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1 **Surface dissolution UV Imaging for characterization of superdisintegrants and their**  
2 **impact on drug dissolution**

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17

18 **Abstract**

19 Superdisintegrants are a key excipient used in immediate release formulations to  
20 promote fast tablet disintegration, therefore understanding the impact of superdisintegrant  
21 variability on product performance is important. The current study examined the impact of  
22 superdisintegrant critical material attributes (viscosity for sodium starch glycolate (SSG),  
23 particle size distribution (PSD) for croscarmellose sodium (CCS)) on their performance  
24 (swelling) and on drug dissolution using surface dissolution UV imaging. Acidic and basic  
25 pharmacopoeia (compendial) media were used to assess the role of varying pH on  
26 superdisintegrant performance and its effect on drug dissolution. A highly soluble  
27 (paracetamol) and a poorly soluble (carbamazepine) drug were used as model compounds and  
28 drug compacts and drug-excipient compacts were prepared for the dissolution experiments.  
29 The presence of a swelled SSG or CCS layer on the compact surface, due to the fast excipient  
30 hydration capacity, upon contact with dissolution medium was visualized. The swelling  
31 behaviour of superdisintegrants depended on excipient critical material attributes and the pH  
32 of the medium. Drug dissolution was faster in presence compared to superdisintegrant absence  
33 due to improved compact wetting or compact disintegration. The improvement in drug  
34 dissolution was less pronounced with increasing SSG viscosity or CCS particle size. Drug  
35 dissolution was slightly more complete in basic compared to acidic conditions in presence of  
36 the studied superdisintegrants for the highly soluble drug attributed to the increased excipient  
37 hydration capacity and the fast drug release through the swelled excipient structure. The  
38 opposite was observed for the poorly soluble drug as potentially the improvement in drug  
39 dissolution was compromised by drug release from the highly swelled structure. The use of  
40 multivariate data analysis revealed the influential role of excipient and drug properties on the  
41 impact of excipient variability on drug dissolution.

42 **Keywords:** excipient viscosity, excipient particle size, sodium starch glycolate, croscarmellose  
43 sodium, excipient swelling, real – time surface dissolution UV imaging

44

## 45        **1. Introduction**

46        The identification and control of the critical material (i.e. excipient) properties are essential  
47 in the pharmaceutical Quality by Design (QbD) for the production of final products with the  
48 desirable critical quality attributes (Yu et al., 2014). Presence of superdisintegrants in oral solid  
49 dosage forms is essential for fast tablet disintegration and improved drug dissolution. Sodium  
50 starch glycolate (SSG) and croscarmellose sodium (CCS) (semisynthetic polymers of starch  
51 and cellulose, respectively) are commonly used as superdisintegrants in tablet manufacturing.  
52 The main mechanism by which superdisintegrants promote tablet disintegration is swelling  
53 (Quodbach and Kleinebudde, 2016). Swelling refers to the volume expansion of the  
54 superdisintegrant particles upon contact with water (Quodbach and Kleinebudde, 2016). The  
55 swelling mechanism of SSG and CCS has been confirmed with the use of real-time magnetic  
56 resonance imaging (Quodbach et al., 2014).

57        SSG and CCS are sodium salts and are present as a neutral form in acidic and ionized form  
58 in basic conditions. They derive from natural polymers after two main modification steps  
59 (carboxymethylation and crosslinking) of the natural polymer chains to improve excipient  
60 functionality (Quodbach and Kleinebudde, 2016). Firstly, carboxymethylation of the natural  
61 polymer backbone increases polymer hydrophilicity and allows water access into the excipient  
62 (Zhao and Augsburger, 2006). Secondly, as natural polymers are partially soluble, and their  
63 dissolution may increase the viscosity of the medium, crosslinking of the polymeric chains  
64 serves in decreasing the soluble content of the polymer. SSG is crosslinked through phosphate  
65 groups (Edge and Miller, 2005) while CCS through ester groups (Guest, 2005) (**Figure 1**). The  
66 superior performance of SSG and CCS as tablet disintegrants, compared to native polymers, is  
67 attributed to these two modification steps.

68        The extensive and fast swelling of SSG and CCS is demonstrated by the increase in their  
69 volume median diameter (average volumetric size) upon contact with water (123  $\mu\text{m}$  upon

70 contact with water vs 35  $\mu\text{m}$  of the dry excipient powder for SSG, 92  $\mu\text{m}$  upon contact with  
71 water vs 45  $\mu\text{m}$  of the dry excipient powder for CCS) and the amount of liquid water uptake  
72 (16 g/g and 10 g/g in 120 sec for SSG and CCS, respectively) (Zhao and Augsburger, 2005).  
73 The differences in the swelling capacity of SSG and CCS, despite their similar structure, have  
74 been attributed to the difference in their dimensional expansion (3-dimensional swelling for  
75 SSG, 2-dimensional swelling for CCS) (Rojas et al., 2012; Zhao and Augsburger, 2005) and  
76 their different crosslinking (the phosphate group of SSG, compared to the ester group of CCS,  
77 allows for more spacing between the polymeric chains) (Rojas et al., 2012). Molecular  
78 properties (degree of substitution, degree of crosslinking), particle properties (particle size  
79 distribution (PSD)) and level have been identified as potential critical material attributes for  
80 SSG and CCS affecting product performance (Zarmpi et al., 2017). Increasing the degree of  
81 substitution of SSG and CCS results in faster water uptake and excipient swelling, however  
82 optimum values need to be defined as high degrees of carboxymethylation may result in an  
83 increase in the viscosity of the medium (Zarmpi et al., 2017). Extensive swelling and faster  
84 disintegration have been reported when increasing the degree of crosslinking, particle size or  
85 level in formulations for SSG and CCS (Zarmpi et al., 2017).

86 The biopharmaceutical implications of superdisintegrant presence or variability on product  
87 performance are not well known. Gastrointestinal factors may impact the performance of  
88 superdisintegrants with pH being the most influential due to the ionization pattern of SSG and  
89 CCS. The hydration capacity of the acid excipient form in acidic media is lower compared to  
90 the ionized excipient form in basic media (acidic and basic media are defined based on the  
91 physiological pH range (Sjogren et al., 2014)) leading to reduced swelling in acidic conditions  
92 (Zhao and Augsburger, 2005). The % increase in the volume media diameter in water and 0.1  
93 N HCl pH 1 was 251% and 43%, respectively for SSG and 104% and 51%, respectively for  
94 CCS (Zhao and Augsburger, 2005). The impact of superdisintegrants on product performance

95 relates also to drug properties. Interaction of cationic drugs with the carboxylic group of CCS  
96 can affect routine drug analysis. Loss of the active pharmaceutical ingredient (API) from a  
97 tablet formulation containing CCS during sample treatment can be expected, as low % recovery  
98 of drugs (metformin (Huang et al., 2006), escitalopram (Larsen and Melander, 2012)) from  
99 solutions in presence of CCS have been reported due to charge drug-excipient interactions.  
100 Delay in the dissolution of cationic drugs from immediate release tablets containing SSG and  
101 CCS has also been attributed to electrostatic drug-excipient interactions (Balasubramaniam et  
102 al., 2008).

103 Current approaches for assessing superdisintegrant performance and variability include the  
104 determination of: disintegration time of formulations, water uptake of powders/tablets,  
105 swelling volume of superdisintegrants, exerted force (force inside tablets that has to surpass  
106 the cohesive tablet forces) during tablet disintegration, dissolution rate of drugs, and size of  
107 generated particles after tablet disintegration (Quodbach and Kleinebudde, 2016). Real – time  
108 surface dissolution UV imaging is currently used in the pharmaceutical field providing  
109 additional information on disintegration/dissolution phenomena. UV dissolution imaging can  
110 be valuable in QbD approaches as it provides a mechanistic understanding into the surface  
111 events at the initial stages of drug dissolution and in early drug discovery to characterize new  
112 drug candidates (Kuentz, 2015; Niederquell and Kuentz, 2014). This technique utilizes a  
113 compact flow-cell integrated with a UV-vis camera and a pump for the infusion of the  
114 dissolution medium under laminar flow (Østergaard et al., 2014). The measured transmittance  
115 of light through the cell allows the characterization of the dissolving substance spatially and  
116 temporally and is useful for the identification of drug intrinsic dissolution rates, surface  
117 swelling/disintegration/dissolution phenomena, concentration gradients and  
118 microenvironmental pH changes (Gordon et al., 2013). Insights in the dissolution behaviour of  
119 APIs (Østergaard et al., 2014), excipients (Pajander et al., 2012) and their interplay (Colombo

120 et al., 2015; Hiew et al., 2018) have been provided with the use of real-time surface dissolution  
121 imaging.

