Mechanism of eutectic formation upon compaction and its effects on tablet properties

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Abstract

The unique property of a eutectic mixture is a lower melting temperature than that of any of its pure components. What differentiates a eutectic mixture from a simple physical mixture is less well understood. This impedes the ability to anticipate and/or detect unintentional eutectic formation during pharmaceutical tablet manufacturing and any potential negative impact. In this study, a thermodynamic/heat transfer approach was used to explain the mechanism of eutectic formation upon exposure to a physical stress, i.e. compaction, and a differential scanning calorimetric (DSC) method was developed to detect and quantify the amount of eutectic formed in the compacts. Furthermore, the mechanism of eutectic formation upon compaction was tested experimentally by correlating the amount of eutectic formed in tablets with the particle size, compaction force, the estimated intimate contact area between the eutectic-forming materials, calculated tablet tensile strength, and tablet porosity. The effect of the presence of eutectics on tablet properties was also investigated. The results show that intimate contact and mutual solubility between eutectic-forming materials are the necessary and sufficient criteria for eutectic formation upon compaction. The systems of acetaminophen (APAP)/caffeine and APAP/propylphenazone were both shown to exhibit eutectic behavior upon compaction and the extent of formation was dependent upon the amount of intimate contact between eutectic-forming materials. Finally, it was found that eutectic had no negative effect on tablet hardness.

Keywords: Mechanism; Eutectic; Compaction; Contact area; Tablet hardness

1. Introduction

Solid dosage forms make up in excess of 85% of all pharmaceutical products in the United States and Europe. By far the most common solid dosage form is the tablet. Tablets offer numerous advantages over other dosage forms, including increased patient compliance resulting from ease of use, ease of packaging, shipping, and storage, high content uniformity, and reproducible dissolution kinetics.

The three major factors leading to compressed tablets being recalled by manufacturers are failed content uniformity, dissolution, and chemical stability. The underlying causes of these failures are numerous [1]. One sub-category of physical cause for tablet failure is change in crystal form during manufacturing. This may include polymorphic transformation,
crystalline/amorphous interconversions, and dehydra-
tion/rehydration of the material. The differences in
solubilities, tablet characteristics, and chemical stabil-
ity that may accompany such changes have been the
subject of books [1,2], product recalls, and numerous
regulatory agency actions.

A less-studied physical phenomenon is the
compaction-induced formation of eutectics among
two or more active ingredients or between the active
ingredients and the excipients in a given tablet for-
mulation. One reason for the lack of study is the limited
understanding of the mechanism of eutectic forma-
tion during compaction. Another equally contentious
issue is the difficulty in identifying and quantifying
the amount of eutectic formed in the tablet during
processing.

Eutectics are intimate crystalline mixtures of one
component in another. The unique property of an eu-
tectic is that it has a lower melting temperature than
that of either pure compound. Its discovery, applica-
tion and development have been thoroughly described
[3]. Eutectics have many of the same properties as
each phase, and yet behave differently from either
component with respect to melting point, solubility,
and (sometimes) chemical stability [4]. The proper-
ties of eutectics may be advantageous (e.g. higher
dissolution rate) or disadvantageous (e.g. poor stabil-
ity). Because eutectics enhance dissolution, they have
been employed to increase permeability in solid dis-
persions and disperse systems [5–9]. However, in the
development of tableted dosage forms, unintentional
eutectic formation (e.g. during pharmaceutical unit
operations such as wet granulation and/or compres-
sion [10,11]) have been reported to lead to unwanted
changes in the physical and/or chemical characteris-
tics of the tablets. This may take the form of stick-
ing, unpredictable hardness, instability, or difficulties
in accelerated assessment of stability. However, the
contribution to historical failures and product recalls
is unknown.

