paste and sodium starch glycolate on the compaction behavior of wet granulated acetaminophen formulations.

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ABSTRACT

The effect, of varying the proportion of binder starch paste (SP) and the disintegrant sodium starch glycolate (SSG), on the compaction behavior of wet granulated acetaminophen (ACM) formulations using a fully instrumented rotary tablet press, was studied. Wet granulation formulations were prepared using ACM, SP as binder (equal to 2.5%, 5% or 10% starch concentration), SSG as disintegrant (0%, 4%, 8%, or 12 % w/w), microcrystalline cellulose (MCC) and magnesium stearate (MS) (1.5 % w/w). Upper and lower punch force-displacement data during in-die compaction was captured using a fully instrumented rotary tablet press at 13.8 rpm at 96 ± 8, 163 ± 13, 235 ±12 MPa compaction pressures. Elastic energy [EE] and tablet tensile strength was determined as a function of starch and SSG concentration and compaction pressure. At a given compaction pressure, increasing the proportion of SSG resulted in higher values of elastic energy (0.28 to 0.76 Nm with increase in SSG from 0% to 12% at 5% starch and 235 ±12 MPa compaction pressures). The negative effect of SSG on the overall compressibility of granules was due to its high elastic energy and decrease in interparticulate bonding. When examining the elastic energy at increasing SP levels, a decrease in elastic energy was evident (0.60, 0.50 and 0.31 Nm for 2.5%, 5% and 10% starch at 4% SSG and 235 ±12 MPa compaction pressures respectively). At a given composition, an increase in compaction pressure led to an increase in elastic energy (0.15, 0.33 and 0.50 Nm at 4% SSG and 5% starch for 96 ± 8, 163 ± 13, 235 ±12 MPa compaction pressures, respectively). When changing SSG and binder (SP) concentration levels tensile strength was indirectly proportional to elastic energy during compaction. Negative influence of SSG on elastic energy indicated by increased EE and decreased tensile strength and positive influence of SP was evident on lower elastic energy and higher tensile strength of tablets.

KEYWORDS: Acetaminophen, starch, sodium starch glycolate, disintegrant, binder, tableting, compaction

INTRODUCTION

Compaction behavior of pharmaceutical materials has been extensively reported using single component or homogeneous systems (1, 2). The finished product, a tablet, is made up of a combination of active pharmaceutical ingredients (APIs) and excipients which are the inactive ingredients. The compaction behavior of a heterogeneous system depends on the type and amount of API(s) and excipient(s) used in the formulation. APIs and excipients used in tableting exhibit different deformation and densification behavior. For example, when compressed under confined compaction conditions, some materials, such as MCC, spray-dried lactose or sodium chloride show

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plastic deformation, dicalcium phosphate (DCP), crystalline lactose or ACM show a tendency to brittle fracture and, sodium starch glycolate (SSG) and ibuprofen show elastic properties (3-6). However, a combination of plastic and brittle materials act synergistically, such that an increased surface area caused by the fragmentation of the brittle materials, provide a larger surface area for interparticulate bonding induced by plastic materials (7). Visco-elastic behavior of the materials/blends governs the available bonding area and bonding strength for successful tableting (8-12). A knowledge of plastic energy and elastic energy is vital in understanding the compaction behavior of formulations. Additionally, the ability to form interparticulate bonds can be influenced by hydrophobic excipients such as MS (13-15). The effect of processing parameters such as moisture content, particle size, crystal habit, polymorphism and amorphism have also been reported (4, 12, 16-20).

Attempts have been made to predict the compaction behavior of mono- and multi-component systems by considering the deformation and densification behavior caused by force-displacement and tabletability profiles (21, 22). Excipients in a formulation can exhibit both positive and a negative effects on the performance of the tablet. Some positive effects are filler-binder, silicon dioxide and plastic deforming materials, whereas SSG (4), MS (14) and elastic deforming materials affect tableting performance negatively.

Problems related to tableting are more frequently observed in formulations containing a high dose and poorly compressible API, as a limited amount of excipients can be incorporated into the formulation. Further, the functionality of the incorporated excipients plays a significant role in determining their overall compaction behavior. Successful tableting of pharmaceutical powders requires an understanding of the fundamental mechanical properties of the tablet components together with the process parameters (23-30). Both can dictate the behavior of the formulation of the tablet. The presence of excipients significantly alter the thermodynamics of the compaction which affects the overall mechanical properties of the formulation such as compressibility, compactability and tabletability. Therefore, to minimize problems related to compaction it is necessary to evaluate the compaction behavior of the formulation in the presence of different excipients.