122 The aims of this study were to assess the swelling performance of superdisintegrants with  
123 different potential critical material attributes and the impact and criticality of superdisintegrant  
124 variability on drug dissolution. Excipient characterization and drug dissolution studies in  
125 absence and presence of excipients were performed with the use of real-time surface dissolution  
126 UV imaging. The impact of excipient variability on excipient swelling and drug dissolution  
127 was studied by selecting three brands of SSG of different viscosity type and two brands of CCS  
128 of different PSD. A highly [paracetamol; Biopharmaceutical Classification System (BCS) class  
129 III (Kalantzi et al., 2006)] and a poorly soluble (carbamazepine; BCS class II (Kovacevic et  
130 al., 2009)) drug were used to assess the interplay of excipient variability and drug  
131 characteristics on drug dissolution. Studies were performed in acidic and basic compendial  
132 media to assess the role of pH on superdisintegrant swelling and drug dissolution.

## 133 2. Materials and Methods

### 134 2.1. Materials

135 APIs: Paracetamol (PRC, form I) was obtained from Fischer Scientific (UK).  
136 Carbamazepine (CBZ, form III) was purchased from Fagron (UK). Excipients: SSG brands:  
137 Glycolys LV [low viscosity (viscosity of aqueous solution at 60 min = 10.8 cP)] and Glycolys  
138 [high viscosity (viscosity of aqueous solution at 60 min = 20.9 cP)] (Roquette, France),  
139 Explotab CLV [low viscosity (viscosity of aqueous solution at 60 min = 12.7 cP)] (JRS Pharma,  
140 USA) and CCS brands: AcDiSol [low particle size ( $d_{90} = 74.2 \mu\text{m}$ )] (FMC, USA), Primellose  
141 [high particle size ( $d_{90} = 109.8 \mu\text{m}$ )] (DFE Pharma, Germany) were obtained from the specified  
142 sources. Chemicals: Hydrochloric acid 36.5–38%, HPLC grade methanol were obtained from  
143 Sigma-Aldrich (UK). Sodium chloride, sodium hydroxide, potassium phosphate monobasic



144 were obtained from Fisher Scientific (UK). Water was ultra-pure (Milli-Q) laboratory grade.  
145 Filters: Polytetrafluoroethylene (PTFE) 13 mm filter 0.45 µm pore size were purchased from  
146 Fisher Scientific (UK).

## 147 **2.2. Instrumentation**

148 Sartorius BP 210 D balance (Sartorius UK Ltd, UK), Mettler Toledo SevenCompact S210  
149 pH meter (Mettler Toledo, Switzerland), Vortex-Genie 2 vortex mixer (Scientific Industries  
150 Inc, USA), Agilent Technologies 1100 series HPLC system, (quaternary pump (G1311A),  
151 autosampler (G1313A), thermostatted column compartment (G1316A), diode array detector  
152 (G1329A) and a Chemstation software (Agilent Technologies, USA), Actipix SDI300  
153 dissolution imaging system (Paraytec Ltd, UK) with an Actipix flow-through dissolution  
154 cartridge CADISS-2, Quickset Minor® torque screwdriver (Torqueleader, UK), Actipress 316  
155 stainless steel press (Paraytec Ltd, UK).

## 156 **2.3. Methods**

### 157 **2.3.1. Media used for *in vitro* dissolution studied**

158 Compendial media (0.1 N HCl pH 1, phosphate buffer pH 6.8) were prepared according to  
159 the method described in the European Pharmacopeia (Ph.Eur., 2014).

### 160 **2.3.2. Preparation of compacts**

161 For the excipient characterization, 20 mg of each excipient were poured into the sample  
162 cup (stainless steel cylinder, inner diameter: 2 mm, height: 2.4 mm) and compacted using a  
163 manual press at a constant torque of 75 cNm for 5 min (Pajander et al., 2012). For the  
164 dissolution studies, compacts of pure APIs (paracetamol (PRC), carbamazepine (CBZ)) and  
165 compacts of superdisintegrants with the APIs were prepared. 10 mg of API (PRC, CBZ) were  
166 poured into the sample cup and compacts of pure API (drug compacts) were prepared using a  
167 manual press at a constant torque of 75 cNm for 5 min (Pajander et al., 2012). 10 mg of API

168 and 1 mg (2% w/w) of each excipient were prepared by vortexing (3 min) and poured into the  
169 sample cup. Compacts of superdisintegrants with APIs (drug-excipient compacts) were  
170 prepared using a manual press at a constant torque of 75 cNm for 5 min (Pajander et al., 2012).

### 171 **2.3.3. *In vitro* real-time surface dissolution UV imaging**

172 Real-time surface dissolution UV Imaging was performed using an Actipix SDI300 surface  
173 dissolution imaging system with an Actipix flow-through-type dissolution cartridge. The flow  
174 cell consisted of an Actipix cartridge fitted with a quartz cell (7 mm height, 4 mm width, 62  
175 mm length) and a polyetheretherketone (PEEK) sample holder. The light source was a pulsed  
176 xenon lamp and a band-pass filter (detection wavelength  $\pm$  10 nm) was used for the selection  
177 of the wavelength of interest. Dissolution medium was infused into the cell through a syringe  
178 pump. A temperature control unit was used to maintain constant temperature. The detection  
179 area of the UV imager was 9 mm  $\times$  7 mm (1280 pixel  $\times$  1024 pixel) with a pixel size of 7  $\mu$ m  
180  $\times$  7  $\mu$ m. Detailed representation of the instrument has been previously presented (Long et al.,  
181 2019; Østergaard et al., 2014).

182 For the excipient characterization, experiments were performed at 254 nm using stagnant  
183 conditions for 5 min at 37 °C in 0.1 N HCl pH 1 and phosphate buffer pH 6.8. *In vitro* drug  
184 dissolution experiments from drug compacts and drug-excipient compacts were performed at  
185 280 nm using 1 mL/min flow rate for 20 min at 37 °C in 0.1 N HCl pH 1 and phosphate buffer  
186 pH 6.8. For both the excipient characterization experiments and *in vitro* drug dissolution  
187 studies, dark (10 s duration with the lamp turned off) and reference (10 s duration with the lamp  
188 turned on) images were recorded with the flow cell filled with dissolution medium in absence  
189 of compact. Data collection was initiated and after 60 s data recording was paused and the  
190 compacts were introduced into the cell. The system was flushed with dissolution media to avoid  
191 presence of air bubbles in the flow cell and data collection was resumed. Pixel intensities within

192 a designated quantification region were converted into absorbance values using the Actipix  
193 D100 software version 1.8.50805 (Paraytec Ltd, UK). In the *in vitro* drug dissolution  
194 experiments, the presence of the swelling excipients (SSG and CCS brands) in the  
195 quantification regions of the UV image resulted in increased scattering or physical blockage of  
196 light (Long et al., 2019). In these cases, the eluting sample was collected at 1 min intervals and  
197 the effluent samples were filtered through PTFE 0.45 µm pore size filters and analysed by  
198 HPLC. Filter adsorption studies were prior performed in triplicate for each drug and confirmed  
199 that there were no adsorption issues for the studied drugs on the filters used. All experiments  
200 were performed in triplicate.

#### 201 **2.3.4. Chromatographic conditions**

202 Dissolution samples (effluent collection) were analysed by HPLC. Analytical HPLC  
203 procedures were modifications of already published methods for PRC (Gao et al., 2014) and  
204 CBZ (Vertzoni et al., 2006). A reversed-phase Spherisorb (Waters) C18 column (250 × 4.6  
205 mm, 5 µm) was used for both drugs. For PRC, the mobile phase consisted of methanol and  
206 water 20:80 (v/v) and the temperature was kept constant at 20 °C. The injection volume was  
207 20 µL and the detection wavelength was at 257 nm. For CBZ, the mobile phase was composed  
208 of methanol and water 60:40 (v/v) and the temperature was kept at 25 °C. The injection volume  
209 was 100 µL and the detection wavelength was at 285 nm. The flow rate was set at 1 mL/min  
210 for both drugs (isocratic flow). The elution times were 6 min and 4 min for PRC and CBZ,  
211 respectively. Drug quantification was made based on calibration curves. Standards were  
212 prepared from concentrated stock solution of drug dissolved in MeOH (PRC: 2 mg/mL, CBZ:  
213 1 mg/mL). The range of the calibration curves were 10 – 300 µg/mL and 0.5 -50 µg/mL for  
214 PRC and CBZ, respectively.

#### 215 **2.3.5. Treatment of *in vitro* dissolution data**

216 For the characterization of the swelling superdisintegrant behaviour, quantitative data of  
217 excipient concentration gradients cannot be obtained due to i. the insolubility of the studied  
218 polymers and ii. the fact that the high absorbance values recorded may be attributed to  
219 absorbance or scattering of light by the swelled polymer or physical blockage of light by  
220 undissolved polymer particles (Pajander et al., 2012). Only qualitative information of the rate  
221 and extent of swelling can be obtained by the absorbance gradients as a function of distance  
222 from the center of the sample cup. Absorbance values (Abs) were automatically calculated  
223 from pixel intensities using the Actipix D100 software version 1.8.50805 (Paraytec Ltd, UK)  
224 (zone dimensions of the images: 4.6 mm × 1.3 mm). The classification gradient maps (image  
225 gradients where changes of the z variable along the x and y directions are illustrated by changes  
226 in colour) depicting the swelling behaviour (absorbance values as a function of distance from  
227 the center of the sample cup) of the studied SSG and CCS brands in 0.1 N HCl pH 1 and  
228 phosphate buffer pH 6.8 were generated using SigmaPlot 13.0 (Systat Software Inc, USA). The  
229 cumulative % of drug dissolved was calculated based on the measured drug concentration in  
230 the samples (based on the HPLC analytical data) and the amount of drug in the compact. The  
231 dissolution profiles of the cumulative % of drug dissolved as a function time were constructed.  
232 Drug dissolution rates ( $\mu\text{g}/\text{min}$ ) at each 1 min interval over the duration of the experiments  
233 were calculated based on the measured drug concentration in the samples (based on the HPLC  
234 analytical data) and the known flow rate of the dissolution experiments. Graphs depicting drug  
235 dissolution rates as a function of time (at 1 min intervals) were constructed and the standard  
236 deviation (SD) of the dissolution rates was presented in the midterm point of the sampling  
237 intervals.

