

# 1 Predictive Identification of Co-formers 2 in Co-amorphous Systems

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## 10 Abstract

11 This work aims to understand the properties of co-formers that form co-amorphous  
12 pharmaceutical materials and to predict co-amorphous system formation. A partial least  
13 square – discriminant analysis (PLS-DA) was performed using known co-amorphous systems  
14 described by 36 variables based on the properties of the co-former and the binding energy of  
15 the system. The PLS-DA investigated the propensity to form co-amorphous material of the  
16 active pharmaceutical ingredients: mebendazole, carvedilol, indomethacin, simvastatin,  
17 carbamazepine and furosemide in combination with 20 amino acid co-formers. The variables  
18 that were found to favour the propensity to form co-amorphous systems appear to be a

19 relatively large value for average molecular weight and the sum of the difference between  
20 hydrogen bond donors and hydrogen bond acceptors for both components, and a relatively  
21 small or negative value for excess enthalpy of mixing, excess enthalpy of hydrogen bonding  
22 and the difference in the Hansen parameter for hydrogen bonding of the coformer and the  
23 active pharmaceutical ingredient (API). To test the predictive power of this model, 29  
24 potential co-formers were used to form either co-amorphous or crystalline two-component  
25 materials with mebendazole. Of these 29 two-component systems, the co-amorphous nature  
26 of a total of 26 materials was correctly predicted by the model, giving a predictive hit rate of  
27 90 %.

## 28 **Keywords**

29 Co-amorphous

30 Partial least squares discriminant analysis

31 Amino acids

32 Multi-variate analysis

33 Molecular descriptors

## 34 **1. Introduction**

35 A large proportion of newly discovered active pharmaceutical ingredients (APIs) display  
36 poor solubility in the gastrointestinal fluids, which is likely to decrease their bioavailability  
37 (Di et al., 2012; Kalepu and Nekkanti, 2015; Khadka et al., 2014; Savjani et al., 2012). To

38 improve the aqueous solubility of APIs, different formulation methods have been designed  
39 including amorphous forms, which have no long-range crystallographic order and higher  
40 internal energy compared with their respective crystalline forms (Berry and Steed, 2017;  
41 Healy et al., 2017; Khodadadi and Meesters, 2018; Williams et al., 2013). However, pure  
42 amorphous APIs are often physically unstable and can crystallise as a result of increased  
43 molecular mobility, especially when stored above their glass transition temperature or in  
44 humid environments (Kissi et al., 2018; Rams-Baron et al., 2018; Sun et al., 2012). Methods  
45 to improve the stability of amorphous APIs include the formation of amorphous solid  
46 dispersions and co-amorphous (COAM) materials (Karagianni et al., 2018; Ma and Williams,  
47 2019; Van Den Mooter, 2012; Wu et al., 2018).

48 Amorphous solid dispersions are formed by (molecularly) dispersing an API in a (usually  
49 amorphous) polymer such as polyvinylpyrrolidone and cellulose based polymers, which act  
50 as an inactive stabilizer (Chavan et al., 2019; Nielsen et al., 2015; Vasconcelos et al., 2016).  
51 Stabilization (even above the solubility limit of the API in the polymer) is caused by the  
52 polymer increasing the glass transition temperature and forming intermolecular interactions,  
53 which in turn result in reduced molecular mobility (Baghel et al., 2016; Frank and Matzger,  
54 2018; Medarević et al., 2019). The main challenges with using amorphous solid dispersions  
55 are their often high hygroscopicity (causing increased molecular mobility of the API), and the  
56 usually large mass ratios of polymer to API (causing downstream formulation problems when  
57 high API dosages are required) (Marsac et al., 2008; Rumondor et al., 2009; Tian et al.,  
58 2015).

59 COAM systems are formed by mixing an API with a low molecular weight compound called  
60 a co-former, which is usually inactive but could also be another API (Gao et al., 2013;

61 Newman et al., 2018; Shayanfar and Jouyban, 2013; Shi et al., 2019). The ratio of API to co-  
62 former can be relatively high which helps in the formation of high API dosage tablets (Jensen  
63 et al., 2016b; Wang et al., 2019). COAM systems are similar to co-crystals with them both  
64 containing two components, usually with one API and one co-former (Karimi-Jafari et al.,  
65 2018). The difference between co-crystals and COAM systems is that co-crystals are based  
66 on a repeating three dimensional crystal lattice whereas COAM systems have no repeating  
67 units and an amorphous structure (Newman et al., 2018). The physical stability of COAM  
68 systems is usually higher than that of pure amorphous materials and COAM systems often  
69 have improved dissolution characteristics compared to pure amorphous APIs (Löbmann et  
70 al., 2013a; Löbmann et al., 2012b). COAM systems are stabilised, for example, by the  
71 formation of hydrogen bonds,  $\pi$ - $\pi$  stacking and ionic bonds between the two compounds, as  
72 shown by infrared spectroscopy (Löbmann et al., 2012a; Löbmann et al., 2013b). Methods to  
73 produce COAM systems include co-melting, solvent evaporation and mechanochemistry  
74 (Chavan et al., 2016). Co-melting involves melting the components followed by rapid cooling  
75 to avoid nucleation and recrystallization (Hoppu et al., 2009; Knapik et al., 2015; Teja et al.,  
76 2015). A key challenge in co-melting is that some of the APIs or co-formers may thermally  
77 degrade if kept at high temperatures for too long (Fan et al., 2019; Goodwin et al., 2018).  
78 Solvent evaporation involves dissolving the two components into a solvent or solvent mixture  
79 followed by rapidly evaporating the solvent to prevent nucleation and recrystallization  
80 (Ahmed Mahmoud Abdelhaleem et al., 2015; Yamamura et al., 2002). However, finding a  
81 solvent or solvent mixture which can dissolve both the co-former and the API without one  
82 component crystallising prematurely is a challenge (Mishra et al., 2018). Mechanochemistry  
83 involves using mechanical stress to reduce crystallinity and induce intimate mixing (Chieng  
84 et al., 2009; Hu et al., 2014). The conventional method used for mechanochemistry is milling.  
85 A low temperature is preferred during milling to promote the formation of an amorphous

86 material by keeping the mixture below the glass transition temperature of the amorphous  
87 system (Blaabjerg et al., 2017).