The purpose of this study was to (i) evaluate the compaction behavior of ACM formulations and (ii) show how the presence of excipients with different deformation behaviors affects thermodynamics and bonding during compaction. Elastic energy (EE) from unloading and tensile strength was used to characterize the mechanical properties of the ACM formulation.

Materials and Methods

Acetaminophen (Arbro Pharmaceuticals Ltd., New Delhi, India), microcrystalline cellulose (Avicel®—PH-112, FMC BioPolymer, Philadelphia, USA), corn starch (400L NF, Roquette America, Inc, Keokuk, IA), magnesium stearate (Synpro stearates, Ferro, Cleveland, USA), sodium starch glycolate (Glycolys®, USP/NF, America, Inc, Keokuk, IA, USA) and starch (Loba Chemie, Mumbai, India) were used in this study.

Identification of the components and process of the formulation

The qualitative formula of acetaminophen tablets (Tylenol®) was obtained from Physician Desk Reference (Physicians' Desk Reference®. 53rd ed. Montvale, NJ: Medical Economics Company, 1999). MCC was used as the diluent, corn starch as the binder and SSG as the disintegrant.

Information about the weight of the innovator tablet (600 mg) allowed for the calculation of the percentage of ACM and excipients

respectively. The formula for the in-house tablet was based on commonly used percentages of the MCC, SSG, and MS used in drug formulations. The concentration levels of the excipients critical to the mechanical properties (SSG and SP) was varied within the range of commonly used concentration levels for these excipients. Wet granulation is the most commonly used process for the manufacturing of ACM tablets (31) and was therefore used in the studies presented here.

A binder (SP) and a disintegrant (SSG), respectively, were identified as critical contributors to the compactability of the tablet. SSG and MS were added to the granules in a concentration of 0%, 4%, 8% or 12% and 2.5%, 5% or 10%, respectively.

Wet granulation

Preparation of starch paste

Starch powder was dispersed in cold water to allow initial wetting, followed by the addition of warm water of 70°C to 80°C to allow gelatinization to occur. The mixture was stirred continuously for about 5-10 minutes until a translucent paste was obtained at a final temperature of about 90°C.

Granulation

83.3 g of ACM and 8.7 g of MCC were dry-mixed in a double cone mixer (DCM-5 Kalweka series, Karnavati Engineering Ltd, Ahmedabad, India) at 20 rpm for 10 minutes. The desired quantity of SP (equivalent to 2.5%, 5% or 10% of dry starch) was mixed with the blend to form a dough-like mass suitable for granulation. The details of the batches with different concentration levels of SP are shown in Table 1. Granules were obtained by passing the wet mass through sieve (British standard sieve (BSS) # 18. The granules were dried in a fluidized bed dryer at 60 °C, so as to achieve a moisture content of 2.5% to 3.0%. After drying the granules were sieved through BSS # 16 and retained on BSS # 20. Different levels of SSG were added to the samples of the granules producing blends containing 0%, 4%, 8% or 12% w/w. The blends were mixed in a double cone mixer at 20 rpm for 10 minutes.

The concentration levels of SSG at 0%, 4%, 8%, or 12% w/w were chosen and the concentration of MS were kept constant at 1.5% w/w in all the blends (Table 1). The percentage was not adjusted to 100% by varying the concentration of MCC, as it would have affected the compaction profile.

Table 1 Qualitative and quantitative composition of various wet granulated batches

	BATCH A				BATCH B				BATCH C			
INGREDIENTS	A1	A2	A3	A4	B1	B2	B3	B4	C1	C2	C3	C4
Starch (% w/w)	2.5	2.5	2.5	2.5	5	5	5	5	10	10	10	10
SSG (% w/w)	-	4	8	12	-	4	8	12	-	4	8	12

Moisture determination

The moisture content of the granules (100-120 mg) was determined by Karl Fisher titration. (Metrohm 794 Basic Titrino, Herisau, Switzerland). The instrument was calibrated with disodium tartrate dihydrate for the accuracy of moisture determination.

Tableting data acquisition and analysis

A rotary tablet press (Mini II, Rimek, Ahmedabad, India) was equipped at one of the 8 stations with a 8 mm D-tooling with a flat punch tip. A feed frame was used for uniform die filling and blind dies were used at all other positions. Precompression rollers were set out of function. The force was varied by adjusting the "pressure-adjustment wheel". Data was acquired by a Portable Press Analyzer™ (PPA) (Data Acquisition and Analyzing System, PuuMan Oy, Kuopio, Finland), through an infrared (IR) telemetric device with a 16-bit analog-to-digital converter (6 kHZ). Force was measured by strain gauges at upper and lower punches (350 Ω, full Wheatstone bridge, I.