238 The area under the curve (AUC) of the dissolution profiles up to last experimental time (20  
239 min), calculated using the method of trapezoids, was used for the characterization of drug

240 dissolution. The Relative Effect (RE) of each superdisintegrant on drug dissolution was  
241 calculated based on equation 1:

$$242 \quad RE = \frac{(AUC_T - AUC_C)}{AUC_C} \times 100 \quad \text{equation 1}$$

243 where  $AUC_C$  and  $AUC_T$  are the areas under the curve of the dissolution profiles of the  
244 control and test compact, respectively. Two sets of comparisons were performed. In the first  
245 set (set 1), the differences in drug dissolution between drug compacts and drug-excipient  
246 compacts in each medium were examined taking the AUCs of the dissolution profiles of the  
247 drug compact and the drug-excipient compact as control and test dissolution profiles,  
248 respectively. In the second set (set 2), differences in drug dissolution within acidic and basic  
249 conditions in each drug-excipient compact were investigated taking the AUCs of the  
250 dissolution profiles in acidic and basic conditions as the control and test dissolution profiles,  
251 respectively. The risk assessment of the impact of excipients on drug dissolution was evaluated  
252 by setting reference range criteria of -20% - 25% (FDA, 2002) on the REs of excipients on the  
253 AUCs of the dissolution profiles (this range was selected as a similar range is set in order to  
254 assess differences in drug exposure after oral administration; i.e. in bioequivalence studies).  
255 REs of excipients on the AUCs of the dissolution profiles outside these values (REs < -20% or  
256 REs > 25%) were considered potentially critical for oral drug performance.

### 257 **2.3.6. Multivariate data analysis of *in vitro* dissolution data**

258 Excipient REs on drug dissolution were correlated to excipient critical material attributes  
259 (viscosity for SSG, PSD for CCS), drug aqueous solubility ( $Drug_{aq.sol.}$ ) and medium (acidic,  
260 basic) characteristics by multiple linear regression (MLR) using the XLSTAT software  
261 (Microsoft, USA). Two models for the REs of excipients on the AUCs of the dissolution  
262 profiles in presence of SSG (Model 1) and CCS (Model 2) were constructed. The evaluated  
263 variables for both models were all categorical and included: i. drug aqueous solubility

264 (Drug<sub>aq.sol.</sub>) [0: poorly soluble, 1: highly soluble; based on the compound's BCS  
265 (Biopharmaceutical Classification System) classification (highly soluble: BCS Class I and III;  
266 poorly soluble: BCS Class II and IV) (FDA, 2017)], ii. medium (0: acidic, 1: basic), iii.  
267 excipient brand (0: low excipient property, 1: high excipient property; based on the measured  
268 viscosity values of SSG and the measured particle size ( $d_{90}$ ) of the CCS brands). Excipient REs  
269 on the AUCs of the dissolution profiles (set 1, section 2.3.5) were used as the response. The  
270 selected interaction terms included each excipient brand combined with each drug aqueous  
271 solubility and medium characteristics (acidic, basic). The generated MLR models were  
272 assessed in terms of goodness of fit ( $R^2$ ) and variance inflation factor (VIF). High  $R^2$  values  
273 and VIF values  $< 5$  were indications of successful models with absence of multicollinearity  
274 among the independent variables (Montgomery and Peck, 1992). Standardized coefficients  
275 were used to show the direction (positive or negative) and extent of each variable on the  
276 response. The significance of the variables was assessed by the p values ( $p < 0.05$  were  
277 considered the most significant in the model (Montgomery and Peck, 1992)). A 95%  
278 confidence interval was used.

### 279 **3. Results and Discussion**

#### 280 **3.1. Characterization of the swelling behaviour of superdisintegrants using** 281 **real-time surface dissolution UV Imaging**

282 The studied excipient types and brands have been previously characterized in terms of  
283 viscosity for SSG and PSD for CCS (Zarmpi et al., 2019). The viscosity after 60 min of the  
284 aqueous dispersions of Glycolys LV (10.8 cP) and Explotab CLV (12.7 cP) was lower  
285 compared to Glycolys (20.9 cP), due to their higher degree of crosslinking and lower soluble  
286 material content (Shah and Augsburger, 2001). Differences in the PSD of the CCS brands were

287 identified, as AcDiSol comprised of smaller particles (d10: 12.8  $\mu\text{m}$ , d50: 31.9  $\mu\text{m}$ , d90: 74.2  
288  $\mu\text{m}$ ) compared to Primellose (d10: 21.8  $\mu\text{m}$ , d50: 52.2  $\mu\text{m}$  d90: 109.8  $\mu\text{m}$ ).

289 Surface dissolution UV imaging was used to study the swelling performance of SSG and  
290 CCS in simple buffers and UV images of the excipient swelling upon contact with the  
291 dissolution media are presented in **Supplementary Figure 1**. The swelling behaviour of the  
292 studied superdisintegrants as a function of time and distance from the centre of the sample cup  
293 in 0.1 N HCl pH 1 is presented in **Figure 2**. Intense signals at the compact location are  
294 indications of dense swollen polymeric structures (Colombo et al., 2015), as the high  
295 absorbance recorded are attributed to light scattering by the swelled superdisintegrants or  
296 physical blockage of light by undissolved excipient particles (as explained in section 2.3.5.).  
297 The fast excipient swelling was demonstrated as all the studied superdisintegrants swelled at a  
298 distance of 1.2 mm from the centre of the sample cup at approximately 20 – 40 s irrespective  
299 of excipient type or brand. For SSG, Glycolys exhibited lower absorbance values (Abs  $\approx$  1.0 –  
300 1.2 AU) compared to Glycolys LV and Explotab CLV (Abs  $\approx$  1.2 – 1.6 AU) probably due to  
301 the higher soluble content of high viscosity brands (Shah and Augsburger, 2001). For CCS, the  
302 higher absorbance values of Primellose (Abs  $\approx$  1.4 – 1.6 AU) compared to AcDiSol (Abs  $\approx$  1.0  
303 – 1.2 AU) can be attributed to the pronounced physical blockage of light by larger particles  
304 (Van Eerdenbrugh et al., 2011).

305 The swelling behaviour of the studied superdisintegrants as a function of time and  
306 distance from the centre of the sample cup in phosphate buffer pH 6.8 is presented in **Figure**  
307 **3**. Slightly faster excipient swelling in phosphate buffer pH 6.8 (< 20 s) was observed compared  
308 to 0.1 N HCl pH 1 (20 – 40 s) explained by the higher liquid uptake (0.1 N HCl pH 1:  
309 approximately 5 g/g liquid uptake by SSG and CCS after 2 min, water: 18 g/g and 10 g/g liquid  
310 uptake by SSG and CCS, respectively after 2 min (Zhao and Augsburger, 2005)) and excipient  
311 swelling of the ionized excipient form in basic media (Zhao and Augsburger, 2005). The

312 absorbance values of the studied brands were lower in phosphate buffer pH 6.8 (SSG brands:  
313 0.6 – 1.2 AU, CCS brands: 1.0 – 1.4 AU) compared to 0.1 N HCl pH 1 (SSG brands: 1.0 – 1.6  
314 AU, CCS brands: 1.0 – 1.6 AU). We hypothesize that the lower absorbance values in the basic  
315 compared to the acidic medium relate to the higher excipient swelling of the ionized excipient  
316 forms in phosphate buffer pH 6.8 (as compared to the unionized excipient forms in 0.1 N HCl  
317 pH 1), as the higher spacing of the swelled polymeric chains (Rojas et al., 2012) could decrease  
318 the scattering or physical blockage of light. Differences in the absorbance values are not  
319 observed within the studied SSG brands (Abs  $\approx$  0.6 – 1.0 AU). For CCS, lower absorbance  
320 values were observed for AcDiSol (Abs  $\approx$  1.0 – 1.2 AU) attributed to its lower particle size  
321 compared to Primellose (Abs  $\approx$  1.2 – 1.4 AU) [24]. The lower absorbance values of the SSG  
322 compared to the CCS brands in phosphate buffer pH 6.8 can indicate a more extensive swelling  
323 by SSG, due to the differences in the dimensional expansion (3 dimensional swelling  
324 (semispherical particles) for SSG and 2 dimensional swelling (fibrous particles) for CCS upon  
325 contact with simulated intestinal fluid have been reported (Rojas et al., 2012)) and type of  
326 crosslinking (phosphate groups for SSG, ester group for CCS) between the two excipient types  
327 (Rojas et al., 2012). The observed differences in excipient performance in the studied media  
328 indicate that differences in tablet disintegration between the stomach and the small intestine  
329 are anticipated (due to the differences in the pH of these two compartments) and could  
330 potentially implicate product performance and drug bioavailability.