88 The possible co-formers used to form COAM systems are numerous but there is no clear  
89 method of predicting whether a certain co-former will form a COAM system with a specific  
90 API. Mizoguchi et al. (2019) linked the formation of COAM systems to the mixing enthalpy  
91 and the difference in lipophilicity ( $\Delta \log P$ ). This work used COSMOquick, a computational  
92 program which uses the Conductor like Screening Model for Real Solvents (COSMO-RS)  
93 method to derive charge density surfaces which describe each molecule and can be used to  
94 calculate interaction energies with other components (Klamt, 2018). COSMOquick can be  
95 used to screen for potential co-crystals and provides values for the Gibbs energy of mixing  
96 ( $\Delta G_{mix}$ ), which determines whether mixing between potential co-crystal formers at constant  
97 temperature and pressure is spontaneous, as well as the excess enthalpy of mixing, which is  
98 the enthalpy released or absorbed upon mixing (Loschen and Klamt, 2015). Ueda et al.  
99 (2016) performed a multivariate analysis of physiochemical variables of co-formers and  
100 concluded that a range of these variables (crystallisation tendency, glass transition  
101 temperature and molecular flexibility) contributed to COAM formation; however, this study  
102 only used one API (naproxen) and a small number of co-formers (felbinac, flufenamic acid,  
103 loxoprofen, ketoprofen, indomethacin, aceclofenac, indoprofen).

104 Meng-Lund et al. (2018) used a range of molecular descriptors to produce a PLS-DA model  
105 to predict the likelihood of success of co-amorphisation between amino acids and an API.  
106 The model used a dataset formed from 6 APIs and 20 amino acids from Kasten et al. (2016).  
107 The variables used include physical properties, Hückel theory descriptors, subdivided surface  
108 areas, atom counts, bond counts, pharmacophore feature descriptors, partial charge

109 descriptors, surface area, volume and shape descriptors. To test the model, one of the six  
110 APIs was left out of the model and used as a validation set. Out of the 20 systems in the  
111 validation set, 19 were correctly assigned. The model showed that polar amino acids were  
112 less likely to form COAM systems and non-polar side chains were more likely to form  
113 COAM systems. However, this model only investigated amino acid co-formers.

114 The current study aims to develop a method to improve the selection of co-formers to  
115 formulate COAM systems. The previously reported COAM screen by Kasten et al. (2016)  
116 was used to understand which variables affect the formation of COAM systems. Variables  
117 used to describe the systems were obtained using COSMOquick to calculate properties that  
118 describe the two-component systems and Pubchem to source physico-chemical variables to  
119 describe the co-formers. The 36 variables from COSMOquick and Pubchem were used to  
120 develop a partial least squares-discriminant analysis (PLS-DA) prediction method to identify  
121 which co-formers are likely to form COAM systems.

## 122 2. Materials and Methods

### 123 2.1 Materials

124 Succinic acid was purchased from Avocado Research Chemicals (Heysham, UK). Glycine  
125 (GLY) was purchased from BDH Chemicals Limited (Hull, UK). Carvedilol (CAR) was  
126 obtained from Cilpa Ltd. (Mumbai, India). L-alanine (ALA), flurbiprofen, furosemide (FUR),  
127 L-isoleucine (ILE), L-leucine (LEU), L-lysine (LYS), mebendazole (MEB) and L-tyrosine  
128 (TYR) were purchased from Flourochem (Hadfield, UK). Indomethacin (IND) was purchased  
129 from Hawkins Pharmaceutical group (Minnesota, USA). Urea was purchased from Lancaster  
130 Synthesis (Lancaster, UK). Maleic acid was purchased from M&B Chemicals (London, UK).  
131 3-aminobenzoic acid, 4-aminobenzoic acid, 4-aminosalicylic acid, 5-aminosalicylic acid, L-

132 arginine (ARG), ascorbic acid, L-asparagine (ASN), L-aspartic acid (ASP), 4,4'-bipyridine,  
133 caffeine, catechol, L-cysteine (CYS), 2,4 dihydroxybenzoic acid, 3,5-dihydroxybenzoic acid,  
134 fumaric acid, gallic acid, L-glutamine (GLN), L-glutamic acid (GLU), glycolic acid, L-  
135 histidine (HIS), imidazole, isonicotinamide, ketoprofen, L-methionine (MET), nicotinamide,  
136 oxalic acid, L-phenylalanine (PHE), phenazine, piperazine, piracetam, L-proline (PRO),  
137 pyrogallol, salicylic acid, L-serine (SER), tartaric acid, theophylline, L-threonine (THR), L-  
138 tryptophan (TRP) and L-valine (VAL) were purchased from Sigma Aldrich (Missouri, USA).

## 139 2.2 Mebendazole co-former screening

140 Ball milling was used to screen for potential COAM systems. A 1:1 molar ratio of API and  
141 co-former (total 100 mg), was placed into a 5 mL milling jar and premixed at a frequency of  
142 30 Hz for 5 minutes without a mixing ball to homogenize the material. A stainless-steel ball  
143 with a diameter of 5 mm was added and the mixture was milled at 30 Hz for 60 min. The  
144 milling time of 60 min was selected due to it matching the original study the model was  
145 produced from (Kasten et al., 2016). Milling was performed using a Mixer mill MM200,  
146 vibrational ball mill, from Retsch GmbH & Co. (Haan, Germany). The mixtures were  
147 analysed by XRPD to assess crystallinity (see below).

## 148 2.3 Film casting mebendazole – gallic acid

149 A 1:1 molar ratio of mebendazole to gallic acid (63.5 mg: 36.5 mg), was dissolved in a  
150 minimum amount of formic acid (approx. 10 mL). The solution was cast onto a petri dish and  
151 the formic acid was left to evaporate. Once the mixture was dry, it was analysed by XRPD  
152 (see below).

## 153 2.4 X-ray powder diffraction (XRPD)

154 XRPD measurements were performed using a Bruker D8 X-ray diffractometer (Billerica,  
155 Massachusetts) with CuK $\alpha$  radiation (1.54187 Å), and acceleration voltage and current of 40  
156 kV and 40 mA, respectively. The samples were scanned in reflectance mode between 2° and  
157 35° 2 $\theta$  with a scan rate of 0.067335° 2 $\theta$ /s and a step size of 0.026°.

## 158 2.5 COSMOquick calculations

159 COSMOquick version 1.7 (COSMOlogic GmbH & Co. KG, Leverkusen, Germany) was used  
160 to calculate the Gibbs energy of mixing ( $\Delta G_{mix}$ ), excess enthalpy of mixing ( $\Delta H_{mix}$ ) and excess  
161 enthalpy of hydrogen bonding ( $\Delta H_{hb}$ ), of the two-component system. For each component the  
162 following variables were calculated and displayed in Table 1: the number of *Rotatable bonds*;  
163 *rotbsdmod*, a general molecular flexibility parameter; *M2*, *M3*, *M4*, *M5* and *M6*, the different  
164 order sigma moments; the dielectric energy; the molecular COSMO volume; *Macc1*, *Macc2*,  
165 *Macc3* and *Macc4*, the different order sigma acceptor moments; *Mdon1*, *Mdon2*, *Mdon3* and  
166 *Mdon4*, the different order sigma donor moments; *avratio*, the surface-volume ratio based on  
167 COSMO; *ovality*, the ratio of the molecular COSMO area to the area of a sphere with the  
168 same volume as the molecule;  $\mu$ , the pseudo chemical potential of the pure solute;  $\delta d$ , the  
169 Hansen parameter for dispersion;  $\delta p$ , the Hansen parameter for permanent dipole-dipole  
170 interaction;  $\delta h$ , the Hansen parameter for hydrogen bonding. The difference between the API  
171 and co-former values were calculated and used as the variables in the PLS-DA.