Holland Tableting Science, Nottingham, UK), which were coupled with displacement transducers (linear potentiometer, 1000 Ω). Upper and lower punch data was recorded and transmitted on separate channels by individual amplifiers ("Boomerangs"). The amplifiers truncated the raw data from 16-bit to 12-bit after measuring to check IR transmission (data transmission rate-50 kbaud, internal data buffer–1024 measurement points). Analysis of compaction data was carried out using PPA Analyzer™ software (Version 1.2, Revision D). The accuracy of force and displacement transducers was 1% and 0.02%, respectively. The contribution from tooling deformation has been corrected according to the manufacture's guidelines. The suitability of the data acquisition system has previously been reported (32).

The main compaction pressure range was 96±8, 163±13, 235±12 MPa, and the tablet weight was kept constant at 300±4 mg. Tableting speed was kept constant at 13.8 rpm and relative humidity (40 ± 5% RH) and temperature conditions (25 ± 2˚C) were maintained throughout the study.

Data analysis

Thermodynamics of compaction - elastic energy

A force-displacement profile was used to calculate energy required during compaction. The integration of the various areas under the curve in the force-displacement profile allows for the accurate calculation of plastic energy (PE) and EE. Figure 1 illustrates the typical force and vertical punch displacement, where A is the punch separation at first measurable force, and B is the minimum punch separation at peak force (after point B, elastic deformation starts), hence the corresponding value at point C represents minimum punch separation. Point D represents punch separation after elastic deformation (or decompression). The area under the curve ABC represents gross energy input, and the area under the curve CBD corresponds to released EE after decompression or unloading. The net energy input, the area under the curve ABD or the PE was determined by calculating the difference between the area ABC and CBD. To determine PE and EE, the area under a curve (AUC), was calculated using the trapezoidal rule.

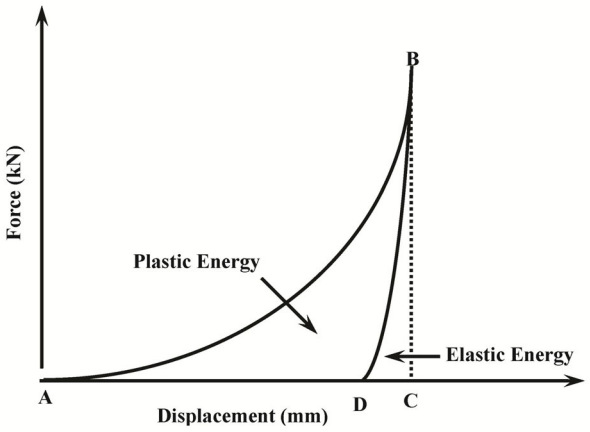


Figure 1 A typical force-displacement plot showing the compression and decompression areas

Tensile strength measurements

The crushing force of the tablets was measured using a tablet hardness tester (TBH 20, Erweka, USA). The tablet dimensions were measured using a digital caliper (Digimatic Mitutoyo Corporation, Japan). To eliminate the undesirable effect of variable tablet thickness on measured crushing force, tensile strength was calculated using the equation below (33, 34).

$$\sigma = 2F/\pi dt \qquad \text{Eq. 1}$$

where,

σ is the tensile strength (MPa), F is the observed crushing force (N), d is the diameter (mm) and t is the thickness of the compact (mm).

Statistical Analysis

Comparison of the mean values was performed by a one-way analysis of variance (one-way ANOVA) followed by multiple comparisons by Student-Newman-Keuls test. Differences between groups was considered significant when $p<0.1$. Design Expert® (version 6.0.8, Stat-Ease Inc. Minneapolis, USA) was employed for response surface analysis (n=6).