## 331 **3.2. Impact of SSG variability on drug dissolution using surface dissolution UV** 332 **Imaging**

### 333 **3.2.1. Highly soluble drug (PRC)**

334 The dissolution profiles and dissolution rates of PRC from drug compacts (control) and  
335 drug-SSG compacts in 0.1 N HCl pH 1 and phosphate buffer pH 6.8 are presented in **Figure**



336 4. Approximately 5% of PRC dissolved from the drug compact in 20 min in both media. The  
337 % of drug dissolved in 20 min from the drug-SSG compacts was increased in 0.1 N HCl pH 1  
338 (21%, 23% and 25% of drug dissolved in the presence of Glycolys LV, Explotab CLV and  
339 Glycolys, respectively) and in phosphate buffer pH 6.8 (22%, 27% and 21% of drug dissolved  
340 in the presence of Glycolys LV, Explotab CLV and Glycolys, respectively). The dissolution  
341 rate of PRC from drug compacts was slow during the experiments in both media studied  
342 (dissolution rates of approximately 20 µg/min and 17 µg/min in 0.1 N HCl pH 1 and phosphate  
343 buffer pH 6.8 at 20 min, respectively). Drug dissolution from drug-SSG compacts was faster  
344 compared to drug dissolution from drug compacts in the studied media, especially at early time  
345 points (1 – 5 min), as indicated by the increased dissolution rates of PRC in excipient presence  
346 (dissolution rates of approximately 200 µg/min from compacts containing Glycolys LV,  
347 Explotab CLV and Glycolys at 5 min in both media). This could be explained by the fast  
348 excipient hydration and swelling (excipient swelling at a distance of 1.2 mm from the centre  
349 of the sample cup within the first 40s, section 3.1) improving compact wetting (Onuki et al.,  
350 2018). Compact disintegration may also have contributed to the faster drug dissolution from  
351 drug-excipient compacts compared to drug compacts, as spread particles around the compact  
352 surface were observed after the end of each experiment only for the drug-excipient compacts.  
353 Comparison of the AUCs of the dissolution profiles revealed that drug dissolution was more  
354 complete from the drug-excipient compacts compared to drug dissolution from the drug  
355 compacts (REs > 25%) (**Figure 5a**). Differences in PRC dissolution from drug-SSG compacts  
356 in acidic and basic conditions for the studied SSG brands were not observed (REs of  
357 approximately 5%, 20% and -20% for Glycolys LV, Explotab CLV and Glycolys,  
358 respectively). The observed minor REs indicate that the pH-dependent swelling performance of  
359 SSG (section 3.1) may not significantly affect the dissolution of a highly soluble drug between  
360 acidic and basic conditions.

### 361 3.2.2. Poorly soluble drug (CBZ)

362 The dissolution profiles and dissolution rates of CBZ from drug compacts (control) and  
363 drug-SSG compacts in 0.1 N HCl pH 1 and phosphate buffer pH 6.8 are presented in **Figure**  
364 **6**. Approximately 0.1% of CBZ dissolved from the drug compact in 20 min in both 0.1 N HCl  
365 pH and phosphate buffer pH 6.8. In 0.1 N HCl pH 1, 2.3%, 1.6% and 1.3% of drug dissolved  
366 in 20 min in presence of Glycolys LV, Explotab CLV and Glycolys, respectively. The % of  
367 CBZ dissolved in excipient presence in phosphate buffer pH 6.8 in 20 min was similar between  
368 the different drug-excipient compacts (approximately 1.5% of CBZ dissolved from drug-  
369 excipient compact containing Glycolys LV, Explotab CLV, Glycolys). The rate of drug  
370 dissolution from the drug compact was slow in both sets of media (dissolution rates of  
371 approximately 0.5 µg/min at 20 min in 0.1 N HCl pH 1 and phosphate buffer pH 6.8). CBZ  
372 dissolution was faster in SSG presence, especially at early time points (1 - 5 min), potentially  
373 due to the fast excipient swelling or compact disintegration (as explained in the case of PRC).  
374 In 0.1 N HCl pH 1, the dissolution rates of CBZ from drug-excipient compacts were 13 µg/min,  
375 8.6 µg/min and 6.2 µg/min at 5 min in presence of Glycolys LV, Explotab CLV and Glycolys,  
376 respectively. The lower amount of drug dissolved in presence of Glycolys compared to the low  
377 viscosity brands (Glycolys LV, Explotab CLV) may be explained by the increase in the  
378 viscosity of the gel around the compact by high viscosity Glycolys (Quodbach and  
379 Kleinebudde, 2016). The pronounced differences in the CBZ dissolution rates from compacts  
380 containing the low and high viscosity SSG brands are diminished at late points. Faster CBZ  
381 dissolution in presence compared to absence of excipient was also observed in phosphate buffer  
382 pH 6.8, with the dissolution rates from the three drug-excipient compacts being similar (CBZ  
383 dissolution rates of approximately 7 µg/min at 5 min in presence of the three studied SSG  
384 brands). CBZ dissolution in presence of excipient was more complete compared to the  
385 excipient absence (REs > 25%) (**Figure 5a**). Differences in drug dissolution from drug-

386 excipient compacts between acidic and basic conditions were observed. For the low viscosity  
387 brands (Glycolys LV, Explotab CLV), the REs on the AUCs of the dissolution profiles between  
388 acidic and basic conditions were negative (REs of -45% and -20% for Glycolys LV and  
389 Explotab CLV, respectively), indicating that the improvement in CBZ dissolution is less  
390 pronounced in phosphate buffer pH 6.8 compared to 0.1 N HCl pH 1. As superdisintegrants  
391 swell more extensively in basic compared to acidic conditions due to their ionization (Rojas et  
392 al., 2012), the presence of a highly swelled layer on top of the sample cup may add a physical  
393 or diffusive barrier for the release of poorly soluble drugs (Long et al., 2019), despite the faster  
394 polymer water uptake in basic conditions (as explained previously in section 3.1). The swelling  
395 of the high viscosity Glycolys is as well more extensive in basic compared to acidic conditions,  
396 however comparison of CBZ dissolution profiles from compacts containing Glycolys between  
397 basic and acidic media reveal slightly more complete dissolution in phosphate buffer pH 6.8  
398 (REs of 30%). This positive RE on the AUCs of the dissolution profiles may relate to the  
399 gelling effects of Glycolys (Quodbach and Kleinebudde, 2016) and the slower CBZ dissolution  
400 observed in 0.1 N HCl pH 1 (compared to the other two excipient brands).

### 401 **3.3. Impact of CCS variability on drug dissolution using surface dissolution UV** 402 **Imaging**

#### 403 **3.3.1. Highly soluble drug (PRC)**

404 The dissolution profiles and dissolution rates of PRC from drug compacts (control) and  
405 drug-CCS compacts in 0.1 N HCl pH 1 and phosphate buffer pH 6.8 are presented in **Figure**  
406 **7**. A higher % of drug dissolved in 20 min was observed in excipient presence in 0.1 N HCl  
407 pH 1 (AcDiSol: 23%, Primellose: 14%) and phosphate buffer pH 6.8 (AcDiSol: 25%,  
408 Primellose: 26%) compared to the % of PRC dissolved from the drug compact (5% of drug  
409 dissolved in 20 min). Faster drug dissolution was revealed in excipient presence compared to

410 excipient absence in both media which may be explained by the enhancement in compact  
411 wetting or compact disintegration due to the hydrophilicity and swelling of CCS (Quodbach  
412 and Kleinebudde, 2016). Differences in drug dissolution rates from the studied drug-CCS  
413 compacts were observed at early time points in 0.1 N HCl pH 1 as the dissolution rate of PRC  
414 was lower in presence of Primellose (98  $\mu\text{g}/\text{min}$  of drug dissolved at 5 min) compared to  
415 AcDiSol (182  $\mu\text{g}/\text{min}$  of drug dissolved at 5 min), probably due to the presence of larger  
416 excipient particles (Primellose) on top of the compact surface (section 3.1). In phosphate buffer  
417 pH 6.8 similar drug dissolution was observed between the drug-CCS compacts containing  
418 AcDiSol and Primellose (dissolution rates of approximately 200  $\mu\text{g}/\text{min}$  in presence of both  
419 CCS brands at 5 min). At late time points, the dissolution rate of PRC gradually decreased in  
420 presence of the CCS brands in both media and any differences in drug dissolution between the  
421 studied CCS brands were diminished. Comparison of the AUCs of the dissolution profiles of  
422 the drug and drug-CCS compacts revealed significantly more complete dissolution from  
423 compacts containing excipient ( $\text{REs} > 25\%$ ) (**Figure 5b**). Differences in drug dissolution from  
424 drug-AcDiSol compacts between acidic and basic conditions were not observed, as revealed  
425 by the REs of AcDiSol on the AUCs of the dissolution profiles between acidic and basic  
426 conditions ( $\text{RE} = 10\%$ ). Drug dissolution from the drug-Primellose compacts was significantly  
427 more complete in phosphate buffer pH 6.8 compared to 0.1 N HCl pH (RE = 97%), potentially  
428 due to the presence of larger excipient particles in 0.1 N HCl pH 1.