172 Table 1: The definitions of all the variables used to find the PLS-DA model.

Variable	Definition
$\Delta G_{mix}$	Gibbs energy of mixing.



$\Delta H_{hb}$	Excess enthalpy of hydrogen bonding.
$\Delta H_{mix}$	Excess enthalpy of mixing.
$\Delta \log P$	The difference between the log of the octanol/water partition coefficient of the API and the co-former
<i>AV. log P</i>	The average value of the log of the octanol/water partition coefficient of the API and the co-former
$\Sigma HBC_{self}$	The sum of the difference of hydrogen bond donors to hydrogen bond acceptors for the individual components, for both the API and co-former. To represent the hydrogen bonding present in the individual components.
$\Sigma HBC_{API-COF}$	The sum of the difference of hydrogen bond donors to hydrogen bond acceptors for the mixed components, for both the API and co-former. To represent the hydrogen bonding between the two components.
<i>AV. TM</i>	The average melting point of the two components.
$\Delta TM$	The difference of the melting point of the co-former and the API.
<i>AV. MW</i>	The average molecular weight of the API and the co-former.
$\Delta MW$	The difference of the molecular weights of the API and the co-former.
<i>AV. TPSA</i>	The average topological polar surface area of the API and the co-former.
$\Delta TPSA$	The difference between the topological polar surface area of the API and the co-former.
<i><math>\Delta rotatable bonds</math></i>	The difference between the number of rotatable bonds of the co-former and the API.
<i><math>\Delta rotbsdmod</math></i>	The difference between the general molecular flexibility parameter of the co-former and the API.
$\Delta M2$	The difference between the second order sigma moments of the co-former and the API.
$\Delta M3$	The difference between the third order sigma moments of the co-former and the API.
$\Delta M4$	The difference between the fourth order sigma moments of the co-former and the API.
$\Delta M5$	The difference between the fifth order sigma moments of the co-former and the API.

$\Delta M6$	The difference between the sixth order sigma moments of the co-former and the API.
$\Delta$ Dielectric energy	The difference between the number of rotatable bonds of the co-former and the API.
$\Delta$ volume	The difference between the dielectric energy of the co-former and the API.
$\Delta M_{acc1}$	The difference between the first order sigma acceptor moments of the co-former and the API.
$\Delta M_{acc2}$	The difference between the second order sigma acceptor moments of the co-former and the API.
$\Delta M_{acc3}$	The difference between the third order sigma acceptor moments of the co-former and the API.
$\Delta M_{acc4}$	The difference between the fourth order sigma acceptor moments of the co-former and the API.
$\Delta M_{don1}$	The difference between the first order sigma donor moments of the co-former and the API.
$\Delta M_{don2}$	The difference between the second order sigma donor moments of the co-former and the API.
$\Delta M_{don3}$	The difference between the third order sigma donor moments of the co-former and the API.
$\Delta M_{don4}$	The difference between the fourth order sigma donor moments of the co-former and the API.
$\Delta$ avratio	The difference between the surface-volume ratio based on COSMO of the co-former and the API.
$\Delta$ ovality	The difference between co-former and the API of the ratio of the molecular COSMO area to the area of a sphere with the same volume as the molecule.
$\Delta\mu$	The difference between the pseudo chemical potential of the pure solute of the API and the co-former.
$\Delta(\delta_d)$	The difference between the Hansen parameter for dispersion in MPa <sup>0.5</sup> of the API and the co-former.
$\Delta(\delta_p)$	The difference between the Hansen parameter for permanent dipole-dipole interactions in MPa <sup>0.5</sup> of the API and the co-former.

$\Delta(\delta h)$

The difference between the Hansen parameter for hydrogen bonding in  $\text{MPa}^{0.5}$  of the API and the co-former.

173

## 174 2. 6 Partial least squares – discriminant analysis

175 Partial least squares – discriminant analysis (PLS-DA) was performed using SIMCA V.16  
176 (Umetrics, Umeå, Sweden) to plot 36 variables for each combination of API and co-former  
177 (Brereton and Lloyd, 2014; Sadeghi-Bazargani et al., 2010). The 36 different variables  
178 plotted were  $\Delta G_{mix}$ ,  $\Delta H_{mix}$ ,  $\Delta H_{hb}$ ,  $\Delta \log P$ ,  $AV.\log P$ ,  $\Sigma HBC_{self}$ ,  $\Sigma HBC_{API-COF}$ ,  $AV.TM$ ,  $\Delta TM$ ,  
179  $AV.MW$ ,  $\Delta MW$ ,  $AV.TPSA$ ,  $\Delta TPSA$ ,  $\Delta Rotatable\ bonds$ ,  $\Delta rotbsdmod$ ,  $\Delta M2$ ,  $\Delta M3$ ,  $\Delta M4$ ,  $\Delta M5$ ,  
180  $\Delta M6$ ,  $\Delta Dielectric\ energy$ ,  $\Delta volume$ ,  $\Delta Macc1$ ,  $\Delta Macc2$ ,  $\Delta Macc3$ ,  $\Delta Macc4$ ,  $\Delta Mdon1$ ,  $\Delta Mdon2$ ,  
181  $\Delta Mdon3$ ,  $\Delta Mdon4$ ,  $\Delta avratio$ ,  $\Delta ovality$ ,  $\Delta \mu$ ,  $\Delta(\delta d)$ ,  $\Delta(\delta p)$  and  $\Delta(\delta h)$  (Table 1). The data was  
182 scaled using unit variance. Each system was assigned as either COAM or not COAM (any  
183 crystalline material present) as determined by Kasten et al. (2016) based on analysing the  
184 mixture by XRPD after ball milling for 60 minutes. The PLS-DA was fitted using two latent  
185 variables and all 36 variables. The quality of the model was assessed using an internal cross-  
186 validation procedure which involved leaving one out using seven cross-validation groups.

187 The prediction ability of the model was assessed by checking the predicted values of COAM  
188 formation of the 120 API-amino acid dataset and comparing the values with the experimental  
189 results. The prediction gives a predicted numerical value with a value closer to one being  
190 COAM and a value closer to zero being not COAM. The prediction of the model was also  
191 assessed by using a dataset of 29 co-formers paired with mebendazole. The predicted values  
192 for the mebendazole-co-former dataset were compared with the experimental values to  
193 determine the prediction ability.

194 Variable selection was used to reduce the number of variables from 36 to 7 based on  
195 optimising the number of correctly predicted samples for the API-amino acid dataset. The  
196 final model was produced in JMP Pro 15 to view the equation used to assign the COAM  
197 value (Equation 1) (JMP, Version Pro 15. 1989-2020).