RESULTS AND DISCUSSION

Effect of SSG and SP concentration on EE

The effect of the concentration levels of SSG on the EE is shown in Figure 2. For a given compaction pressure, as the concentration of SSG was increased, a greater amount of stored energy was released by elastic deformation, thus yielding higher values of EE. All the formulations exhibited a pressure dependent increase in EE due to the inability of the formulation to release stress and undergo further plastic deformation. This was attributed to the poor compaction behavior of ACM which undergoes stress relaxation by elastic deformation as pressure is increased. Similar results for ACM have been reported (23, 24, 35-37). Some additional observations are (i) an increase of the concentration levels of SSG resulted in an increase in EE across the range of SP concentration levels and compaction pressure, (ii) EE increased with increasing compaction pressure at 0% SSG. The increase in SP concentration levels significantly reduced the EE at compaction pressures of 96±8 and 163±13 MPa. However, a less obvious decrease in the EE was seen at 235±12 MPa. This indicates that concentration of the binder was insufficient to counter the EE of the system at the higher compaction pressure, (iii) A concentration level of 10 % of SP significantly increased the EE due to increasing SSG concentration levels but, the effect was less obvious at higher compaction pressures and, (iv) an overall increase in the SP concentration levels reduced the EE, though the effect was more obvious at higher SP concentration levels and lower compaction pressures.

The negative effect of SSG on compressibility of the granules can be explained in two ways (i) the high elastic deformation of SSG itself, which imparts concentration dependent increase in the EE of the overall formulation blend (4) and (ii) extra granular distribution of SSG across the granule surface, which reduces

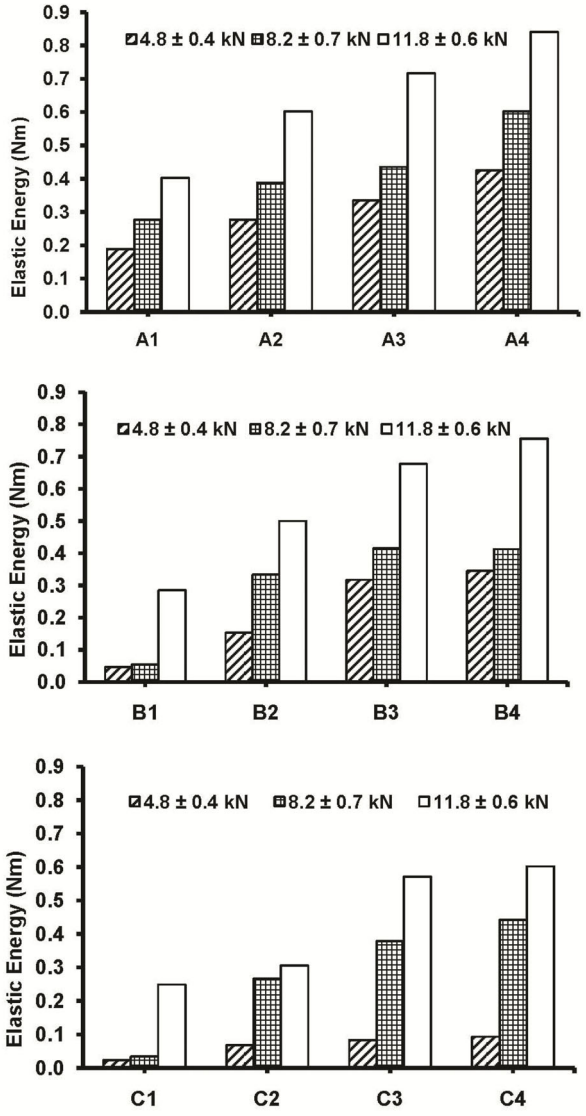


Figure 2 Values of elastic energy obtained at three different compression forces (4.8±0.4, 8.2±0.7 and 11.8±0.6kN) for batches containing concentrations of SSG; A1, B1, C1 - 0% SSG; A2, B2, C2 - 4% SSG; A3, B3, C3 - 8% SSG and A4, B4, C4 - 12% SSG. A, B and C series contained 2.5%, 5.0% and 10.0% starch respectively

the available bonding area and interparticulate bonding, and thus results in enhanced elastic deformation. The elastic nature of SSG was apparent from the pressure dependent increase in EE as a result of an increase of concentration levels of SSG (0% to 12%).

SP, as a binder, contributed positively by decreasing the EE in a concentration dependent manner. This is in accordance with previous findings (20) which has been explained as (i) a concentration dependent increase in the gel strength of the binder that results in the formation of strong interparticulate bridges upon drying and subsequent compaction and (ii) increased plastic deformation and bonding area upon compaction (38).