### 429 **3.3.2. Poorly soluble drug (CBZ)**

430 The dissolution profiles and dissolution rates of CBZ from drug compacts and drug-CCS  
431 compacts in 0.1 N HCl pH 1 and phosphate buffer pH 6.8 are presented in **Figure 8**. CBZ  
432 dissolution reached approximately 1.8% and 1.5% from compacts containing AcDiSol and  
433 Primellose, respectively in 0.1 N HCl pH 1 and 1.3% and 1.0% in phosphate buffer pH 6.8.  
434 The fast excipient swelling at early time points (section 3.1) resulted in faster drug dissolution

435 from drug-CCS compacts compared to the drug compacts in both sets of media, especially at  
436 early time points. Drug dissolution was slower in presence of Primellose (7  $\mu\text{g}/\text{min}$  and 5  
437  $\mu\text{g}/\text{min}$  in acidic and basic conditions, respectively) compared to AcDiSol (9  $\mu\text{g}/\text{min}$  and 7  
438  $\mu\text{g}/\text{min}$  in the acidic and basic medium, respectively), probably due to the presence of larger  
439 excipient particles (Primellose) on top of the compact surface (section 3.1). Differences in drug  
440 dissolution between the studied brands were smaller at late time points. In presence of  
441 excipient, drug dissolution was significantly more complete compared to the control sample in  
442 both experimental conditions ( $\text{REs} > 25\%$ ) (**Figure 5b**). The enhancement in CBZ dissolution  
443 by CCS presence was more pronounced in acidic compared to basic conditions ( $\text{REs}$  on the  
444 AUCs of the dissolution profiles between acidic and basic conditions of -30% and -20% for  
445 AcDiSol and Primellose, respectively). The faster water uptake of the excipients in basic media  
446 (Rojas et al., 2012) would be expected to result in faster drug dissolution due to the improved  
447 compact wetting, however this is not observed as potentially the presence of a swelled layer  
448 on top of the compact surface created a physical or diffusive barrier delaying drug release  
449 (Long et al., 2019).

450 For the dissolution experiments in the absence of excipients, high variability (coefficient  
451 of variation ( $\text{CV}\%$ )  $> 20\%$ ) was observed in some cases only at the first 3 min, and a lower  
452 variability was observed in later time points ( $\text{CV}\% < 20\%$ ). For the dissolution experiments in  
453 excipient presence, cases of increased variability were identified ( $15\% < \text{CV}\% < 70\%$  and  $15\%$   
454  $< \text{CV}\% < 50\%$  at early and late time points, respectively) that may relate to the heterogeneous  
455 nature of the physical mixtures (Koester et al., 2003a; Koester et al., 2003b; Zarmpi et al.,  
456 2019). The preparation process of the physical mixtures could be further optimized in future  
457 studies along with the use of more replicates.

#### 458 **3.4. Multivariate data analysis of *in vitro* dissolution data**

459 The standardized coefficients of the variables for the SSG and CCS model are presented in  
460 **Figure 9**. The two models showed a good fit (SSG:  $R^2 = 0.5$ , CCS:  $R^2 = 0.5$ ). For SSG,  
461 excipient brand (negative effect,  $p < 0.05$ ),  $Drug_{aq.sol.}$  (negative effect,  $p < 0.05$ ) and medium  
462 (negative effect,  $p < 0.05$ ) were the critical variables in the model. The negative effect of the  
463 excipient brand indicates that increasing the viscosity type of SSG resulted in less pronounced  
464 dissolution enhancement compared to the low viscosity SSG brands. Enhanced compact  
465 wetting by low viscosity SSG brands is expected due to their faster water uptake and higher  
466 swelling (Abraham et al., 2016). Formation of gelling layer by high viscosity SSG brands  
467 which delays drug dissolution (Quodbach and Kleinebudde, 2016) could also explain this  
468 finding. The impact of varying SSG viscosity was more pronounced for the poorly soluble  
469 drug, indicated by the significance of the variable  $Drug_{aq.sol.}$  in the model, as poorly soluble  
470 drugs will benefit more by an improvement in compact wetting. The negative effect of the  
471 variable medium reveals the pronounced enhancement in drug dissolution by SSG presence in  
472 acidic compared to basic conditions (especially, for the poorly soluble drug).

473 For CCS, excipient brand (negative effect,  $p < 0.05$ ) and  $Drug_{aq.sol.}$  (negative effect,  $p <$   
474  $0.05$ ) were critical variables in the model. Increasing the particle size of CCS will result in less  
475 pronounced improvement in drug dissolution probably due to the formation of physical or  
476 diffusive barrier for drug dissolution by larger excipient particles. The negative effect of the  
477 variable  $Drug_{aq.sol.}$  indicates that the improved wetting or compact disintegration by CCS  
478 presence will contribute more to the dissolution of poorly soluble drugs. The multivariate data  
479 analysis revealed that CCS variability may be critical for the initial stages of drug dissolution.

#### 480 **4. Conclusions**

481 Superdisintegrant variability and interchangeability may be challenging for oral product  
482 performance, as the presence of superdisintegrants in pharmaceutical formulations directly

483 affects drug dissolution. In this study, the use of surface dissolution UV imaging allowed the  
484 semi-qualitative analysis of SSG and CCS swelling and their impact on drug dissolution. The  
485 fast swelling ability of SSG and CCS was confirmed, which depended on the critical excipient  
486 material attributes and the pH of the dissolution medium. These results reveal that SSG and  
487 CCS should not be considered interchangeable with each other in oral solid dosage forms.  
488 Presence of superdisintegrants in compacts containing highly and poorly soluble compounds  
489 resulted in significantly faster drug dissolution for both drugs probably due to the enhanced  
490 compact wetting or compact disintegration by the hydrophilic excipients. Changing excipients  
491 with varying material properties needs to be carefully consider in oral drug development as the  
492 different excipient critical material attributes affected the extent of drug dissolution  
493 (pronounced dissolution enhancement was observed by low viscosity SSG or low particle size  
494 CCS brands, especially for the poorly soluble drug). The potential biopharmaceutical  
495 implications of superdisintegrants were revealed, as in superdisintegrant presence, an interplay  
496 between drug aqueous solubility and medium characteristics was found that could affect  
497 product performance (highly soluble drug: faster drug dissolution in basic compared to acidic  
498 media due to the increased excipient hydration capacity; poorly soluble drug: slower drug  
499 dissolution in basic compared to acidic media potentially due to the presence of a swollen  
500 excipient structure on top of the compact). SSG viscosity type, CCS particle size and drug  
501 aqueous solubility were considered critical biopharmaceutical factors affecting the  
502 performance and the impact of superdisintegrant variability on drug dissolution. It is concluded  
503 that excipient variability can be challenging for oral drug performance and that  
504 biopharmaceutical considerations need to be taken into account when changes in excipient  
505 brands/grades are necessary in oral product development. Further studies to assess the impact  
506 and interplay of other superdisintegrant properties using a wide range of compounds would be  
507 beneficial in delineating the impact of excipient variability on drug dissolution.

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631 **Figure captions**

632 **Figure 1:** Chemical structure of a. Sodium Starch Glycolate and b. Croscarmellose Sodium  
633 (ChemDraw Professional 15)

634 **Figure 2:** Absorbance values (Abs) of the studied superdisintegrant types and brands as a  
635 function of distance from the center of the sample cup (mm) in 0.1 N HCl pH 1 (SDi1, 0  
636 mL/min, 37 °C, 254 nm) presented up to 2.5 min.

637 **Figure 3:** Absorbance values (Abs) of the studied superdisintegrant types and brands as a  
638 function of distance from the center of the sample cup (mm) in phosphate buffer pH 6.8 (SDi1,  
639 0 mL/min, 37 °C, 254 nm) up to 2.5 min.

640 **Figure 4:** Cumulative % dissolved (top) and dissolution rates (bottom) of PRC from compacts  
641 in a. 0.1 N HCl pH 1 and b. phosphate buffer pH 6.8 using real-time surface dissolution UV  
642 imaging (SDi1, 1 mL/min, 37°C) in absence (control: black circles/colour) and presence of the  
643 studied SSG brands (Glycolys LV: green squares/colour, Explotab CLV: blue  
644 diamonds/colour, Glycolys: red triangles/colour). (Mean  $\pm$ SD, n =3)

645 **Figure 5:** a. Relative effects of excipients on the AUCs of the dissolution profiles for a. PRC  
646 and b. CBZ in presence of the studied SSG brands (Glycolys LV: green colour, Explotab CLV:  
647 blue colour, Glycolys: red colour) in 0.1 N HCl pH 1 and phosphate buffer pH 6.8. b. Relative  
648 effects of excipients on the AUCs of the dissolution profiles for a. PRC and b. CBZ in presence  
649 of the studied CCS brands (AcDiSol: blue colour, Primellose: red colour) in 0.1 N HCl pH 1  
650 and phosphate buffer pH 6.8.