198 Predicted COAM value

$$\begin{aligned} 199 &= (-0.123 \times \Delta H_{hb}) + (-0.136 \times \Delta H_{mix}) + (-0.00350 \times \Sigma HBC_{self}) \\ 200 &+ (0.00297 \times AV.MW) + (-0.00176 \times \Delta TPSA) + (0.0105 \times \Delta \mu) \\ 201 &+ (-0.0441 \times \Delta(\delta h)) + (-0.204) \end{aligned}$$

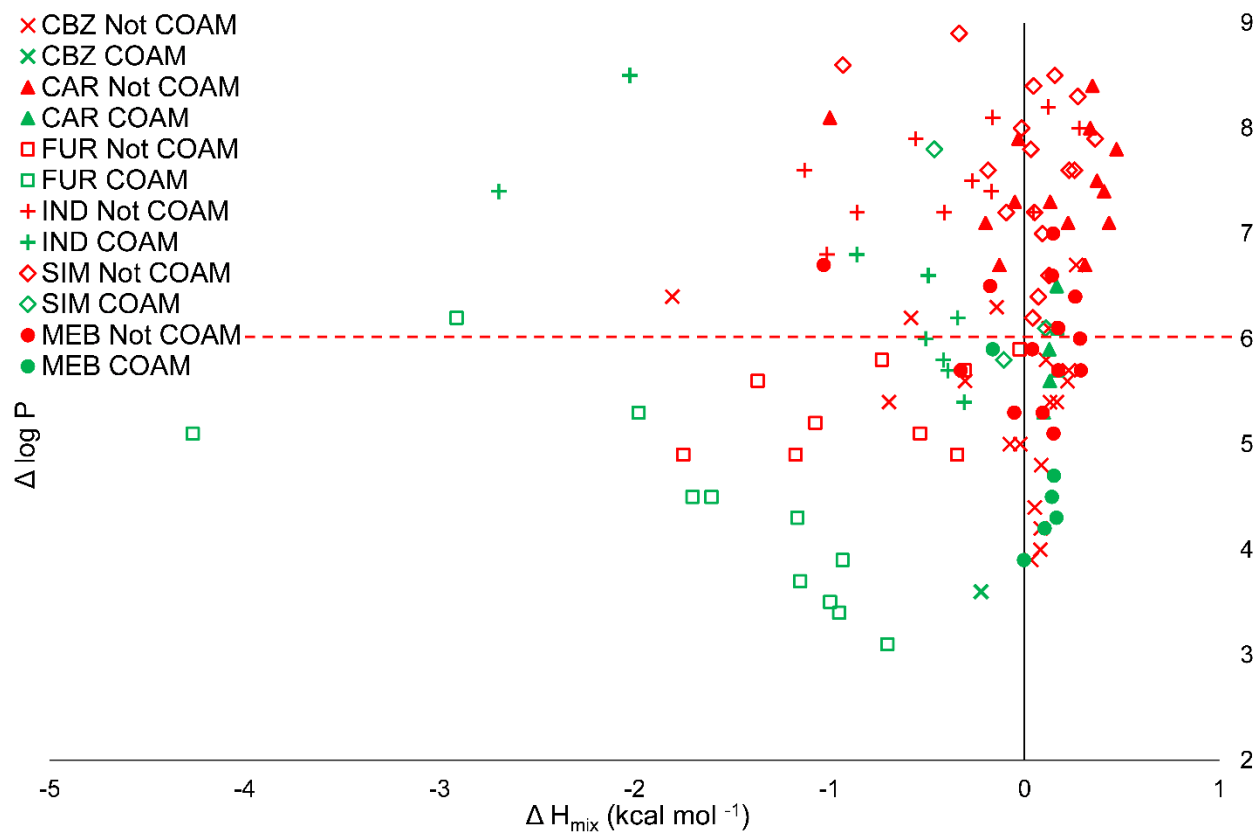
202 Equation 1: The equation to describe the relation of the seven key variables to the predicted  
203 COAM value. All numbers have been rounded to 3 significant figures. A value closer to one  
204 indicates the system should be COAM and a value closer to zero indicates it should not be  
205 COAM.

## 206 3. Results and Discussion

### 207 3.1 Correlation of $\Delta H_{mix}$ and $\Delta \log P$ with co-amorphisation

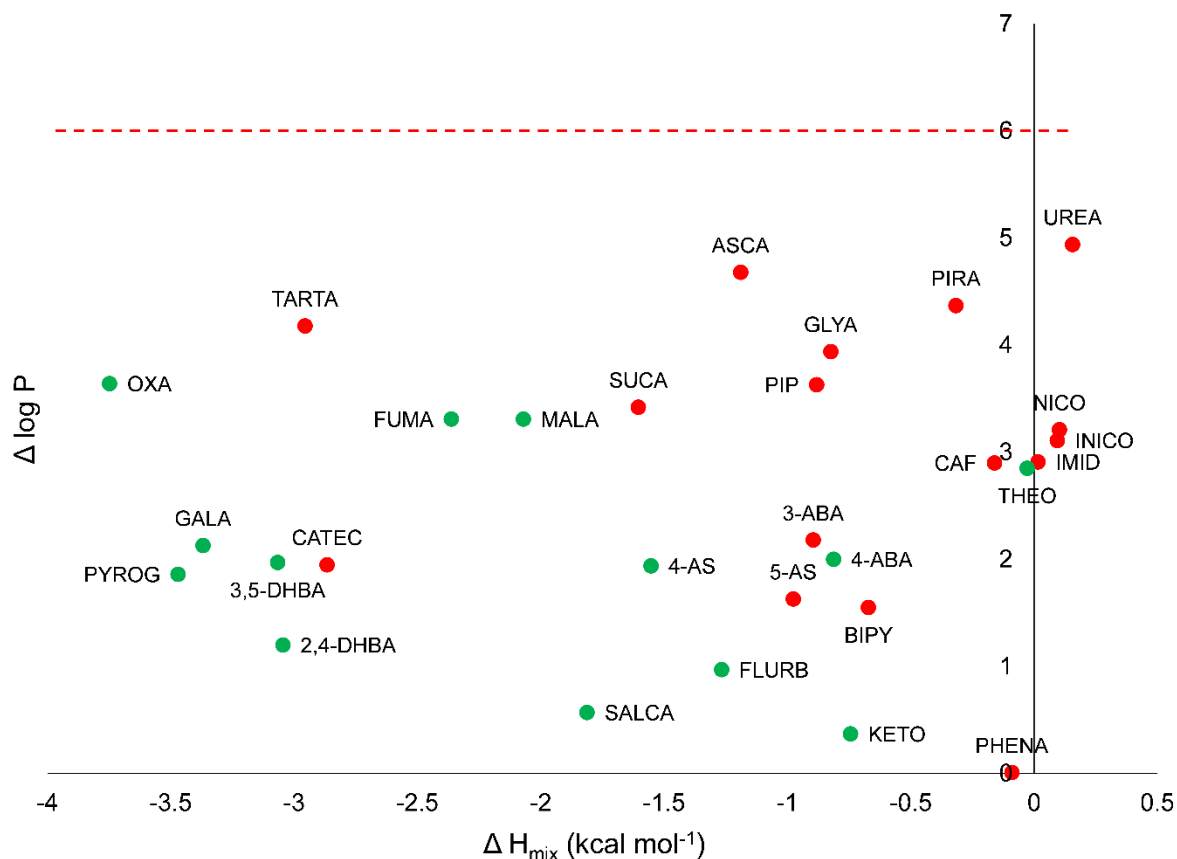
208 The COAM systems used in this screen were experimentally identified by Kasten et al.  
209 (2016) and the responses listed in supplementary materials Table S1 indicate which systems  
210 formed COAM materials after 60 min of ball milling. The APIs used were carvedilol (CAR),  
211 furosemide (FUR), indomethacin (IND) simvastatin (SIM), carbamazepine (CBZ) and  
212 mebendazole (MEB). Previous research on theoretical descriptors for the prediction of the  
213 formation of a COAM system identified two indicators ( $\Delta H_{mix}$  and  $\Delta \log P$ ) using a  
214 combination of APIs with other APIs or sugars to screen for COAM systems using  
215 differential scanning calorimetry (Mizoguchi et al., 2019). The  $\Delta H_{mix}$  was calculated using