Two theories have been put forward to explain eu-
tectic or contact melting [12], but both conflict with
much of the existing experimental data [12,13]. Con-
sideration of the thermodynamics of contact melting
suggests that it must be entropy-driven. If it is assumed
that A and B are two eutectic-forming components,
the eutectic composition is XA and XB (where XA = 1 − XB) and Te the eutectic melting temperature. The
total entropy change, when compounds A and B melt
separately, is given by

\[ \Delta S_T = X_A \Delta S_A + X_B \Delta S_B \] (1)

where \( \Delta S_T \) is the total entropy change, and \( \Delta S_A, \Delta S_B \)
the entropies of fusion of compounds A and B, respec-
tively. The total entropy change, however, will be

\[ \Delta S_T = X_A \Delta S_A + X_B \Delta S_B + RX_A \ln \left( \frac{1}{X_A} \right) + RX_B \ln \left( \frac{1}{X_B} \right) + \Delta S_{ex} \] (2)

where \( \Delta S_{ex} \) is the entropy change due to the non-ideal
mixing. This relationship shows that \( \Delta S_T \) must in-
crease in proportion to the mutual solubility (consis-
tent with Schoeder and van Laar [14]). The lattice
energy, or heat of fusion, of the eutectic is a simple
weighted sum of the individual components assuming
ideal mixing in the liquid state. The melting tempera-
ture must, therefore, decrease due to the increase in
entropy (i.e. \( T_e = \Delta H_f/\Delta S_T \) where \( \Delta H_f \) is the, con-
stant, total heat of fusion).

The model proposed suggests that intimate contact
in the solid state and mutual solubility in the liquid
state are the essential criteria for the formation of eu-
tectics. Intimate contact in the solid state is necessary
for contact-induced melting point depression to oc-
cur. If eutectic-forming compounds are not in contact,
no increase in \( \Delta S_T \) would occur, and eutectic melting
would not be observed.

The logically derived hypothesis is that eutectic be-
behavior in tablets does not require the eutectic tem-
perature to be exceeded, as has been proposed [14],
but rather the mixture may form due to mechanical
stress, which facilitates intimate contact between the
eutectic-forming materials (just as melting and so-
lidification process did during eutectic preparation).
An important extension of the hypothesis is that the
amount of eutectic formed should be a function of in-
timate contact.

In this study, the mechanism of eutectic forma-
tion upon compaction was investigated, a differential
scanning calorimetric (DSC) method to quantify the
amount of eutectic formed in the tablet was devel-
oped, and testing the hypothesis of eutectic formation
upon compaction and the effect of eutectic formation
on tablet properties were addressed.
2. Experimental

Acetaminophen (APAP) USP/EP crystal, Lot: ACBL 099 was obtained from, BASF, Bulk Pharmaceuticals and Intermediates, Bishop, TX. Caffeine (CAFF) anhydrous, Lot: 23100 was obtained from, Knoll AG, D-6700 Ludwigshafen, BASF Gruppe. Propyphenazone (PP) was obtained from Wako Chemicals USA, Richmond, VA.

2.1. Phase diagram construction for the model compounds

Binary mixtures of APAP/CAFF and APAP/PP in ratios (w/w) of 100/0, 90/10, 80/20, 70/30, 65/35, 60/40, 50/50, 40/60, 30/70, 20/80, 10/90, and 0/100, respectively, were prepared for thermal analysis. Each mixture was placed in a glass vial, which was immersed in an oil bath and heated to a temperature 2 °C above that of complete fusion of both compounds. The fused mixtures were stirred to ensure complete mixing and then allowed to cool to room temperature. The solidified materials were gently ground (using a mortar and pestle) and size fractions were separated through a nest of sieves (US Standard Sieve Series, ASTM E-11 Specifications, American Scientific Products, Division of American Hospital Supply, McGaw Park, IL). Particles having sizes between 125 and 150 μm were collected for construction of temperature–composition phase diagrams. Samples (5.0 ± 0.2 mg) from each composition were weighed in aluminum DSC pans (part no. L7189 and L7182, Rheometric Scientific, Piscataway, NJ, USA). The pans were hermetically sealed and scanned with a differential scanning calorimeter (DSC 2920, TA Instruments, New Castle, DE, USA) with an empty pan on the reference side. DSC baseline, temperature, and cell constant were calibrated with indium prior to each experiment at a heating rate of 5 °C/min. A nitrogen flow rate of 20 ml/min was used for each DSC run. The fused APAP/PP samples were heated at a constant rate of 10 °C/min from 20 to 35 °C followed by 5 °C/min over the temperature range of 35–180 °C. The eutectic peak temperature for this system occurs at 142 °C. The peak maxima were used to construct temperature–composition phase diagrams, by plotting the DSC peak melting temperatures vs. the (w/w) compositions for at least two replicate runs at each composition.