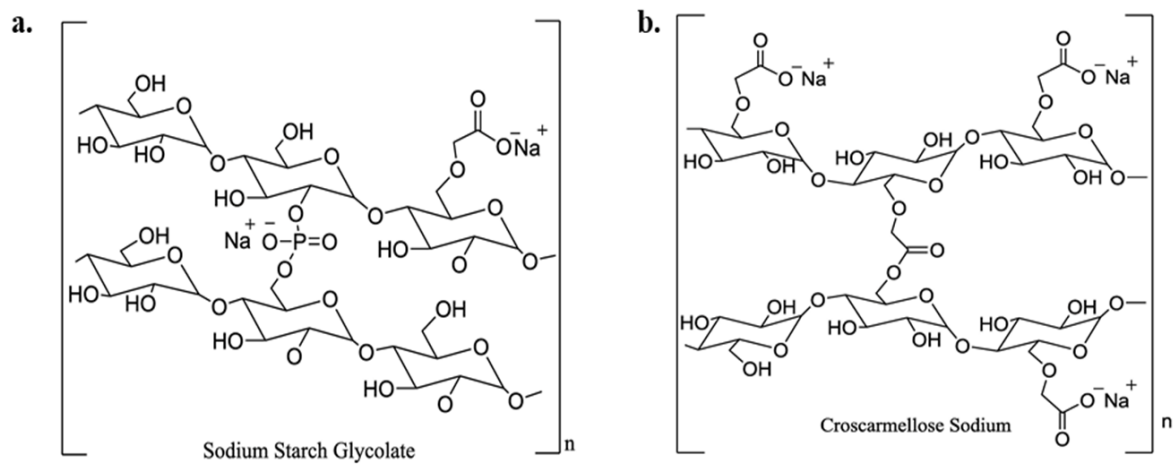
651 **Figure 6:** Cumulative % dissolved (top) and dissolution rates (bottom) of CBZ from compacts  
652 in a. 0.1 N HCl pH 1 and b. phosphate buffer pH 6.8 using real-time surface dissolution UV  
653 imaging (SDi1, 1 mL/min, 37°C) in absence (control: black circles/colour) and presence of the

654 studied SSG brands (Glycolys LV: green squares/colour, Explotab CLV: blue  
655 diamonds/colour, Glycolys: red triangles/colour). (Mean  $\pm$ SD, n =3)

656 **Figure 7:** Cumulative % dissolved (top) and dissolution rates (bottom) of PRC from compacts  
657 in a. 0.1 N HCl pH 1 and b. phosphate buffer pH 6.8 using real-time surface dissolution UV  
658 imaging (SDi1, 1 mL/min, 37°C) in absence (control: black circles/colour) and presence of the  
659 studied CCS brands (AcDiSol: blue squares/colour, Primellose: red diamonds/colour). (Mean  
660  $\pm$ SD, n =3)

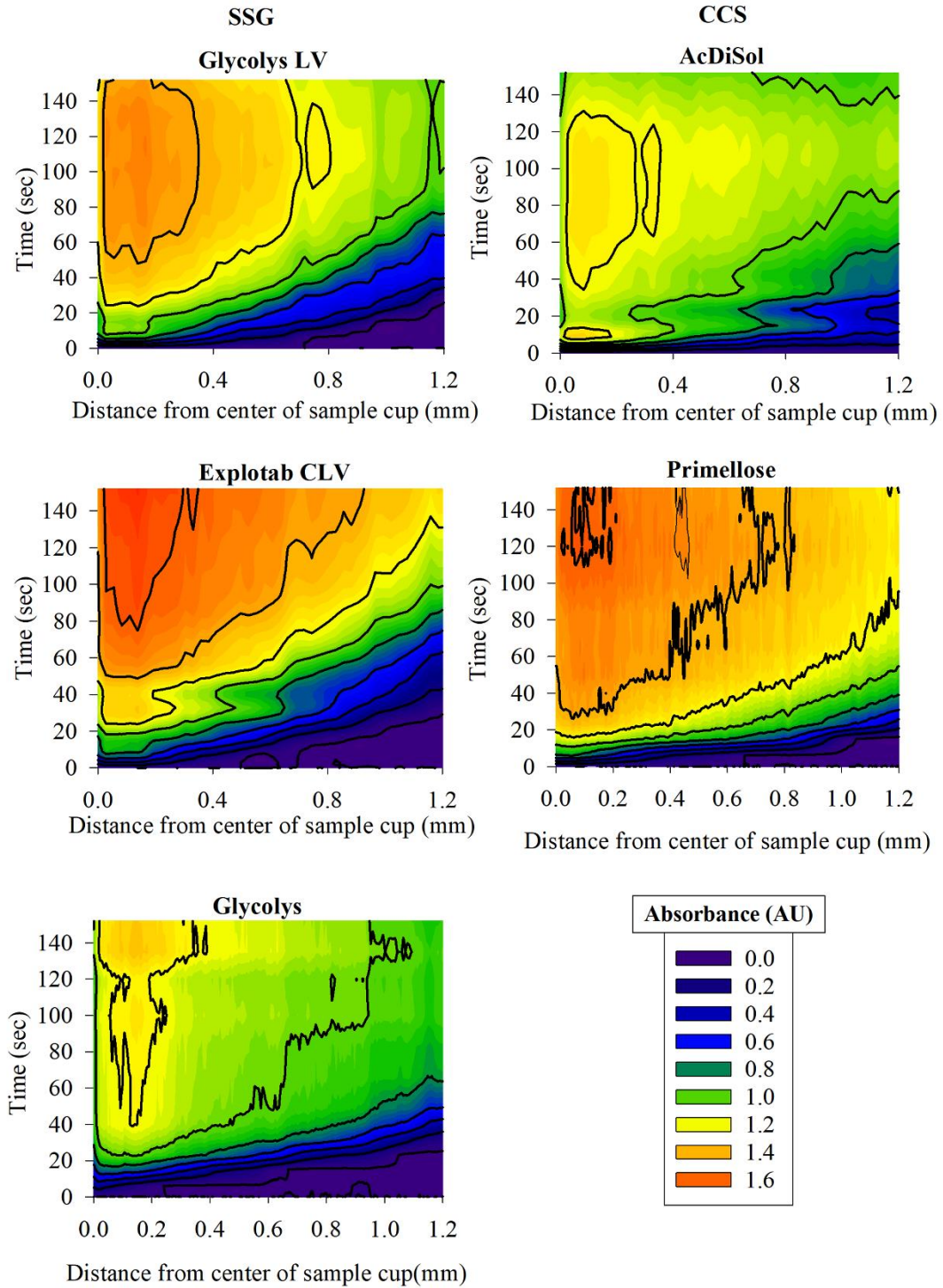
661 **Figure 8:** Cumulative % dissolved (top) and dissolution rates (bottom) of CBZ from compacts  
662 in a. 0.1 N HCl pH 1 and b. phosphate buffer pH 6.8 using real-time surface dissolution UV  
663 imaging (1 mL/min, 37°C) in absence (control: black circles/colour) and presence of the  
664 studied CCS brands (AcDiSol: blue squares/colour, Primellose: red diamonds/colour). (Mean  
665  $\pm$ SD, n =3)