216 COSMOquick and the  $\Delta \log P$  was sourced from Pubchem; it was found that COAM systems  
217 form with a  $\Delta \log P$  below 6 and a negative  $\Delta H_{mix}$  and a clear divide between the COAM  
218 systems and the crystalline systems was observed. When the  $\Delta H_{mix}$  and  $\Delta \log P$  for the  
219 API/amino acids systems tested by Kasten et al. (2016) were plotted against each other the  
220 same clear divide was not evident (Figure 1). The data indicates that COAM materials tend to  
221 form in systems with a lower value of  $\Delta \log P$  and a negative  $\Delta H_{mix}$ . However, many  
222 combinations break these trends; a few COAM systems form with a  $\Delta \log P$  above 6 and  
223 many systems with a  $\Delta \log P$  below 6 remain crystalline. Furthermore, COAM systems form  
224 with positive values of  $\Delta H_{mix}$ . To further assess the prediction ability for COAM formation of  
225 the two variables a range of 29 different co-formers (supplementary materials Table S2) were  
226 paired with mebendazole and analysed using the two variables. The 29 different co-formers  
227 were then ball milled with mebendazole to determine whether they formed COAM mixtures  
228 and the results were compared with the predicted trends. Figure 2 shows that all the systems  
229 including COAM and not COAM have a  $\Delta \log P$  below 6 suggesting  $\Delta \log P$  is not a good  
230 predictor of COAM material formation. Figure 2 also shows that the majority of the 29  
231 systems have negative values of  $\Delta H_{mix}$  but not all the systems are COAM and there is no clear  
232 divide between COAM and not COAM systems. Using these two variables to predict the  
233 formation of co-amorphous API-co-former systems was insufficient suggesting that more  
234 variables were required to predict the propensity to form COAM systems.



235

236 Figure 1. Relationship between the formation of COAM systems from Kasten et al. (2016),  
 237  $\Delta H_{\text{mix}}$  and  $\Delta \log P$ . Green markers indicate COAM systems were formed and red markers  
 238 indicate not COAM systems. The red dotted line is the expected boundary line between  
 239 COAM and not COAM systems (Mizoguchi et al., 2019).



241

242 Figure 2. Relationship between the formation of COAM systems of mebendazole with 29 co-  
 243 formers,  $\Delta H_{\text{mix}}$  and  $\Delta \log P$ . Green markers indicate COAM systems were formed and red  
 244 markers indicate not COAM systems were formed. The red dotted line is the expected  
 245 boundary line between COAM and not COAM systems based on previous research by  
 246 Mizoguchi et al. (2019). Abbreviations of the coformers are as follows: 2,4-dihydroxybenzoic  
 247 acid (2,4-DHBA), 3,5-dihydroxybenzoic acid (3,5-DHBA), 3-aminobenzoic acid (3-ABA),  
 248 4,4'-bipyridine (BIPY), 4-aminobenzoic (4-ABA), 4-aminosalicylic acid (4-AS), 5-  
 249 aminosalicylic acid (5-AS), ascorbic acid (ASCA), caffeine (CAF), catechol (CATEC),  
 250 flurbiprofen (FLURB), fumaric acid (FUMA), gallic acid (GALA), glycolic acid (GLYA),  
 251 imidazole (IMID), isonicotinamide (INICO), ketoprofen (KETO), maleic acid (MALA),

252 nicotinamide (NICO), oxalic acid (OXA), phenazine (PHENA), piperazine (PIP), piracetam  
253 (PIRA), pyrogallol (PYROG), salicylic acid (SALCA), succinic acid (SUCA), tartaric acid  
254 (TARTA), theophylline (THEO), and urea (UREA).