2.2. DSC method for the quantification of eutectics in tablets

The following definitions were adopted to differentiate the species present or expected in this study:

1. Preformed eutectics, which are defined as eutectic mixtures formed by fusing and solidifying known eutectic-forming materials at the eutectic composition.

2. Thermally induced eutectic behavior is observed when eutectic-forming materials in a mixture of particles of the pure material at the eutectic composition are heated through the eutectic temperature. The relatively few points of contact melt, facilitating formation of the eutectic. This process dictates that thermally induced eutectic behavior will have a time lag relative to that of a preformed eutectic.

3. Preformed-eutectic tablets, which are defined as tablets (having a weight of 10 mg) compacted from the preformed eutectics (with particle sizes between 150 and 250 μm) using 3/16 in. flat-face punches at 5.0 × 10^6 Pa. The tablets prepared with the above conditions have very low, operationally “zero”, porosity (99.5% of true density) and are assumed to have as complete intimate contact between the eutectic-forming materials as possible.

4. Eutectic-mixture tablets (having a weight of 10 mg) compacted from mixtures of eutectic-forming materials at the eutectic composition with different compaction forces, or with different particle size ranges.

The amount of eutectic formed in the eutectic-mixture tablets refers to the amount formed at points of interparticulate contact due to the mechanical stress. A DSC method was developed and tested for the quantification of the amount of eutectic formed in the tablets. The intact tablets were placed in crimped aluminum DSC pans and scanned using the same heating rates described as above. Fig. 1 illustrates the procedures for the quantification by DSC of the amount of eutectic formed in the eutectic-mixture tablets.
Fig. 1. Schematic illustration of eutectic quantification by the DSC method.

Fig. 1a shows the schematic illustration of the thermo-analytical curve that would be generated by heating a preformed-eutectic tablet. The peak in Fig. 1a was integrated using the universal analysis program contained in the instrument software. The peak was divided into half by extending a line perpendicular to the baseline from the maximum height. A relative enthalpy of melting in area 1 was then calculated for later use. Fig. 1b shows the schematic representation of the DSC curve resulting from heating the eutectic-mixture tablets. Fig. 1c shows an overlay of Fig. 1a and b; curve b is then subtracted from curve a by using baseline function in DSC universal analysis program, resulting in the profile shown in Fig. 1d. Once again, a perpendicular line is subtended from the peak maximum to the baseline, and area 3 (as indicated in the Fig. 1d) is calculated. The amount of eutectic in the physical-mixture tablets was assumed by
the model discussed below to be proportional to area 2 (Fig. 1b). This area can be calculated by subtracting area 3 from area 1, which allows quantification of the amount of eutectic by simple proportional comparison with that of a preformed-eutectic compact (Fig. 1a).

2.3. Estimation of contact area between
eutectic-forming materials in the tablet

A lack of a method or adequate model to estimate intimate contact area in the compact [15] necessitated the development of a new model.

First, it is assumed that the total surface area of the tablet \( S_t \) may be expressed as

\[
S_t = S_p + S_f - S_b \tag{3}
\]

where \( S_p \) is the powder surface area before compaction, \( S_f \) the surface area generated due to initial fragmentation of the powder particles due to the compaction and \( S_b \) the reduction in powder surface area due to the contact or bonding of powder particles after one compaction cycle.

If \( S_c \) is the surface area difference before and after compaction, then

\[
S_c = S_t - S_p \tag{4a}
\]

but

\[
S_c = S_f - S_b \tag{4b}
\]

so

\[
S_b = S_f - S_c \tag{4c}
\]

Thus, the contacting area \( S_b \) may be calculated from the difference between the BET surface area of the sample before and after compaction if \( S_f \) is known.

A eutectic-forming system typically exhibits more plastic behavior in response to stress, in part because the eutectic melting temperature is much lower than those of pure compounds [16–19]. This supports the assumption that \( S_f \) will be, approximately, constant as a function of force after initial compaction. A specific relationship can be derived to relate \( S_b \) to the compaction forces. If it is assumed that the available non-contact surface of a particle is the reactant and the contact area is the product of a compaction-induced reaction, then

\[
\frac{dS_b}{dP} = k(S_0 - S_b)^2 \tag{5}
\]

where \( P \) is the compaction pressure, \( 2S_0 = S_p + S_f \) the total non-contact surface area after initial fragmentation, and \( k \) the second-order reaction rate constant.