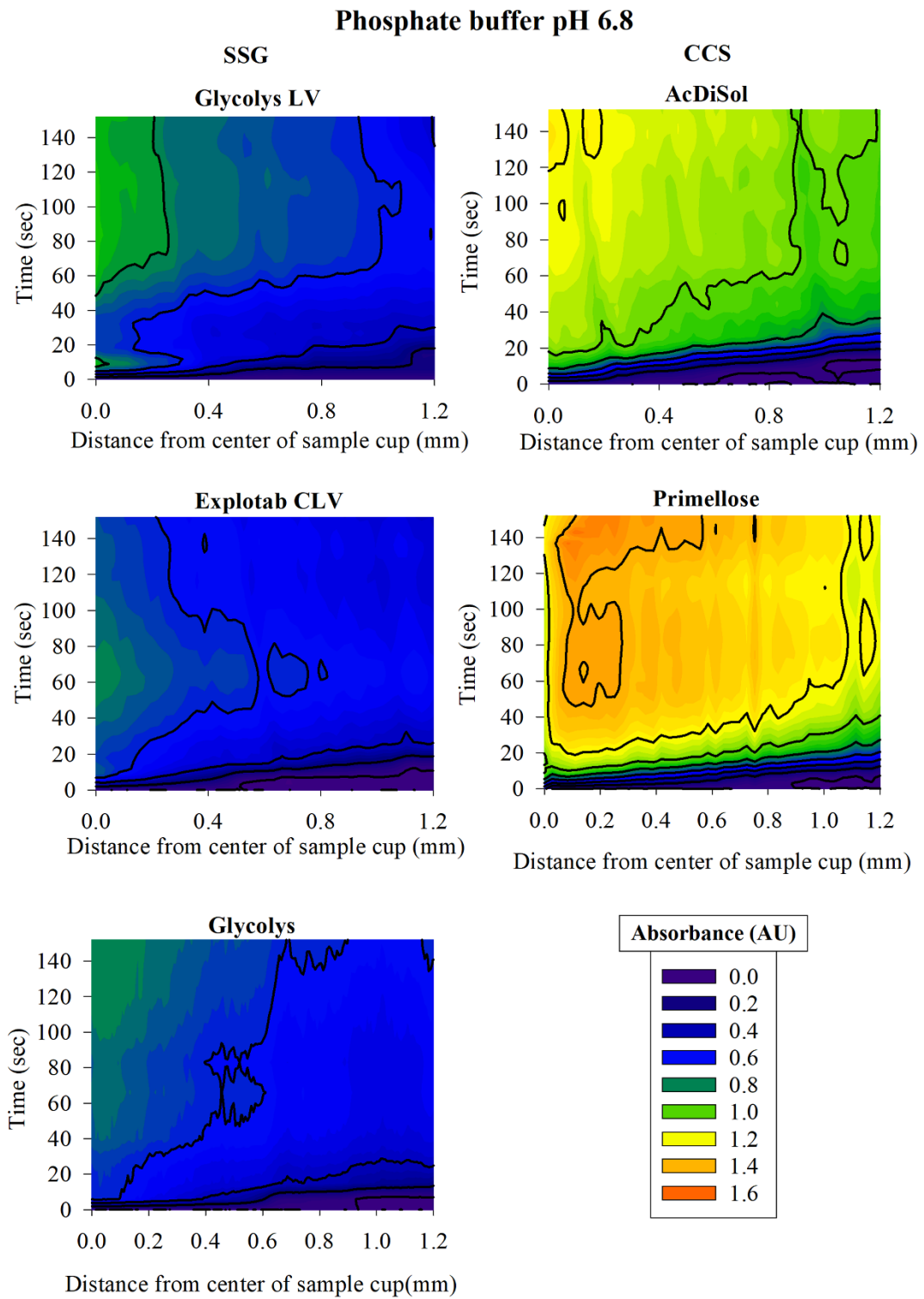
666 **Figure 9:** Standardized coefficients corresponding to the studied variables (and their  
667 interactions) for SSG (blue colour) and CCS (red colour). \* denotes coefficients with  $p < 0.05$ .  
668 (Mean, - SE) [Exc. Brand: viscosity type for SSG, particle size for CCS].