### 255 3.2 PLS-DA

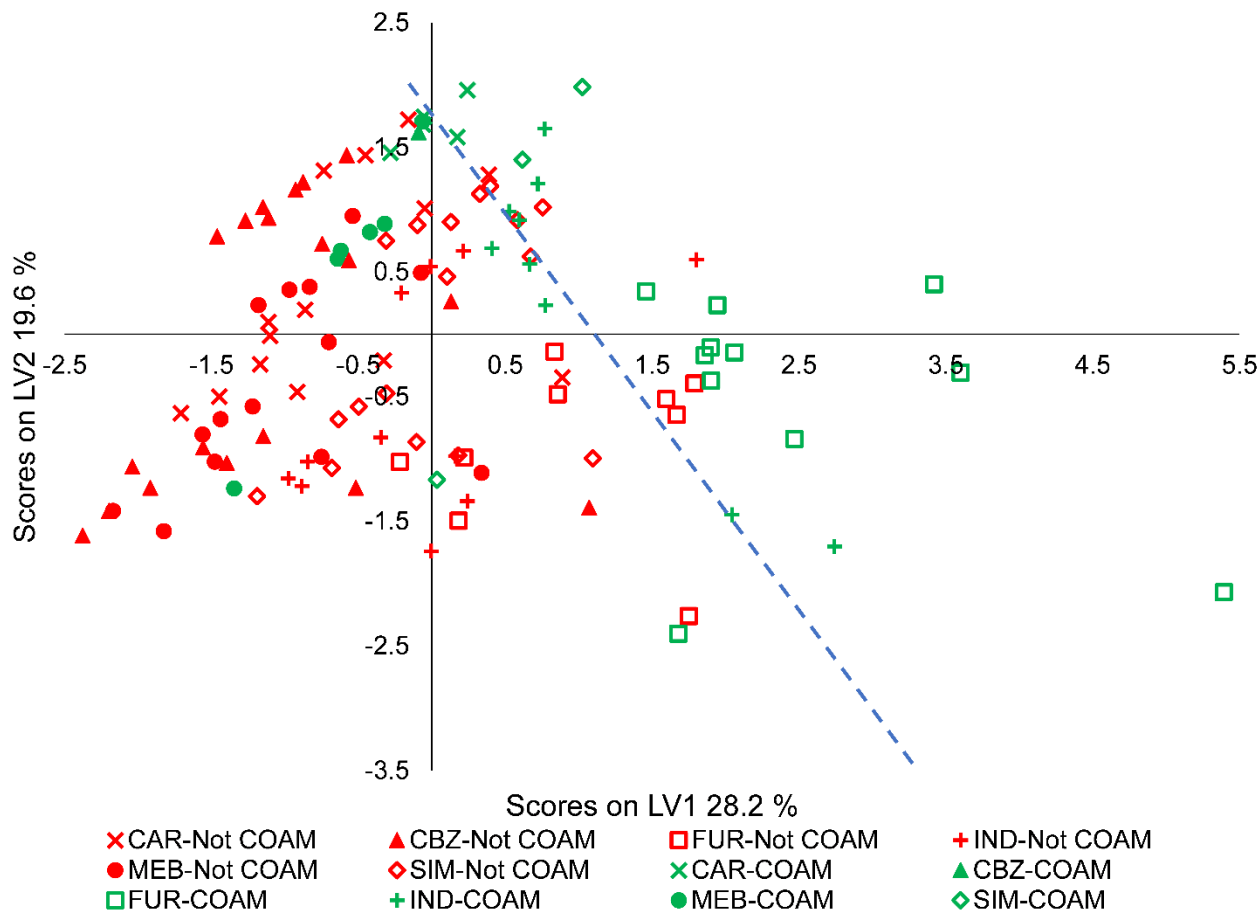
256 To improve the prediction of COAM systems, 34 additional variables were selected to  
257 describe the properties and interactions of the two components and combined with  $\Delta H_{mix}$  and  
258  $\Delta \log P$ . These 36 variables (Table 1) were used to produce a PLS-DA model to understand  
259 which variables affect COAM system formation. Variable selection was then used to reduce  
260 the initial 36 variables to seven key variables. Variable selection was performed by removing  
261 variables one after the other and checking the effect on the prediction ability of the model for  
262 the API amino acid data set; if the variable had no effect it was removed and if the prediction  
263 ability was reduced it was retained. The variables selected describe differences between the  
264 API and co-former allowing the model to be applied to systems where the API and co-former  
265 cannot be easily defined, such as systems formed from two APIs. The final PLS-DA model  
266 includes the seven descriptors (Table 1):  $\Delta H_{hb}$ ,  $\Delta H_{mix}$ ,  $\Sigma HBC_{self}$ ,  $AV.MW$ ,  $\Delta TPSA$ ,  $\Delta \mu$  and  
267  $\Delta(\delta h)$ . The goodness of fit is  $R^2Y = 33.0\%$ ,  $R^2X = 47.8\%$  and the goodness of prediction is  
268  $Q^2 = 29.0\%$  based on two latent variables. Latent variables are variables which cannot be  
269 measured and are inferred from mathematical models.

### 270 3.3 Model

271 The score scatter plot of the PLS-DA model for the API amino acid systems (Figure 3) shows  
272 a division between COAM and not COAM systems with COAM systems appearing more in  
273 the top right quadrant. The dotted line in Figure 3 shows the predicted separation for  
274 visualization purposes between the COAM and not COAM systems. The not COAM systems

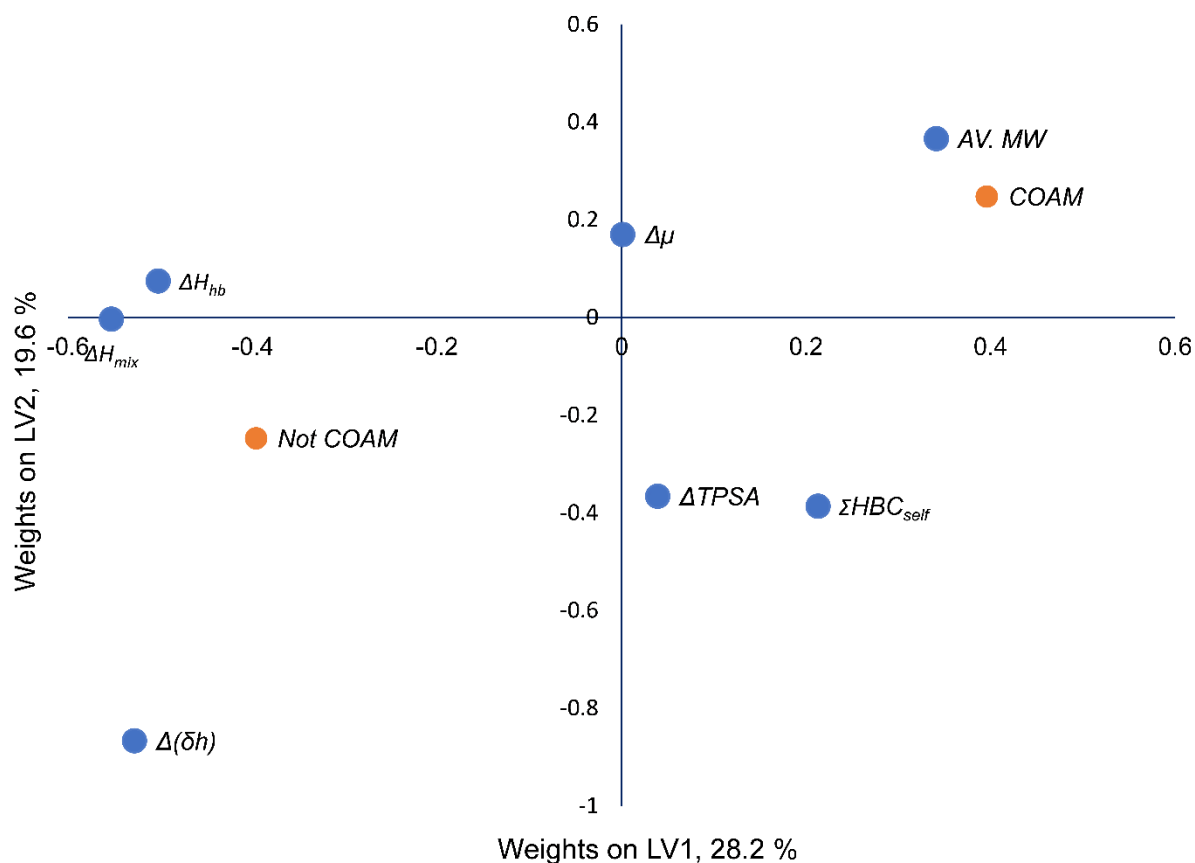


275 occur on the left of the plot and mainly in the bottom left quadrant. Equation 1 shows the  
276 relationship of each variable to the overall prediction.