Effect of SSG and SP concentration levels on tensile strength

All the formulations exhibited compaction pressure dependent increase in tensile strength, indicative of better tabletability. Increased concentration levels of SSG reduced tabletability across all the SP concentration levels and compaction pressure. Increased concentration levels of SP increased tabletability across the SSG concentration levels and compaction pressures. The effect, however, was less obvious at higher concentration levels of SSG. At 0% SSG a steep increase in tabletability was observed with increasing compaction pressure at all SP concentration levels. A less obvious pressure dependency of tensile strength was observed in batches containing 4%, 8% or 12% of SSG (Figure 3). The negative effect of SSG concentration levels was blunted by the highest SP concentration level at 10%, whereas the formula with 4%, 8% or 12% of SSG showed close tabletability profiles. The results of EE and tabletability provide complementary findings. Overall the results suggests that SP increases the available bonding strength and bonding area therefore providing better tabletability. SSG reduces tensile strength due to a smaller bonding area available through it. Statistical differences in mean values of tensile strength is apparent for all pressures studied, except for batch A granules.

Relationship between the studied parameters

The relationship between the dependent (EE

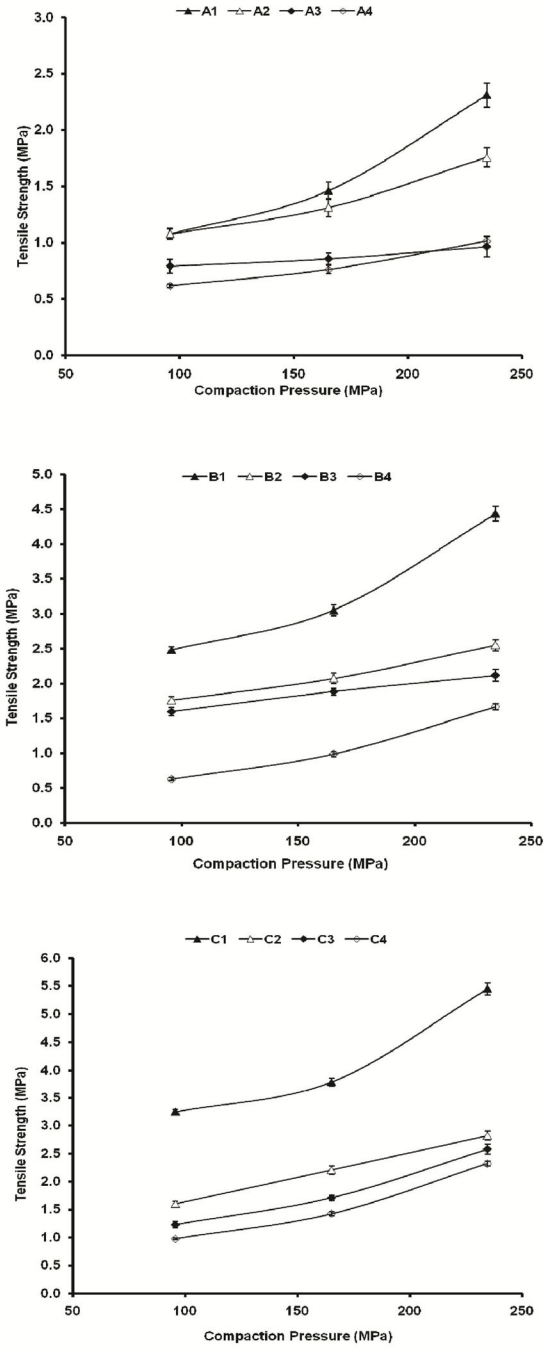


Figure 3 Values of tablet tensile strength obtained at three different compaction pressures (95.5±8.0, 163.2±13.9 and 234.9±11.9 MPa) for batches containing concentrations of SSG; A1, B1, C1 - 0% SSG; A2, B2, C2 - 4% SSG; A3, B3, C3 - 8% SSG and A4, B4, C4 - 12% SSG. A, B and C series contained 2.5%, 5.0% and 10.0% starch respectively

and tensile strength) and independent variables (SP and SSG) was drawn using response surface plots. An example of a response surface plot eliciting the effect of SP and SSG and their interaction on ER and tensile strength at 96±8 MPa is shown in Figure 4.