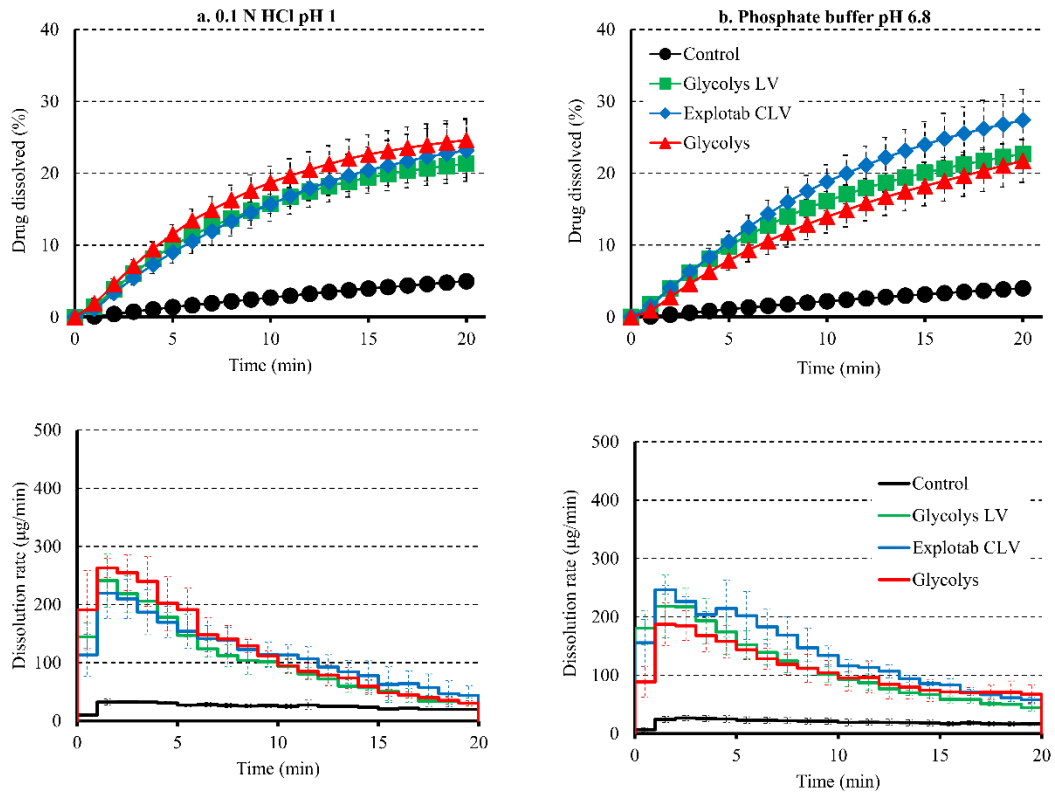


**0.1 N HCl pH 1**

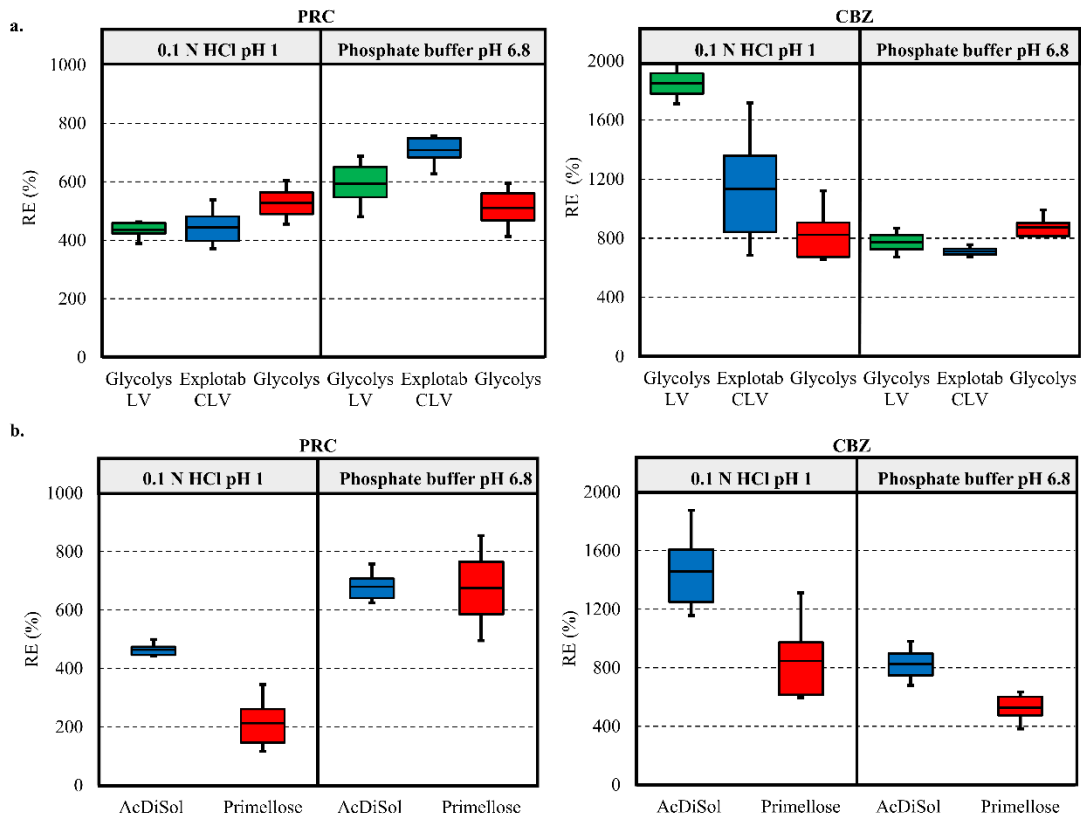




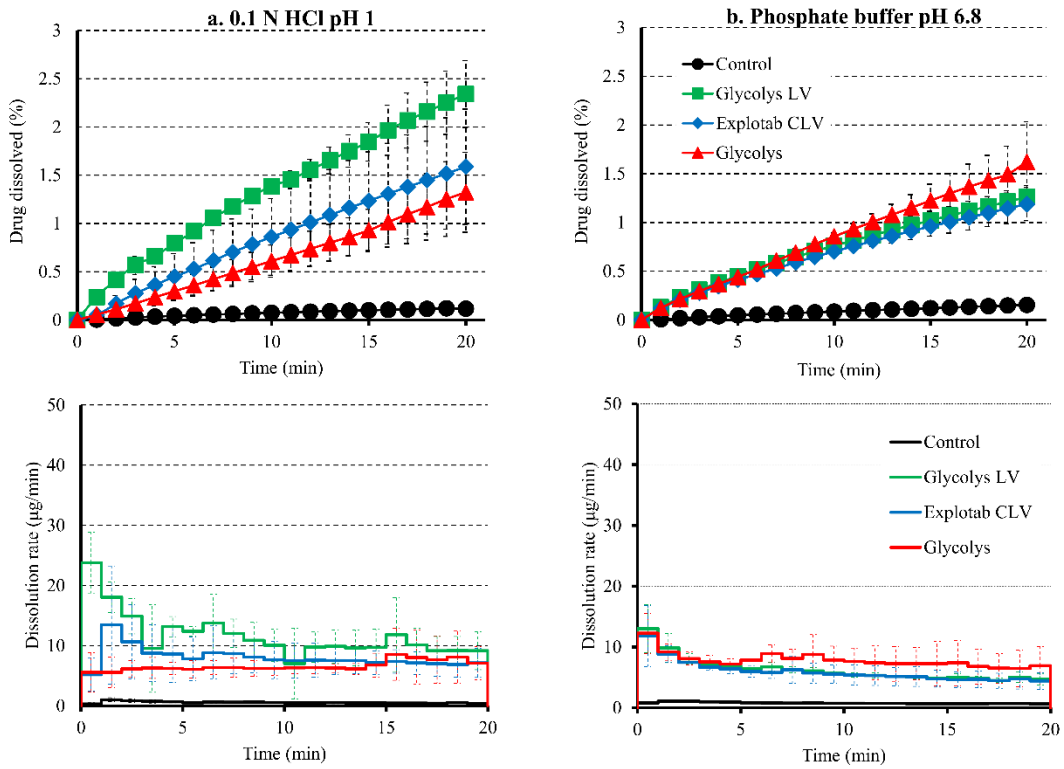
675 **Figure 4**



676

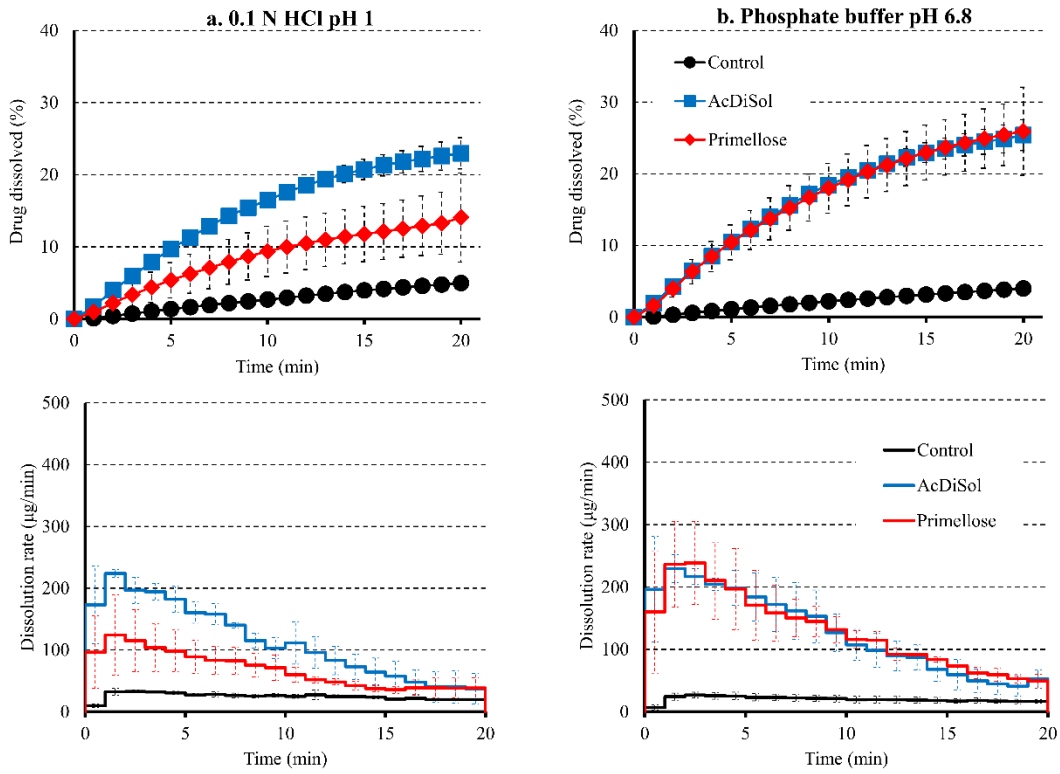


679 **Figure 6**



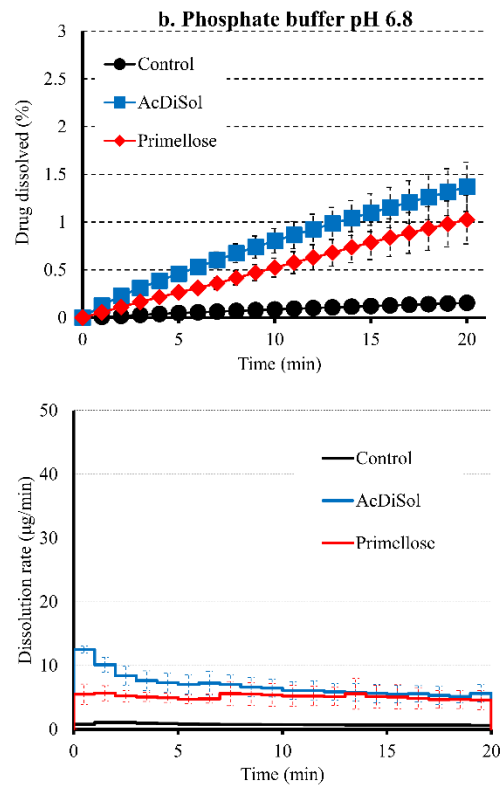
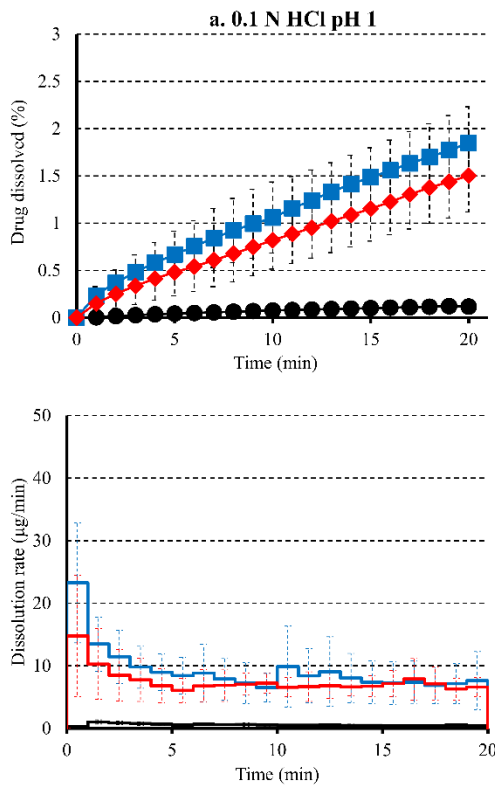
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681 **Figure 7**



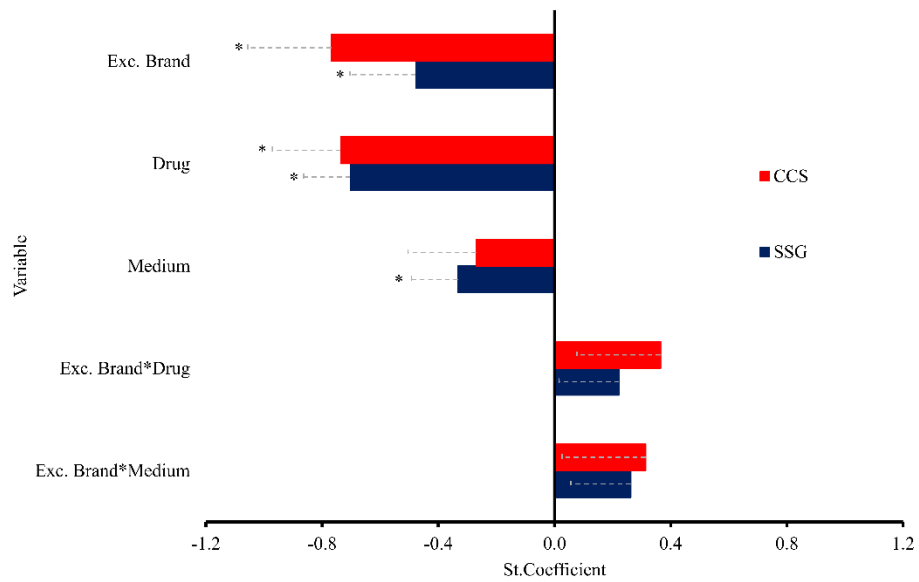
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683 **Figure 8**



684

685 **Figure 9**



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