278 Figure 3. PLS-DA score scatter plot of latent variables (LV) 1 and 2. The red markers  
279 indicate not COAM systems and the green markers show COAM systems. The APIs are  
280 displayed with different markers with carvedilol (CAR) displayed as an X, carbamazepine  
281 (CBZ) as a triangle, furoseimide (FUR) as a hollow square, indomethacin (IND) as a cross,  
282 mebendazole (MEB) as a circle and simvastatin (SIM) as a hollow diamond. The dashed blue  
283 line shows the predicted separation between COAM and Not COAM systems for  
284 visualization purposes.

285 The loading plot (Figure 4) shows how each variable is related to COAM formation. The  
286 variables closest to the COAM response are linked to COAM formation and the variables  
287 closest to the not COAM response are linked to not COAM formation. The two variables  
288  $\Delta TPSA$  and  $\Delta\mu$  are located roughly in the middle between the COAM and not COAM point  
289 and therefore, do not appear to influence the COAM formation to a strong degree, however,  
290 when they are removed the prediction ability of the model is reduced. The variables related to  
291 COAM formation, therefore, appear to be a relatively large value of  $AV.MW$  and  $\Sigma HBC_{self}$ ,  
292 and a relatively small or negative value of  $\Delta H_{mix}$ ,  $\Delta H_{hb}$ , and  $\Delta(\delta h)$ . A large  $AV.MW$  seems to  
293 correlate with COAM formation possibly due to slower diffusion which would inhibit  
294 recrystallization. A large value of  $\Sigma HBC_{self}$  correlates with COAM formation, which is  
295 expected due to molecules that do not have a similar number of hydrogen bond donor atoms  
296 and hydrogen bond acceptor atoms are unlikely to form as strong crystal structures and may  
297 be more likely to interact with the other component (Corpinot and Bučar, 2019). A negative  
298 value of  $\Delta H_{mix}$  favours COAM formation, as expected since negative values indicate that the  
299 mixed system has a lower free energy state due to stronger attractive forces between the  
300 mixed molecules compared to the individual component interaction. A negative value  $\Delta H_{hb}$   
301 also favours COAM formation which is due to stronger hydrogen bonding between the mixed  
302 molecules when compared with the individual components. A small  $\Delta(\delta h)$  seems to favour  
303 COAM formation suggesting molecules with similar hydrogen-bonding potential are more  
304 likely to interact and stabilise a COAM system.



305

306 Figure 4. PLS-DA loading weights scatter plot of the latent variables (LV) 1 and 2. The  
 307 responses are shown with orange circles and the variables with blue circles. The responses  
 308 show how the two groups are related to the variables.

309 The score plot (Figure 3) shows the two clusters of COAM and not COAM samples overlap  
 310 to some degree. Overall, the misclassification table (which shows if the prediction matches  
 311 the experimental result) (Table 2) of the 120 API – amino acid dataset shows that 81 % of the  
 312 data points are correctly placed, suggesting the PLS-DA model is successful at modelling the  
 313 amino acid data. Out of the 23 misplaced systems, 18 are close to the separation line and five  
 314 are very far from the separation line, these five systems are MEB with LYS, LEU and ILE,  
 315 SIM with LYS, and IND with HIS. The MEB with LYS, LEU and ILE and SIM with LYS  
 316 systems were shown by Kasten et al. (2019) to have a low stability and underwent

317 crystallisation within a few weeks suggesting the model helps identify stable COAM systems.  
 318 The fifth system furthest from the separation line was IND with HIS which was not COAM  
 319 by milling, however a study by Jensen et al. (2016a) showed IND with HIS system was co-  
 320 amorphous when spray dried, this suggest the model could be valid for other co-amorphous  
 321 production methods.

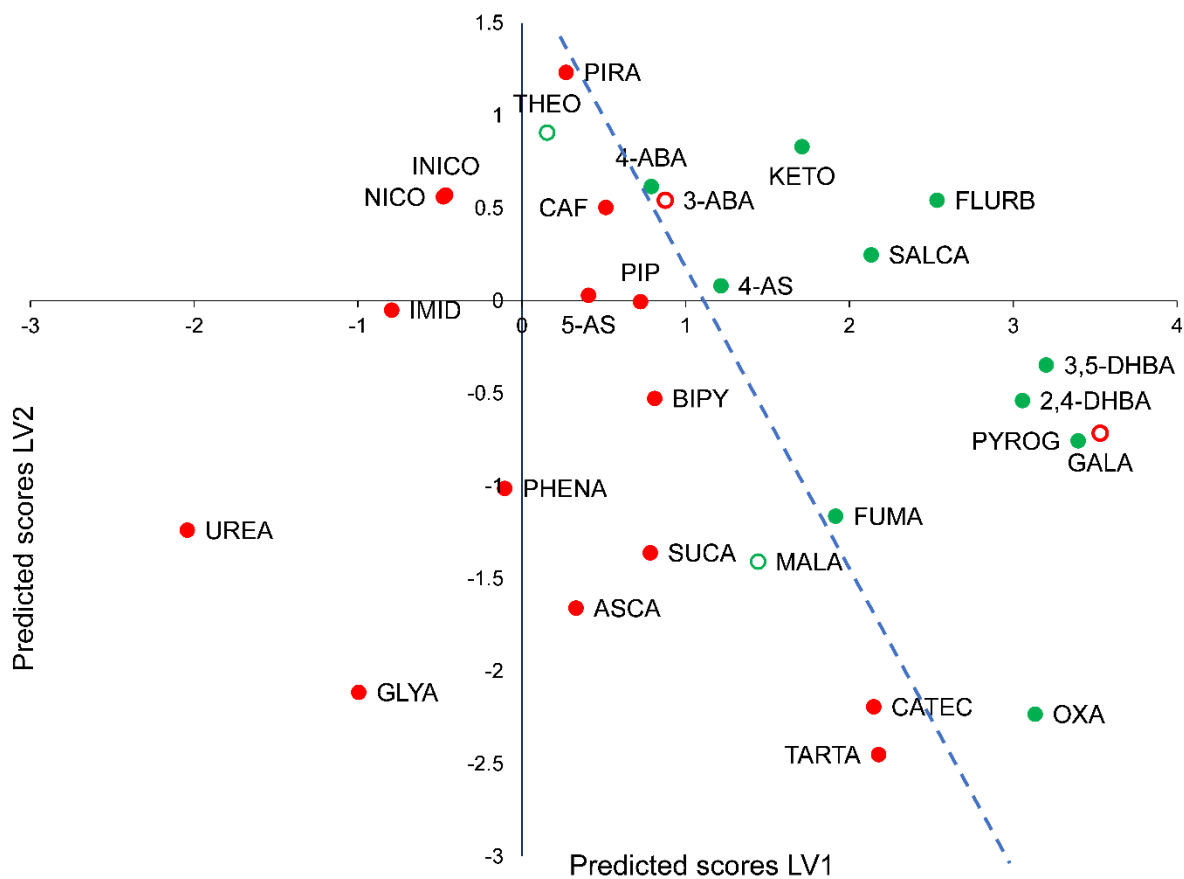
322 Table 2. Misclassification table showing the percentage of correctly assigned observations of  
 323 the 120 API-amino acid combinations. Fisher's probability of  $4.7 \times 10^{-8}$ .