Integrating yields

\[
S_b = S_0 - \frac{1}{kP + 1/S_0} \tag{6}
\]

substituting Eq. (6) into (4b) results in

\[
S_c = S_f - \left( S_0 - \frac{1}{kP + 1/S_0} \right) \tag{7}
\]

\( S_f \) can be calculated by extrapolating a plot of \( S_c \) vs. the compaction force \( P \). \( S_0 \) should be equivalent to \( S_f \) when the compaction force approaches zero. \( S_b \) can then be calculated using Eq. (4) at each compaction force.

2.4. Tablet tensile strength and porosity
measurement

Using 400 mg of the materials collected between 150 and 250 \( \mu \)m, physical mixtures at eutectic composition for each eutectic-forming system were uniformly mixed and compacted into the tablets with a pair of flat-face punches (1.1 cm diameter) at different compaction forces. The tablets were carefully removed from the die, weighed, and their diameter and thickness measured using a micrometer. The volume of the tablets was calculated as a function of tablet diameter and thickness, and the apparent density of the tablets as a function of compaction forces was calculated by using the formula:

\[
\text{Apparent density} = \frac{\text{tablet weight}}{\text{tablet volume}}
\]

The true density of the tablets was calculated from crystallographic data or determined by pycnometry. The tablet porosity was calculated by the following equation [20]:

\[
\text{Tablet porosity} = \frac{\text{true density} - \text{apparent density}}{\text{true density}}
\]

The tensile strength of the tablets was measured by the application of the diametral-compression test, which consisted of compressing tablets diametrically between the platens of tablet hardness tester at the rate of 0.1 cm/min. To ensure that the tablets fractured
Table 1

<table>
<thead>
<tr>
<th>Tablet no.</th>
<th>APAP/CAFF (mg/mg)</th>
<th>APAP/PP (mg/mg)</th>
<th>Preformed eutectics (%/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>240/160</td>
<td>260/140</td>
<td>0/0</td>
</tr>
<tr>
<td>2</td>
<td>226/150</td>
<td>244/132</td>
<td>6/24</td>
</tr>
<tr>
<td>3</td>
<td>216/144</td>
<td>236/126</td>
<td>10/40</td>
</tr>
<tr>
<td>4</td>
<td>204/136</td>
<td>221/119</td>
<td>15/60</td>
</tr>
</tbody>
</table>

↓

Compaction
↓

Hardness tester

Tablet performances and their correlations to the eutectic formed upon compaction.

In tension, various thickness of paper, cardboard, and blotting paper, were placed between the tablet and the steel platens to reduce any local crushing artifact and the mode of fracture was observed. Of the materials tested, it was found that three sheets of blotting paper, each 0.3 mm thick, produced the conditions that resulted in tensile failure of the specimens. During the measurement, the force needed to cleave the tablet was recorded and the tablet tensile strength was calculated based on the following formula: $\sigma = \frac{2P}{\pi DH}$ [21], where $P$ is the force needed to cleave the tablet, and $D$ and $H$ the diameter and thickness of the tablet, respectively.

2.5. Eutectic effects on tablet hardness

Uniform physical mixtures at eutectic composition for each eutectic-forming system were prepared and a specific amount of preformed eutectic was added into each above physical mixture and uniformly mixed. The final weight of mixtures (size fraction collected between the 150 and 250 μm) was 400 mg. All the mixtures containing a specific amount of preformed eutectic were compacted into the tablets using 1.1 cm diameter flat-face punches at $8.26 \times 10^7$ Pa. The hardness of the tablets was determined by using tablet hardness tester, and the results were correlated as a function of the amount of preformed eutectic in the tablets. Table 1 shows the experimental design.