Quadratic relationships between the SP and SSG concentration on EE at 96 ± 8 (Equation 2), 163±13 (Equation 3), and 235±12 MPa pressures (Equation 4) are shown in the equations ($R^2 \geq 0.95$).

$$EE = 0.2223 + (0.0365 * SSG) - (0.0305*SP) - (0.0006*SSG^2) + (0.0009*SP^2) - (0.0021*SSG*SP) \quad \text{Eq. 2}$$

$$EE = 0.4474 + (0.0483*SSG) - (0.0989*SP) - (0.0021*SSG^2) + (0.0059*SP^2) + (0.0010*SSG*SP) \quad \text{Eq. 3}$$

$$EE = 0.4884 + (0.0539*SSG) - (0.0411*SP) - (0.0012*SSG^2) + (0.0013*SP^2) - (0.0005*SSG*SP) \quad \text{Eq. 4}$$

The relative values of the coefficients of SP and SSG in the equations above indicate the significant contributions of these variables on EE. Moreover, the much larger regression coefficient for SSG in all the regression equations (Equations 2 to 4) indicates the positive correlation between SSG concentration and EE. Addition of SP reduces EE, as is apparent from the negative regression coefficient.

Quadratic relationships between the SP and SSG concentration levels on tensile strength at three compaction pressures 96 ± 8 (Eqation 5), 163±13 (Equation 6) and 235±12 (Equation 7) MPa pressures are shown below ($R^2 \geq 0.93$).

$$TS = 1.089 - (0.300*SSG) + (1.062*SP) + (0.018*SSG^2) - (0.046*SP^2) - (0.038*SSG*SP) \quad \text{Eq. 5}$$

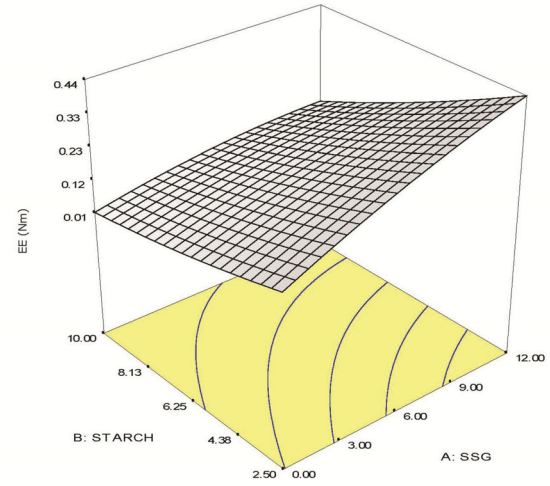
$$TS = 1.644 - (0.404*SSG) + (1.284*SP) + (0.020*SSG^2) - (0.061*SP^2) - (0.034*SSG*SP) \quad \text{Eq. 6}$$

$$TS = 1.109 - (0.672*SSG) + (2.459*SP) + (0.030*SSG^2) - (0.136*SP^2) - (0.035*SSG*SP) \quad \text{Eq. 7}$$

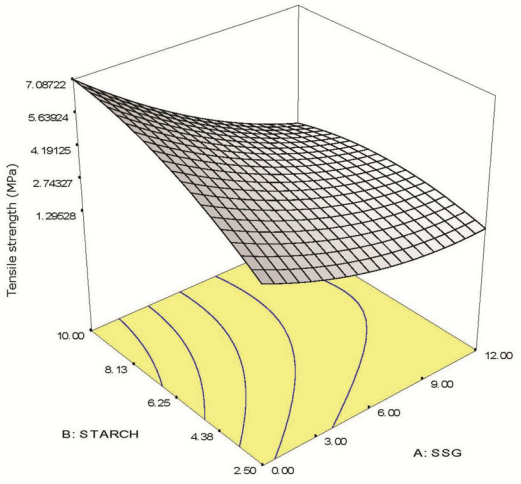
The larger coefficient for SP in all the regression equations (Equations 5 to 7) indicates a positive effect of SP concentration levels on tensile strength. The above equations also show the negative effect of SSG on tensile strength at all compaction pressures.

CONCLUSION

This study of the formulation of a high dose, poorly compressible drug can be used as a practical example to predict compaction behavior and minimize problems related to tableting. Formulations containing a mixture of excipients with opposing compaction behavior, influence compactability depending on the dominant deformation behavior and quantity of



(a)



(b)

Figure 4 Response surface plots showing the effect of independent variables (SP and SSG concentrations) on (a) EE and (b) tensile strength at the compaction force of 4.8±0.4 kN

the component. This has significant implications since these excipients play a critical role in the formulation of high dose drugs by influencing the overall compaction behavior of a formulation. The concentration dependence of positive and negative effects in determining the compressibility of a formulation can be considered as the pressure-displacement parameter (EE) and tablet tensile strength. SSG negatively affected the tablet tensile strength and was responsible for the elastic deformation of the formulation, whereas SP as the binder contributed positively to tableting.

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