Model	Members	Correct	Not COAM	COAM
Not COAM	84	90.48%	76	8
COAM	36	58.33%	15	21
Total	120	80.83%	91	29

### 324 3.5 Prediction of co-amorphous formation by mebendazole with 29 co-formers

325 To test the applicability of the PLS-DA model (Figure 3, Figure 4) to other non-amino acid  
 326 systems, a new dataset of 29 different co-formers with mebendazole was used. Mebendazole  
 327 was selected due to it forming a range of both of COAM and not COAM systems with the  
 328 amino acids; therefore, it was expected to form a range of both co-amorphous and not COAM  
 329 systems with other co-formers. The 29 co-formers were selected on the basis of being small  
 330 molecules capable of forming a range of different hydrogen-bonding motifs. The model was  
 331 applied to predict the classification of the mebendazole co-former mixtures and the prediction  
 332 was compared to experimental data. The misclassification table (Table 3) shows that overall,  
 333 86 % of the samples were predicted correctly and only four of 29 mixtures were predicted  
 334 incorrectly. The score plot of the predicted scores (Figure 5) shows a clear divide between

335 systems that were COAM and systems that were not COAM, with only a slight overlap of the  
 336 two clusters.



337  
 338 Figure 5. Score scatter plot of the predicted scores for the mebendazole-co-former  
 339 combinations. COAM samples are shown in green, not COAM samples are shown in red.  
 340 The hollow circles indicate samples which have been predicted incorrectly. The blue dashed  
 341 line shows the predicted separation line for visualization purposes.

342 Table 3. Misclassification table showing the percentage of correctly assigned observation of  
 343 the 29 MEB-co-former combinations. Fisher's probability of  $1.8 \times 10^{-4}$ .

Model	Members	Correct	Not COAM	COAM
-------	---------	---------	----------	------

Not COAM	17	88.24%	15	2
COAM	12	83.33%	2	10
Total	29	86.21%	17	12

344 The four samples that were predicted incorrectly were MEB combinations with theophylline,  
345 3-aminobenzoic acid, maleic acid and gallic acid, with predicted COAM values of 0.43, 0.52,  
346 0.40 and 0.86, respectively. The COAM values indicate how close the prediction is to  
347 assigning the system as COAM or not COAM with a value above 0.5 indicating COAM and  
348 a value below 0.5 indicating not COAM. Three of the samples had COAM values close to the  
349 cross over point at 0.5, suggesting they were close to being predicted correctly and may have  
350 been misplaced by one or two variables having extreme values. Theophylline appears to be  
351 incorrectly predicted due to the system having a relatively high value of  $\Delta H_{mix}$  and  $\Delta H_{hb}$   
352 compared to the other systems. 3-aminobenzoic acid was misplaced due to a relatively  
353 small/negative  $\Delta H_{mix}$  and  $\Delta H_{hb}$  and a small  $\Delta(\delta h)$ . Maleic acid is misplaced due to a small  
354 MW. The gallic acid system is the furthest away from the crossover line between COAM and  
355 not COAM systems, suggesting it should be COAM. The mebendazole gallic acid system  
356 was investigated using film casting which resulted in a COAM system, this suggests the  
357 model is not limited to system produced by only ball milling. Film casting was selected  
358 because it involves a thermodynamic pathway with the initial solution containing no  
359 crystalline material compared to ball milling which is a kinetic pathway involving the  
360 disruption of the crystal lattice (Karagianni et al., 2018). Therefore, film casting is likely to  
361 help the formation of a co-amorphous system if the initial crystalline material is too stable to  
362 be broken down by ball milling. With the mebendazole gallic acid system now being classed  
363 as COAM the misclassification table improves and the correct prediction percentage is now  
364 90 % (Table 4). The model now shows an even clearer divide between the two clusters with

365 only a few outliers which are close to the cross over line. Film casting was not used to test  
 366 other systems due to other co-amorphous formation methods usually producing a similar  
 367 result (Karmwar et al., 2011; Lim et al., 2016).

368 Table 4: Misclassification table showing the percentage of correctly assigned observations of  
 369 the 29 MEB-co-former combinations after gallic acid was confirmed as being COAM by film  
 370 casting. Fisher's probability of  $2.4 \times 10^{-5}$ .

Model	Members	Correct	Not COAM	COAM
Not COAM	16	93.75%	15	1
COAM	13	84.62%	2	11
Total	29	89.66%	17	12

371

#### 372 4. Conclusion

373 Known COAM systems formed with APIs and amino acid co-formers were analysed to  
 374 identify properties of the co-former that correlate with COAM material formation (Kasten et  
 375 al., 2016). A range of 36 variables was used to describe the properties of the API-amino acid  
 376 systems and a multivariate PLS-DA was used to create a prediction model. The initial 36  
 377 variables were reduced to seven variables including  $\Delta H_{hb}$ ,  $\Delta H_{mix}$ ,  $\Sigma HBC_{self}$ ,  $AV$ ,  $MW$ ,  $\Delta TPSA$ ,  
 378  $\Delta \mu$  and  $\Delta(\delta h)$ . The model predicts 81 % of the API-amino acid systems correctly. The model  
 379 was tested using a dataset of mebendazole with 29 different co-formers and 90 % of the  
 380 systems were correctly predicted. Overall, the model can predict the potential COAM

381 formation of a range of co-formers significantly expanding its applicability beyond the  
382 relatively limited set of amino acid co-formers.

### 383 CRediT authorship contribution statement

384 **Luke I. Chambers:** Conceptualization, Methodology, Validation, Formal analysis,  
385 Investigation, Resources, Data curation, Writing – Original Draft, Visualization, Project  
386 administration. **Holger Grohganz:** Conceptualization, Methodology, Writing – Review &  
387 Editing, Supervision. **Henrik Palmelund:** Validation, Investigation, Writing – Review &  
388 Editing. **Korbinian Löbmann:** Conceptualization, Writing – Review & Editing, Supervision.  
389 **Thomas Rades:** Conceptualization, Writing – Review & Editing, Supervision. **Osama M.**  
390 **Musa:** Supervision, Funding acquisition. **Jonathan W. Steed:** Conceptualization, Writing –  
391 Review & Editing, Supervision.

### 392 Conflicts of interest

393 The author declares no conflicts of interest.

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