![Fig. 2. DSC temperature–composition phase diagrams of APAP/CAFF and APAP/PP systems.](image-url)
3. Results and discussions

Fig. 2 shows the temperature-composition phase diagrams for both APAP/CAFF and APAP/PP systems. The theoretical curves were generated from the Schroeder–van Laar model[14]. These phase diagrams indicate that both model systems form eutectics. Fig. 2 also shows that the APAP/CAFF system is more nearly ideal than APAP/PP system as evidenced by the fact that the experimentally determined phase diagram is closer to the Schroeder–van Laar model which is derived from ideal mixing theory.

The basis for the DSC method lies in the melting kinetic differences between the preformed eutectic and the thermally induced eutectic behavior. The following factors are hypothesized to account for the observed differences.

First, the rate of contact melting depends on the extent of intimate contact, more intimate contact will lead to more melting per unit time (i.e. less resistance to heat transfer). It is well established[22,23] that preformed eutectics have significantly more intimate contact area than that of eutectic mixtures; therefore, the amount of preformed eutectic fused per unit time should be greater than that of a eutectic mixture. The preformed-eutectic tablet should give a higher heat flow per unit time relative to that of the eutectic-mixture tablet even though the total heat of fusion for both preformed eutectics and eutectic mixtures is approximately equal. The reason is that the physical-mixture tablet not only exhibits preformed-eutectic behavior, but also exhibits thermally induced eutectic behavior due to thermally induced intimacy. Thermally induced eutectic behavior should, and appears to, have a response lag time to the heat flow when compared to that of preformed eutectics. This is due to the relatively larger separation between components. The eutectic formed in the tablet can be quantified by the relative offset of the eutectic endotherm from that of a preformed eutectic given sufficient sensitivity and resolving ability of the instrument.

Second, the more intimate the contact (separation distance) the less is the thermal contact resistance at the interface [24–33]. The preformed-eutectic tablets should, once again, have higher thermal conductivity and a smaller thermal gradient should exist in the preformed-eutectic tablet compared to that of a eutectic-mixture tablet. The time required for the top layer of preformed-eutectic tablets to reach the eutectic temperature is shorter than that of eutectic-mixture tablets. This means that the mass melted per unit time will be higher for the preformed-eutectic tablet than that of a eutectic-mixture tablet.

Since the intimate contact and thermal conductivity of eutectic mixtures compacted by increasing forces are expected to increase, the heat flow/eutectic formation should increase too.

The effective thermal conductivity and intimate contact as a function of compaction forces were calculated by using the upper bound model [34,35] shown below:

\[ k = k_m \left[ 1 + \frac{3 \epsilon(1 - k_m/k_f)}{1 - \epsilon + k_m/k_f(2 + \epsilon)} \right] \]  \hspace{1cm} (8)

where \( k_m \) is the thermal conductivity of the solid matrix, \( k_f \) the thermal conductivity of the fluid (nitrogen in the present study) and \( \epsilon \) the matrix porosity. When the thermal conductivity of gas is much smaller than the matrix solid, upper bound model can be simplified to the following form:

\[ k = k_m \left( 1 - \frac{3 \epsilon}{2 + \epsilon} \right) \]  \hspace{1cm} (9)

<table>
<thead>
<tr>
<th>Tablet no.</th>
<th>Compaction forces (× 10^8 Pa)</th>
<th>Tablet porosity</th>
<th>Effective thermal conductivity (W K⁻¹ m⁻¹)</th>
<th>Tablet thickness (mm)</th>
<th>Thermal height (mm s⁻¹)</th>
<th>% Intimate contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25</td>
<td>0.0974</td>
<td>0.1608k_m</td>
<td>0.5352</td>
<td>0.3562</td>
<td>7.2580</td>
</tr>
<tr>
<td>2</td>
<td>0.75</td>
<td>0.0735</td>
<td>0.1822k_m</td>
<td>0.4791</td>
<td>0.4035</td>
<td>32.7544</td>
</tr>
<tr>
<td>3</td>
<td>1.25</td>
<td>0.0563</td>
<td>0.1864k_m</td>
<td>0.4993</td>
<td>0.4133</td>
<td>44.6474</td>
</tr>
<tr>
<td>4</td>
<td>2.50</td>
<td>0.0340</td>
<td>0.1928k_m</td>
<td>0.4566</td>
<td>0.4269</td>
<td>75.9058</td>
</tr>
<tr>
<td>5</td>
<td>Infinity</td>
<td>0.0000</td>
<td>0.2000k_m</td>
<td>0.4429</td>
<td>0.4429</td>
<td>100.0000</td>
</tr>
</tbody>
</table>
The upper bound model has been shown to be predictive for a range of systems [36]. Convective and radiative heat transfer are neglected in the calculation because the temperature used in the study is relatively low and the tablet pore size is small [37]. Table 2 shows that the thermal conductance of eutectic-mixture tablets increased as the compaction forces increased. Since the heat flux is approximately constant, the relative thermal height compared to that of a eutectic-mixture tablet with zero porosity can be calculated (assuming it has a typical thermal conductivity 0.26 W K$^{-1}$ m$^{-1}$, where $k$ can assume any value but will be cancelled during the calculation). The thermal height is defined as the distance passed through by the heat in the tablet along the direction perpendicular to the DSC cell surface per unit time. Table 2 shows that a eutectic-mixture tablet compacted at a higher force has a larger thermal height (i.e. heat travels farther in the same amount of time).

The intimate contact area covered by the thermal height was calculated as follows. It has been shown that the degree of intimate contact is proportional to the tablet tensile strength [38,39], and is described by the following relationship:

$$\sigma = \frac{\lambda A}{a}$$

(10)

where $\sigma$ is the tablet tensile strength, $A$ the total intimate contact area, $a$ the contact area for each bonding point, and $\lambda$ a proportionality constant. The intimate contact of physical-mixture tablets at each compaction force was calculated assuming the total intimate contact of the eutectic-mixture tablet with zero porosity was $A$ ($A$ is a constant that cancels), and the density of intimate contact was calculated by the ratio of total intimate contact (proportional to tablet tensile strength) over the tablet volume. The percentage of intimate contact covered by the thermal height compared to

![Graph](image)

Fig. 3. Particle size effect on eutectic formation
that of a eutectic-mixture tablet with zero porosity was then calculated for all eutectic-mixture tablets compacted at different forces. The results are shown in Table 2 indicating that the total intimate contact covered by the thermal height increased significantly with compaction forces.

The above analysis argues that the heat transfer and extent of intimate contact are responsible for the heat flow/eutectic formation differences between tablets. The proportionality between the intimate contact and the heat flow is what allows the amount of eutectic formed in the tablet to be quantified. The phenomenon was evaluated by comparing the DSC-monitored heat flow of eutectic-mixture tablets compacted at different forces and different particle sizes.

Independent verification of the phenomena described above was effected with several approaches to relate intimate contact to other tablet compact, experimental and material properties.

Figs. 3 and 4 illustrate the particle size and compaction force effect on the amount of eutectic formed in the tablets, respectively. The results show that the amount of eutectic formed in the tablets is qualitatively a function of intimate contact.

Fig. 5 shows the quantitative correlation between the amount of eutectic formed and estimated intimate contact area.
contact area, which supports that the amount of eutectic formed is a function of contact area.

Fig. 6 shows the correlation between the estimated intimate contact area and the tablet tensile strength. In 1984, Leuenberger and Jetzer [38] developed a relationship relating tensile strength to density:

\[ \sigma = \sigma_0 [1 - \exp(-\gamma p)] \]  

(11)

where \( \sigma_0 \) is the maximum tablet tensile strength at infinite high pressure, \( \gamma \) the compressibility, \( p \) the compaction force, \( \rho \) the relative density of the tablet, which is the ratio of apparent density over true density of powder compact.

This model has been tested successfully in many systems [38–41]. In the development of this model, the authors assumed that the tablet tensile strength is proportional to the number of bonding points \( N_b \):

\[ \sigma = \lambda N_b \]  

(12)
Corresponding to each bonding point, there is a small intimate contact area, $a$, which is assumed constant. The total intimate contact area can be expressed by the following formula:

$$ A = N_a a $$

(13)

From Eqs. (12) and (13), the relationship between the tablet tensile strength and total contact area can be expressed as

$$ \sigma = \frac{\lambda A}{a} $$

(14)

Since $\lambda$ and $a$ are constants, the tablet tensile strength is proportional to the total intimate contact area, a conclusion supported by the results shown in Fig. 6.

Fig. 7 shows that the amount of eutectic formed as a function of tablet tensile strength, showing that the amount of eutectic formed is a function of intimate contact area. Fig. 8a shows the correlation between the amount of eutectic formed with the tablet porosity. It has been established that the tablet tensile strength exponentially decays with the tablet porosity [42]; therefore, the intimate contact area should also exponentially decay with the tablet porosity based on the above argument.

From the literature cited [38]

$$ \sigma = \sigma_0 [1 - \exp(-0.4p_s)] $$

and from Eq. (14):
Fig. 8. (a) Percentage eutectics formed vs. tablet porosity; (b) the linearized plot of estimated contact area vs. tablet porosity; (c) a linearized plot of amount of eutectics formed vs. tablet porosity.

\[ \sigma = \frac{A}{a} \]

replacement of \( \sigma \) by \( A \), yields

\[ A = A_0 \{1 - \exp[\gamma_p(\varepsilon - 1)]\} \]

(15)

where \( A_0 = \sigma_0 A/\lambda \) and \( \varepsilon \) the tablet porosity.

Eq. (15) indicates that the intimate contact area indeed "decays" exponentially with tablet porosity. The amount of eutectic formed also decay exponentially with tablet porosity as shown in Fig. 8a. The amount of eutectic formed is therefore a function of intimate contact area, which is further supported by the results shown in Fig. 8b and c.

Finally, a potential negative effect of eutectic formation in tablets was investigated, i.e. reported decreased tablet hardness. Fig. 9 illustrates that there is no negative effect of eutectic on tablet hardness. This may be due to the more plastic properties of preformed eutectic [16–19], both compatibility and compressibility of the materials are improved and strong tablets are generated. Another explanation for the lack of effect on tablet hardness is that the melting temperatures of these eutectic systems are much higher than room temperature, and the compaction strain rate is very low. Both of these conditions would tend to preclude pressure-induced melting during tablet compression [43–48], often associated with poor physical properties in tablets. However, if a eutectic system has a very low eutectic temperature (<40 °C) and high-speed tabletting process is applied, then the temperature within the
die may be higher than the eutectic temperature, causing the tablet hardness or tensile strength to decrease and leading to sticking of the melted material to the punch or die.

4. Conclusions

The hypothesis presented for eutectic or contact melting is that it is an entropy-driven phenomenon. The criteria for eutectic formation are that the eutectic-forming compounds are in intimate contact in solid state and are mutually soluble in each other in the molten state. The intimate contact in the solid state guarantees the compounds will melt as if a single phase. Being mutually soluble in the liquid state insures the net entropy change is greater than the additive melting-entropy change from the individual compounds. This dictates that the eutectic melting temperature is lower than that of either pure eutectic-forming compound. The function of melting and solidification process typically used to form eutectic is only to facilitate the intimate contact between the eutectic-forming compounds. It has been shown here that compaction can also facilitate some degree of intimate contact between the eutectic-forming compounds, and compaction-induced intimate contact can be equivalent to the intimate contact induced by melting and solidification process. In order to quantify the amount of eutectic formed in the tablet, a DSC method was developed that distinguishes the preformed eutectic from thermally induced eutectic behavior in compacts. The amount of eutectic formed in the tablet compact is rationalized theoretically to be a function of the intimate contact area between the eutectic-forming materials. Experimentally, the amount of eutectic formed in the tablets increased with the intimate contact area, which is consistent with the hypothesis that the amount of eutectic formed in the tablets is a function of intimate contact area. It was also found that the amount of eutectic formed in the tablets is a function of compaction force. It was shown that different compaction forces can generate different intimate contact areas and, therefore, different amount of eutectic in the tablet. In this study, the intimate contact area between eutectic-forming materials in the tablets as a function of compaction force was also estimated and calculated. The correlations between the amount of eutectic formed and the estimated/calculated contact area support the concept that mechanically induced contact can cause eutectic behavior equivalent to that observed in eutectics formed by fusion. This study also showed that eutectic has no
negative effect on tablet hardness, which is explained due to the higher eutectic melting temperature of the model systems and slow strain rate used in tablet Carver Press.

The models and concepts developed to estimate the impact of the processing conditions on eutectic formation may serve as a guide during materials science and process development studies to anticipate any undesired eutectic formation.

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References